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Pyrethroid insecticides
Chapter IVa. Reactivity of chrysanthemic acid and its lower esters

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To my wife Anne for constant support and all her love

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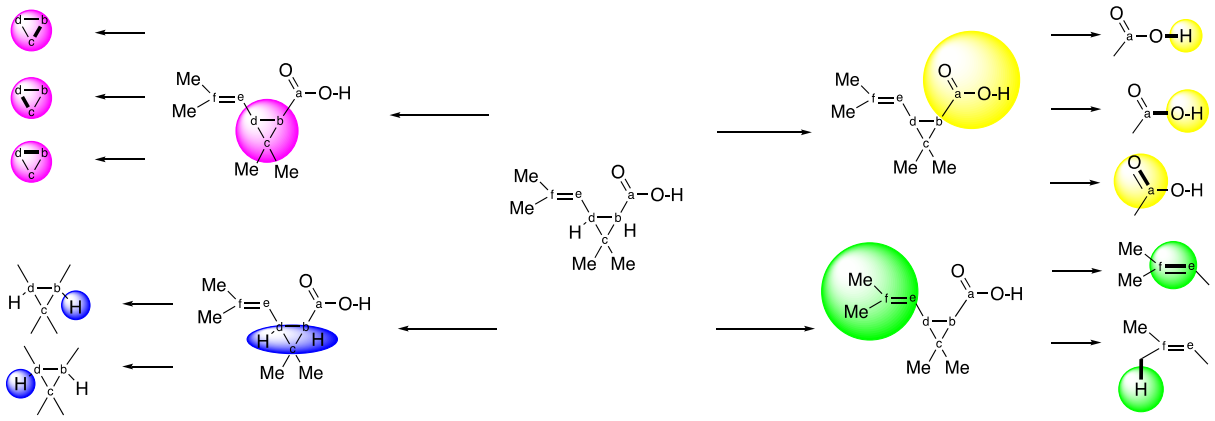
Abstract

The reactivity of chrysanthemic acid and of its "lower esters" (methyl, ethyl, isopropyl and *t*-butyl) has played a crucial role in their structure elucidation, the discovery of new insecticides and in the understanding of their environmental fate.

The reactivity of the carboxylic acid moiety and of its esters, that of the isobutenyl moiety and that of the cyclopropane ring are orthogonal to each other. The fact that this compound class is of relevance for industry has increased the diversity of the reactions disclosed especially that in the patented literature that associates science and economy and is at the roots of the green chemistry.



Keywords: Cyclopropanes, carboxylic acids, trisubstituted alkenes, esters, reactivity

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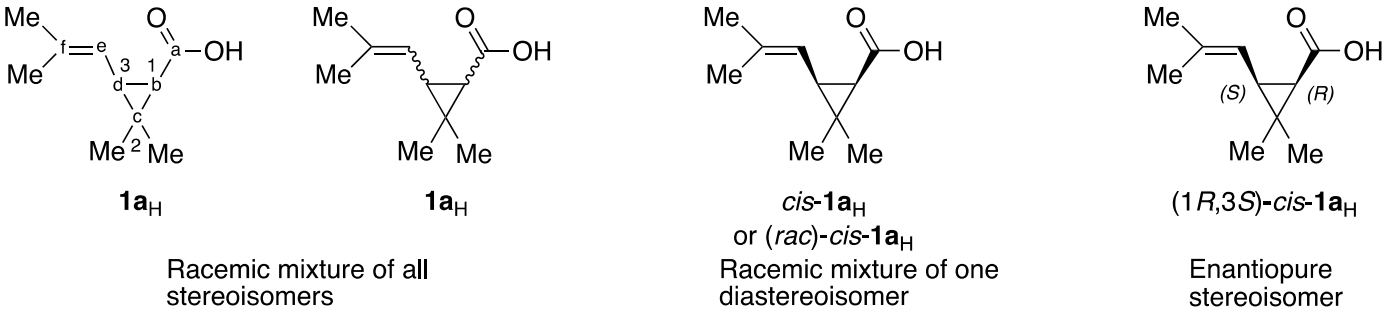
Coding Rules

Numbering is related to the basic code found in Figures 1-5

Rules used to code chemical structures:



1a$_H$ **1a**$_H$ *cis*-**1a**$_H$ or (*rac*)-*cis*-**1a**$_H$ (1*R*,3*S*)-*cis*-**1a**$_H$

Racemic mixture of all stereoisomers

Racemic mixture of one diastereoisomer

Enantiopure stereoisomer

Figure 1

1. Introduction

1.1. Reactivity of chrysanthemic acid and its lower esters as a driver for innovation

The reactivity of chrysanthemic acid (**1a**$_H$) and that of its esters **1a**$_R$ has been essential for their structure elucidation, the discovery of new insecticides and is also of prime importance to understand their environmental fate.

These compounds possess an exceptional reactivity since chrysanthemic acid concentrates on a ten-carbon monoterpenoid scaffold an extremely large number of "functional groups" that act alone or in combination.

Organic compounds are usually viewed as composed of an inert backbone to which are attached or in which are embedded "reactive" functional groups. This is not the case for chrysanthemic acid and its "lower esters" ((**1a**$_{Me}$) R: Me, (**1a**$_{Et}$) R: Et, (**1a**$_{iPr}$) R*: i*-Pr, (**1a**$_{tBu}$) R: *t*-Bu) since the cyclopropane ring plays, beside the acid (ester) and the isobutenyl groups, the role of a functional group in its own right.

These features lead to an extremely rich panel of chemical reactions that involves an exceptionally small number of atoms. Interestingly, several reactions are highly selective (see below, Scheme 10, Scheme 11, Scheme 13). Furthermore, chrysanthemic acid and its "lower esters" possess four asymmetric centers and therefore exist as four different compounds that can be mutually classified as enantiomers or diastereoisomers.

The diastereoisomers often behave differently towards different type of reagents and conditions such as H_2, O_2, HCl, NaOH, heat, light or amines, while the enantiomers react differntly with enantiopure amines or lipases, among others.

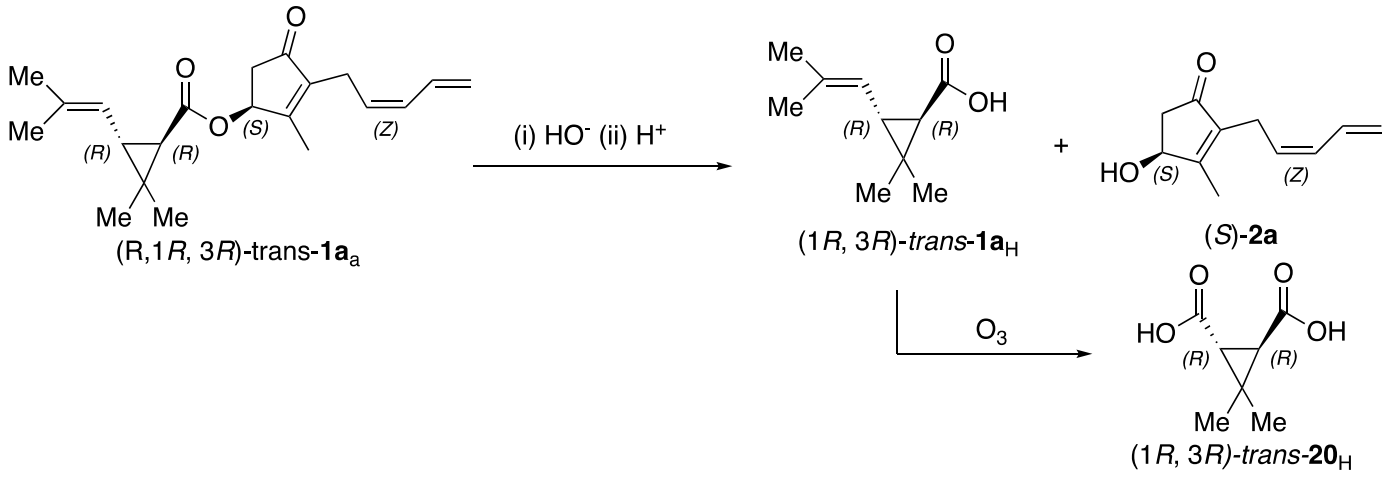
Therefore, chrysanthemic acid and its "lower esters" can be used as an exceptional model of chemical reactivity.

Compounds that have aroused similar interest are rare: chemical, biochemical, industrial, economical ecological aspects are important and only few chemicals have led to such an exceptionally large number of publications that have appeared in the academic as well as in the patent literatures. The scale at which reactions have been performed is exceptionally broad (mg to tons). Several reagents have been tested and compared at several occasions to propose cost-effective reactions. This is the subject of this chapter (Chapter IVa).

Some of the reactions have been used to achieve a purpose that requires a series of consecutive transformations. Those will be described in a subsequent chapter (Chapter IVb).

1.1.1. Tackling the reactivity of chrysanthemic ester to allow their structure determination. Discovery of the insecticidal properties of pyrethrum the natural extract of *Chrysanthemum cinerariifolium*,[1,2] has opened intensive interdisciplinary research in the field over the last 100 years. Due to the number of bioactive components of the natural extract, the complexity of their structures, and the absence of modern spectroscopic methods, their structure elucidation took several years.[1,2]

The structure elucidation of natural pyrethrins[2] has been initiated at the beginning of the 20th century when spectroscopic methods where missing and has been carried out until the early 1950's. The first results have been achieved by saponification of pyrethrin I, the major ingredient of pyrethrins or its semicarbazone,[3] which delivers chrysanthemic acid (**1a**$_H$) on acidic treatment and has allowed its structure elucidation by transformation to the known caronic acid (1*R*,3*R*)-*trans*-(**20**$_H$) on further "oxidative" ozonolysis (Scheme 1).



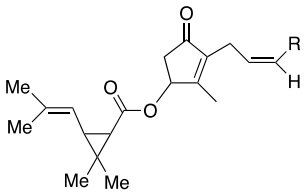
Scheme 1. Original reactions involved in structure determination of pyrethrin I.[3]

1.1.2. Tackling the reactivity of chrysanthemic acid to produce bioactive analogues. It becomes rapidly temping to produce analogues possessing similar or even stronger insecticidal properties, simpler structures, easier to synthesize and at lower cost.[1-6] This proved to be the case of allethrin (**1a**$_b$), the structure of which is related to most bioactive enantiomer of (**1a**$_a$) (Figure 2).[1,2,7]

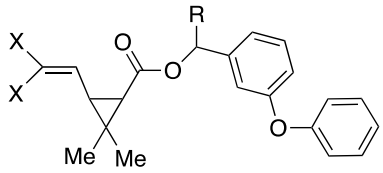
More than 50.000 analogues have been prepared and tested. Only a small number have been selected as insecticides and an even smaller number went to advanced insecticidal testing.[1,2]

The strategy for the synthesis of these compounds, at least at the early stage, use chrysanthemic acid (**1a**$_H$) (Figure 3) as the starting material to produce rapidly a large array of analogues for testing.[1,2] It is commercially available as a *trans*/*cis* mixture of stereoisomer (60/40 to 70/30) mainly arising from cyclopropanation of 2,5-dimethyl-2,4-hexadiene with ethyl diazoacetate, using the original synthetic method of Staudinger[2,8]

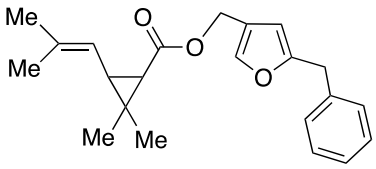
industrialized by the Sumitomo Company (see the following Chapter V).[1] Racemic *trans*-chrysanthemic acid can be synthesized easily using the Roussel-Uclaf method (see the following Chapter V).[9]



1a$_a$ Pyrethrin I R: $CH=CH_2$
1a$_b$ Allethrin R: H



1a$_c$ Phenothrin X= Me, R: H
1b$_c$ Permethrin X= Cl, R: H
1a$_d$ Cyphenothrin X= Me, R: CN
1b$_d$ Cypermethrin X= Cl, R: CN
1c$_d$ Deltamethrin X= Br, R: CN



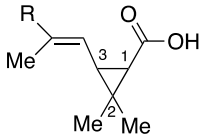
1a$_e$ Resmethrin

Figure 2. Gross structure of some (natural) pyrethrins and (unnatural) pyrethroids whose stereochemistry at each carbon has been omitted (see Figure 1 for the convention applied to this chapter).

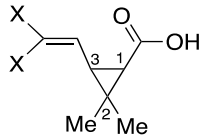
The most obvious modification involves an esterification with a series of alcohol of either (i) chrysanthemic acid (**1a**$_H$) (Scheme 2) or related vinylcyclopropane carboxylic acids such as cypermethrinic acid (**1b**$_H$) and deltamethrinic acid (**1c**$_H$) (Scheme 3).[2]

This is the case of allethrin **1a**$_b$ (Figure 2) derived fom the hydroxy-cyclopentenolone family[1,2,8] that includes pyrethrolone (**2a**) and allethrolone (**2b**) (Figure 3); phenothrin (**1a**$_c$) and cyphenothrin (**1a**$_d$) (Figure 2) derived from the benzyl alcohol family[10] such as 3-phenoxybenzylalcohol (**2c**) or 3-phenoxymandelonitrile (**2d**) (Figure 3) resmethrin (**1a**$_e$) (Figure 2) from 3-(hydroxymethyl)-5 benzylfuran (**2e**) a member of the furfuryl alcohol family[2] (Figure 3).

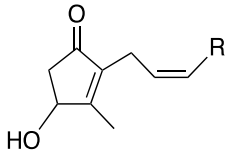
The synthesis of cypermethrin (**1b**$_c$) from chrysanthemic acid (**1a**$_H$) requires the formal replacement of the two vinylic methyl groups by two halogen atoms before esterification with 3-phenoxy mandelonitrile (**2d**). It has been formerly achieved by replacement of the-2-propylidene moiety of **1a**$_H$ by the dichloromethylene moiety that involves the cleavage of–the C=C double bond of the chryasanthemic acid by reductive ozonolysis to hemicaronic aldehyde (**19$_H$**) (Scheme 2, entry d).



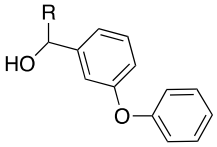
1a$_H$ Chrysanthemic acid R: Me
1d$_H$ Pyrethric acid R: CO_2Me
1e$_H$ Nor-chrysanthemic acid R: H



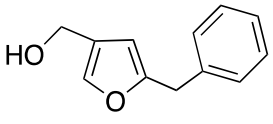
1b$_H$ Cypermethrinic acid X: Cl
1c$_H$ Deltamethrinic acid X: Br



2a pyrethrolone R: $CH=CH_2$
2b allethrolone R: H

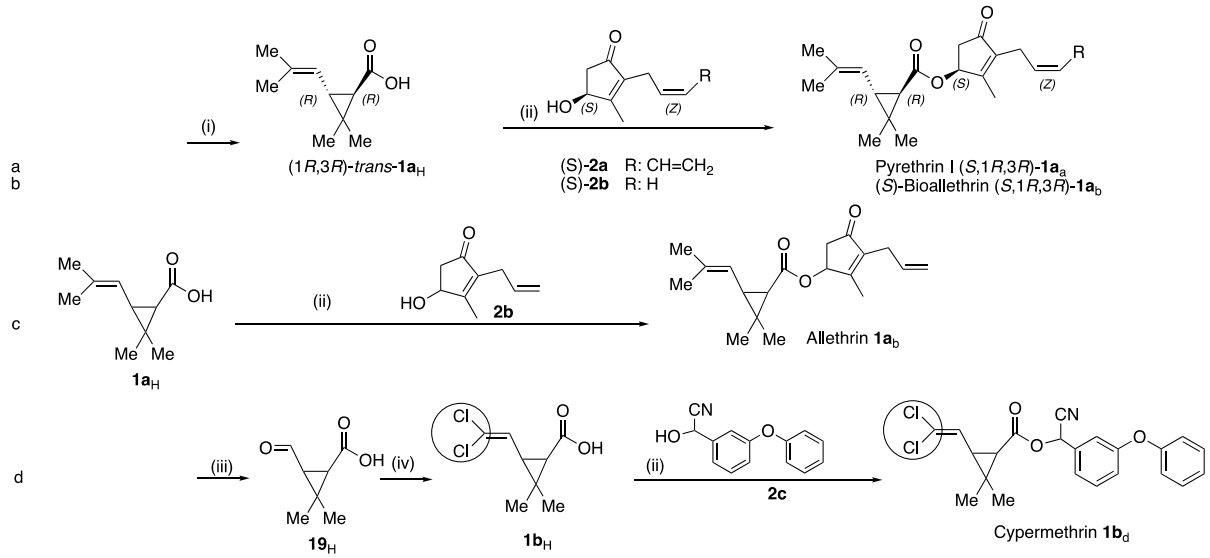


2c 3-phenoxybenzylalcohol R: H
2d 3-phenoxymandelonitrile R: CN



2e 3-(hydroxymethyl)-5 benzylfuran

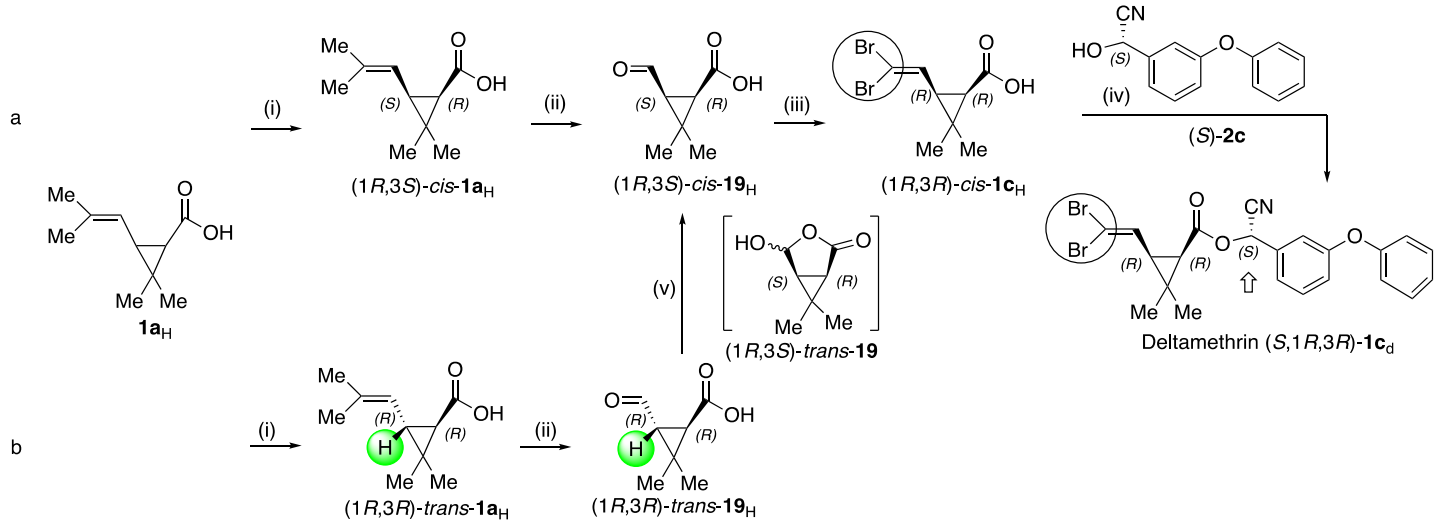
Figure 3. Gross structure of some of the precursors of commercially available pyrethrins and pyrethroids.



Scheme 2. Basic reactions involved in the synthesis of commercial pyrethroids.

The synthesis of (*S*)-bioalletrin, the most active stereoisomer of allethrin (**1a**$_b$), requires isolation of the enantiopure chrysanthemic acid (1*R*,3*R*)-*trans*-**1a**$_H$ from the mixture by stepwise separation of the *trans*-stereoisomer from the *cis*-stereoisomer and resolution of the *trans*-**1a**$_H$ racemate (Scheme 2, entry d), a procedure that has been recently revisited.[11]

The synthesis of deltamethrin, (*S*,1*R*,3*R*)-(**1c**$_d$) (Figure 2) from the isomeric mixture of chrysanthemic acid (**1a**$_H$) requires a more complex procedure. It involves sequential separation of the *cis*/*trans* mixture of stereoisomer and resolution of each of the two racemate (Scheme 3).[11] The straightforward route uses reductive ozonolysis of (1*R*,3*S*)-*cis*-chrysanthemic acid (1*R*,3*S*)-*cis*-(**1a**$_H$) and building the dibromo-vinyl unit leading to (1*R*,3*R*)-*cis*-(**1c**$_H$) followed by esterification with (*S*)-**2c** (Scheme 3, entry a).



Scheme 3. Examples of complex transformations from chrysanthemic acid to pyrethroids.

Another approach uses (1*R*,3*R*)-*trans*-chrysanthemic acid (1*R*,3*R*)-*trans*-(**1a**$_H$) and requires as an extra step, the contrathermodynamic epimerization at C-3 of the hemicaronic aldehyde (1*R*,3*R*)-*trans*-(**19**$_H$) to (1*R*,3*S*)-*cis*-(**19**$_H$) favored by the intramolecular formation of biocartol (**19**), a bicyclic [3.1.0]lactol (Scheme 3, entry b).

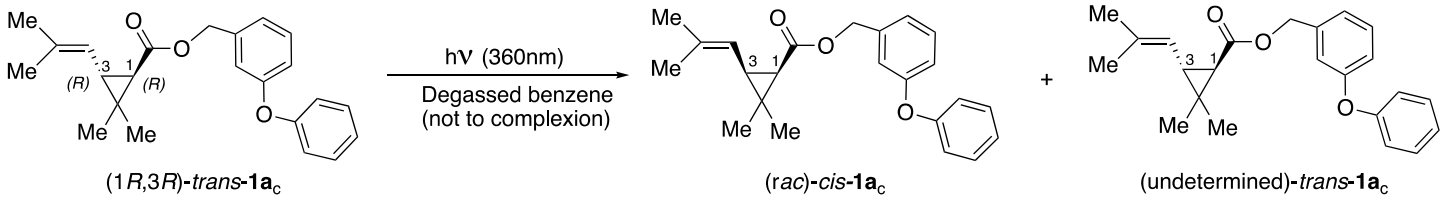
The strategy disclosed above that use chrysanthemic acid (**1a**$_H$) as the starting material for the synthesis of almost all pyrethroids has been used at the discovery stage. Once the active compound was identified, novel synthetic strategies have been devised as for accessing cypermethrin and deltamethrin. However, synthesizing those compounds from a common intermediate offers advantage as it will be discussed in a forthcoming chapter.

1.1.3. Tackling the reactivity of chrysanthemic acid to understand and predict the degradation of pyrethrins and pyrethroids in the environment. The reactivity of pyrethrin I and pyrethroids in the environment especially their propensity to be degraded by the environment upon the time under usual circumstance such as oxygen, water, sunlight and plant leaves, is crucial for their biological action and long-lasting activity. The nature of the products resulting from their degradation have also played a crucial role.

This action has been considered to design pyrethroids that possess stronger or longer actions as deltamethrin in which (i) the 3-phenoxymandelonitrile moiety is less photodegradable than that of pyrethrolones, (ii) the vinylic bromine also prevent the allylic oxidation that takes usually place on the vinylic methyl groups. Furthermore, since ester hydrolysis is one of the ways pyrethrins and pyrethroids are degraded, avoiding this process enhance its lifetime. With that respect it has been found that due to steric hindrance around its carbonyl group, deltamethrin that possesses the *cis*-stereochemistry is more robust than pyrethrin I that carries the vinyl and the carboxy group *trans* to each other.

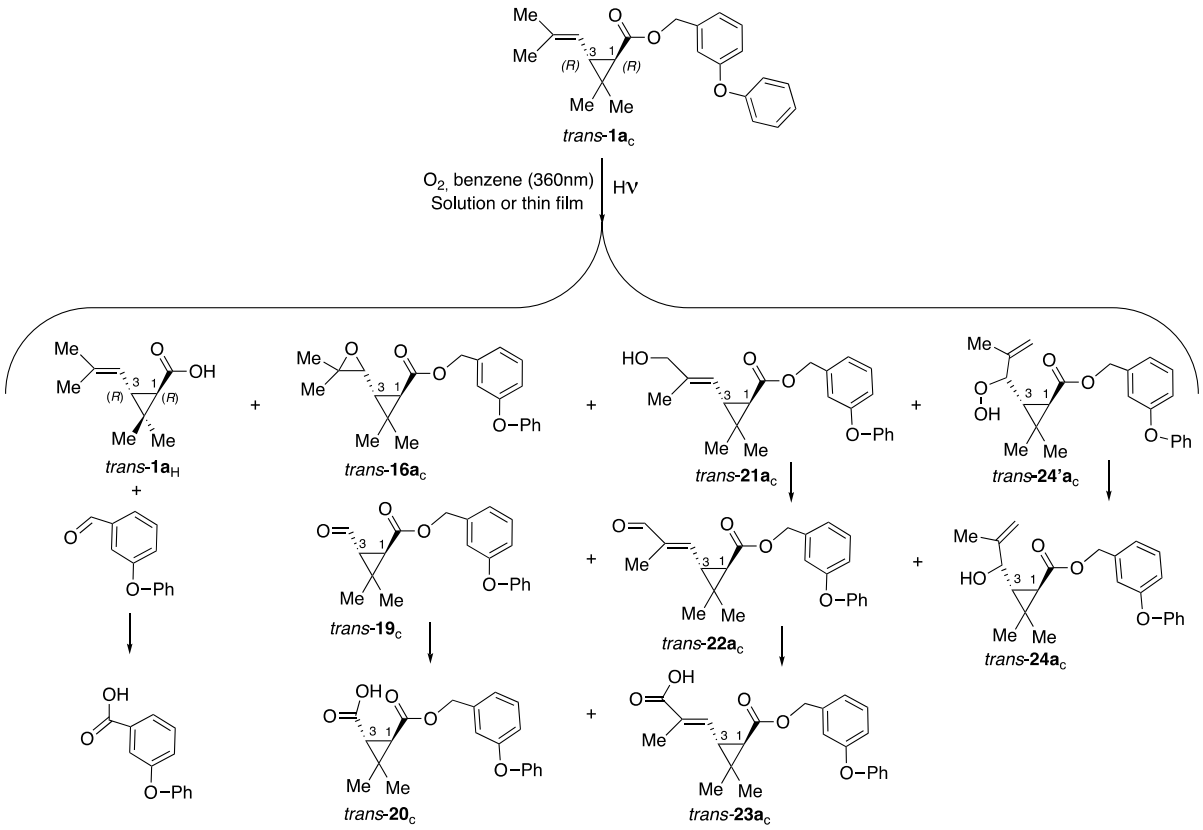
We have selected in Scheme 4,[12] Scheme 5[12] and Scheme 6[13] examples of pyrethroids that have been reacted under conditions close to those present in nature understanding the difficulty to achieve such small-scale experiments that produces in minute amounts a huge number of products resulting from their degradation. In fact, structure elucidation of these compounds relates to comparison with authentic samples.

It has been found, for example, that (1*R*,3*R*)-*trans*-phenothrin (1*R*,3*R*)-(**1a**$_c$), on irradiation in degassed benzene at 360 nm or in solid phase under sunlight, is exclusively isomerized to its less stable *cis*-stereoisomer (*rac*)-*cis*-**1a**$_c$ (Scheme 4).[12] Loss of the stereochemical integrity in the process lets suggest that it might results from the cleavage and recombination of the [C^1-C^3] bond of the cyclopropane ring and since the reaction does not go to completion *trans*-compound is still present in the medium.



Scheme 4. Products resulting from irradiation of (1*R*,3*R*)-*trans*-phenothrin in sunlight.[12]

Performing the same reaction in the presence of oxygen leads to a great variety of products, the production of which is 5-10 fold faster than the previous reaction since most of the products possess the *trans*-stereochemistry at least at the early stage of the reaction.[12] The nature of the photoproducts is similar at 5 and 50% conversion rate. But their relative proportion varies depending upon the irradiation time: the amount of more oxidized compounds increases as well as that of the *cis*-stereoisomer (Scheme 5).[12]



Scheme 5. Products resulting from irradiation of (1*R*,3*R*)-*trans*-phenothrin in air.[12]

The major products resulting from mimicking the action of the environment involve[12] (Scheme 5):

(i) the photo-induced cleavage of the C−O bond. It leads to chrysanthemic acid (1*R*,3*R*)-(**1a**$_H$), and 3-phenoxy benzaldehyde the product of oxidation of the corresponding alcohol **2c** that is further oxidized to the corresponding carboxylic acid,

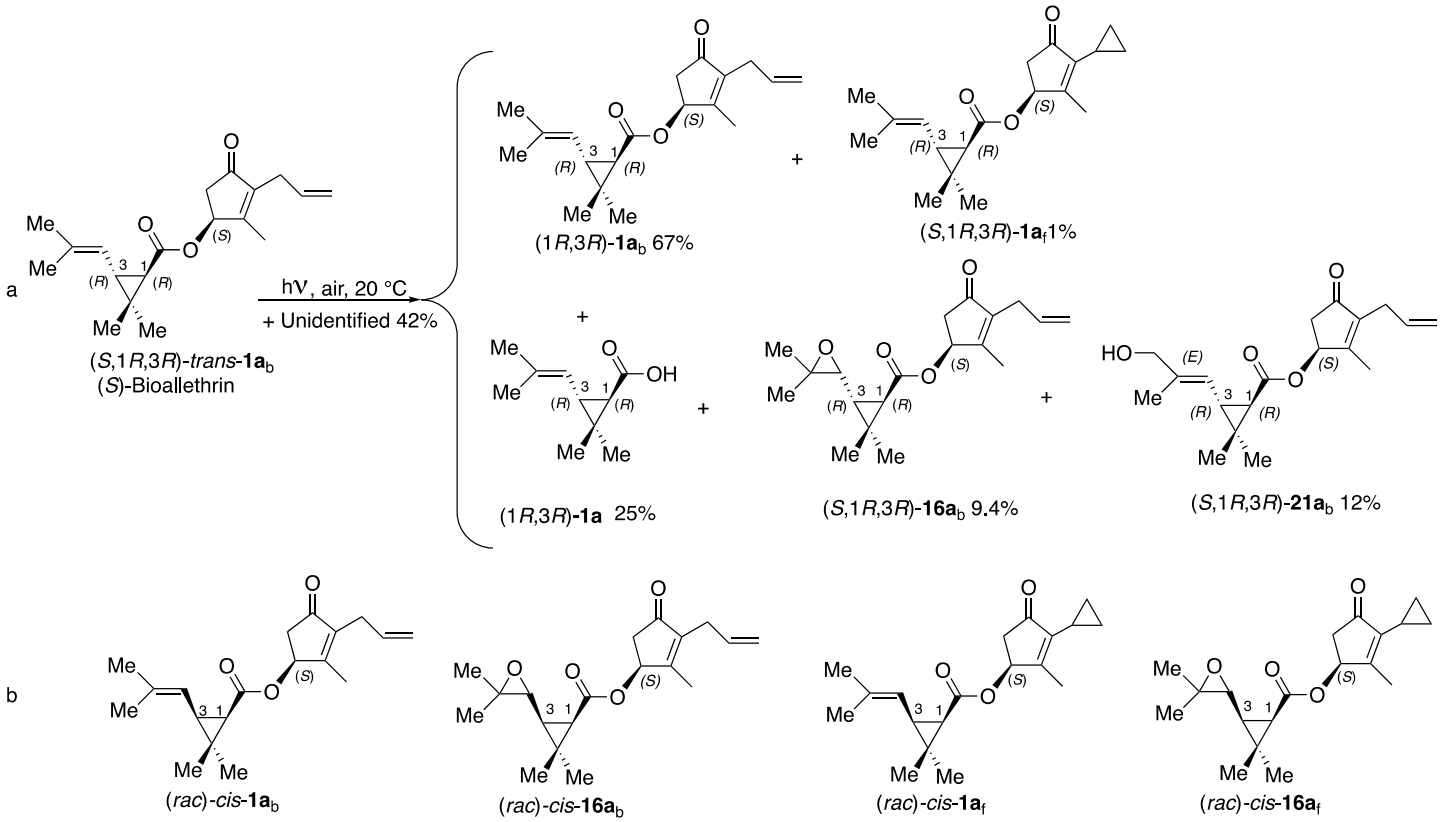
(ii) the photoxidation of the isobutenyl side chain especially of its:

(a) C=C double bond leading to the oxido-phenothrin (1*R*,3*R*)-(**16a**$_c$) by oxidative addition reaction and to the hemicaronate (1*R*,3*R*)-**19**$_c$ by C=C bond cleavage then to the caronic acid monoester (1*R*,3*R*)-**20**$_c$ on further oxidation,

(b) *trans*-methyl vinylic group that results in the formation of the allylic alcohol (1*R*,3*R*)-**21a**$_c$ by direct replacement of the allylic hydrogen, then to the unsaturated aldehyde (1*R*,3*R*)-**22a**$_c$ and to the related acid (1*R*,3*R*)-**23a**$_c$,

(c) the hydroperoxide (1*R*,3*R*)-**24'a** that results from an allylic rearrangement and that finally leads to the allyl alcohol (1*R*,3*R*)-**24a**$_c$ an isomer of **21a**$_c$.

Related results have been observed on photoxidation on thin film of the more labile (*S*)-bioallethrin (*S*,1*R*,3*R*)-*trans*-(**1a**$_b$) (Scheme 6).[13] But, in complement, products resulting from the di-pi-methane rearrangement of the allethronyl moiety such as chrysanthemic ester (*S*,1*R*,3*R*)-*trans*-**1a**$_f$ are formed (Scheme 6, entry a)[13]. They include (*rac*)-*cis*-**1a**$_f$ that results from the cleavage/recombination of the C^1-C^3 bond of the cyclopropane moiety of (*S*,1*R*,3*R*)-*trans*-**1a**$_f$ and the related epoxide (*rac*)-*cis*-**16a**$_f$ that results from its epoxidation (Scheme 6, entry b).[13] Note that several unidentified products that include those resulting from the degradation of the allethronyl part are also produced especially if the reaction proceeds for longer time.[13]



Scheme 6. Products resulting from irradiation of (S)-bioallethrin in air.[13]

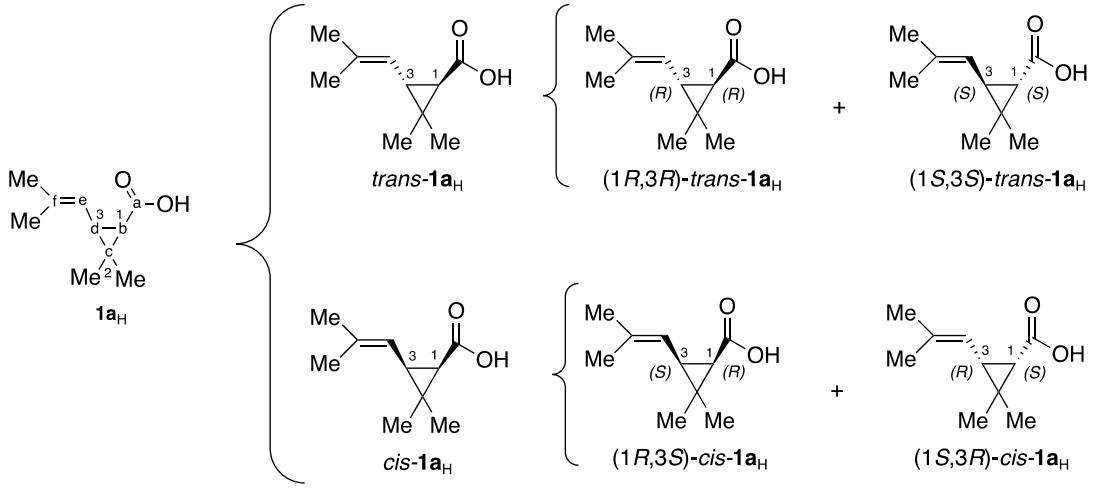
1.2. Generalities about the reactivity of chrysanthemic acid and its lower esters

1.2.1. Not one compound but four stereoisomers. Chrysanthemic acid ($C_{10}H_{16}O_2$) is a monoterpene (Scheme 7) that possesses a cyclopropane moiety flanked by two geminal methyl groups at [Cc], a carboxy group and a hydrogen at [Cb], and an isobutenyl group and a hydrogen at [Cd]. It possesses two asymmetric centers at [Cb] and [Cd] and therefore exists as two (*cis*/*trans*) diastereoisomers and a total of four stereoisomers (1*R*,3*R*)-*trans*-**1a**$_H$, (1*S*,3*S*)-*trans*-**1a**$_H$, (1*R*,3*S*)-*cis*-**1a**$_H$, (1*S*,3*R*)-*cis*-**1a**$_H$ from which a single one, the (1*R*,3*R*)-*trans*-**1a**$_H$ form derives from the natural sources.

The reactivity of the *cis*-diastereoisomer often differs from its *trans*-diastereoisomer due to the presence of the carboxyl and the isobutenyl groups in close proximity in the *cis*-series and far from each other in the *trans*-series and the restriction of movement around the rigid three-membered ring to which they are attached in vicinal position.

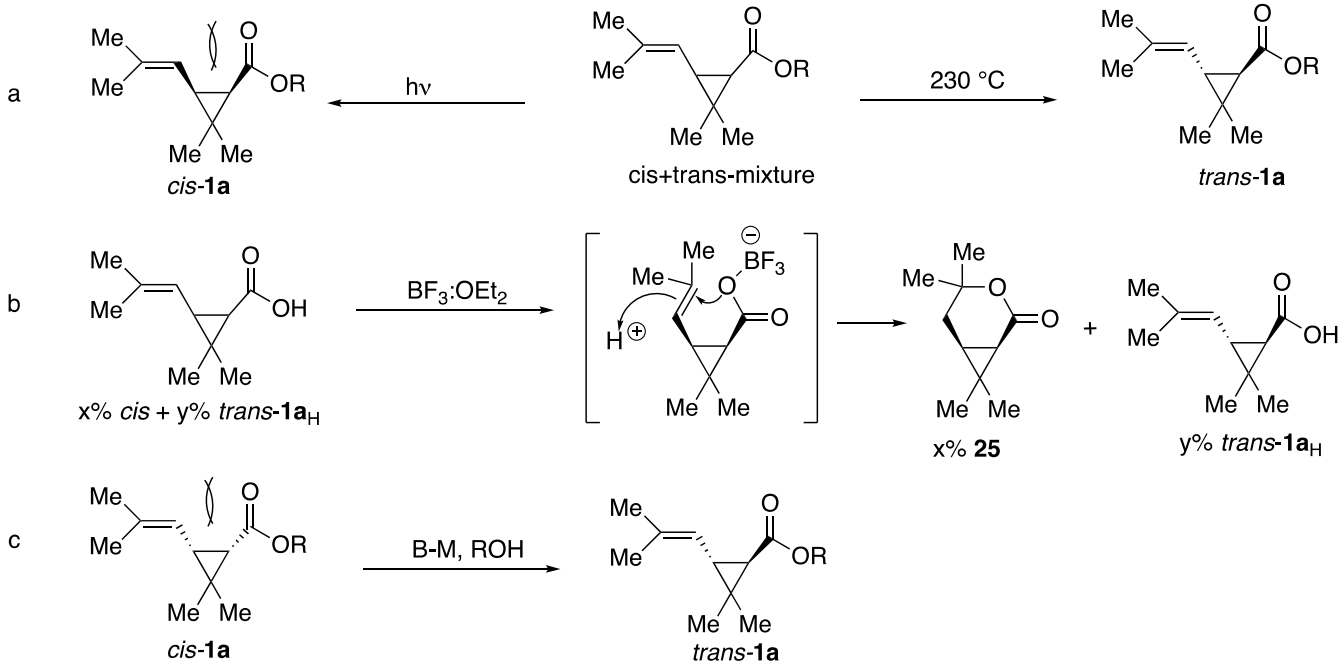
Those groups are shielded in the *cis*-series that hinders the approach of reagents susceptible to attack them. This proximity also favors intramolecular assistance in some cases and even intramolecular reaction that leads to the formation of bicyclic compounds.

For example, the content of alkyl *cis*-chrysantemates *cis*-**1a**$_R$ increases on irradiation of *cis*+*trans*-mixtures of chrysanthemates belonging to the "lower ester family" whereas on thermolysis at around 250°C this is the content of alkyl *trans*-chrysantemates *trans*-**1a**$_R$ that increases (Scheme 8, entry a).



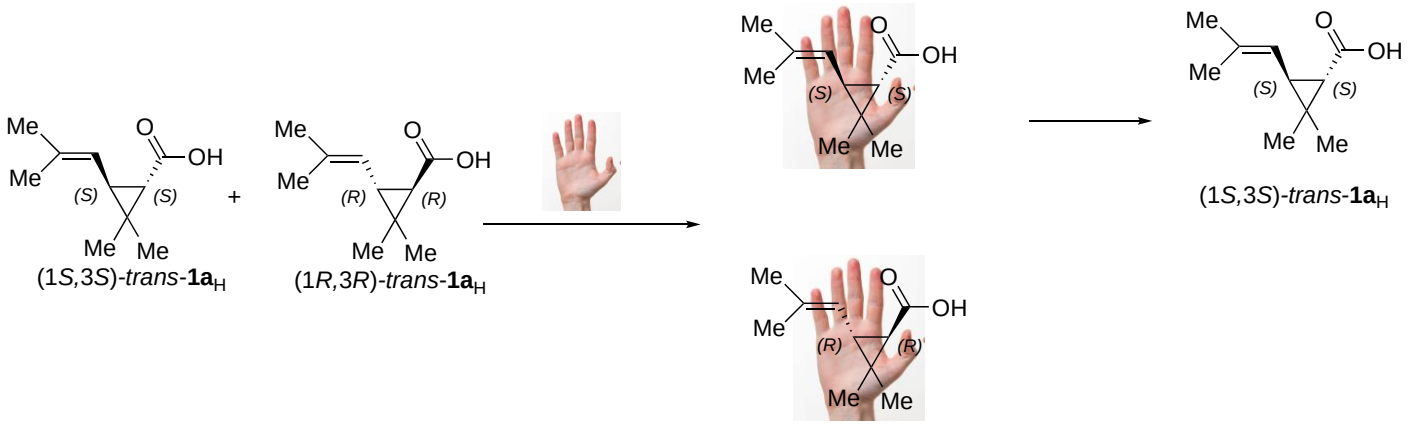
Scheme 7. Structure of *cis*-/*trans*-diastereoisomers and of the four stereoisomers of chrysanthemic acid.

The proximity of the isobutenyl and the carboxylic groups in the *cis*-chrysanthemic acid *cis*-(**1a**$_H$) promotes, in the presence of Lewis acids, the formation of the bicylic (3.1.0)-lactone **25** (Scheme 8, entry b) whereas the *trans*-analogue *trans*-**1a**$_H$ is not affected. This feature has been successfully used to isolate the *trans*-diastereoisomer from a cis/trans-mixture. The same proximity has been used to isomerize in basic media the least stable *cis*-chrysanthemates *cis*-**1a**$_R$ to the *trans*-chrysanthemates *trans*-**1a**$_R$ in which the two vicinal group on the cyclopropane ring fall apart (Scheme 8, entry c).



Scheme 8. Differentiated reactivity of *cis*- and *trans*-chrysanthemic acid and esters.

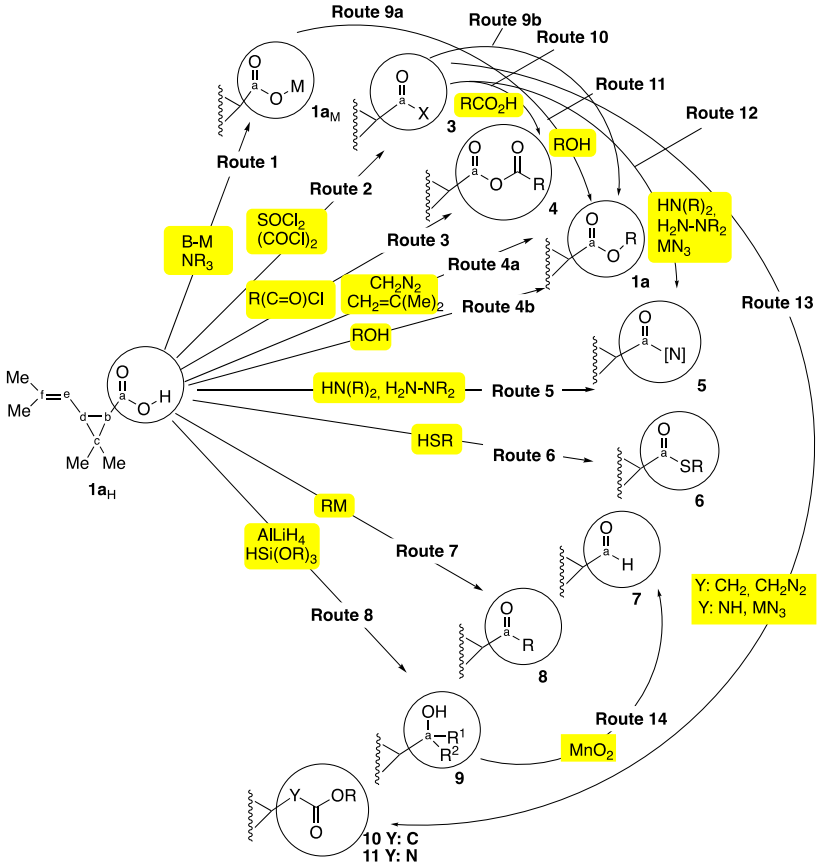
Each enantiomer of chrysanthemic acid behaves differently towards chiral objects and reagents through diastereoisomeric interactions (Scheme 9). It has been used to separate racemates using for example enantiopure chiral amines (See below Scheme 21).



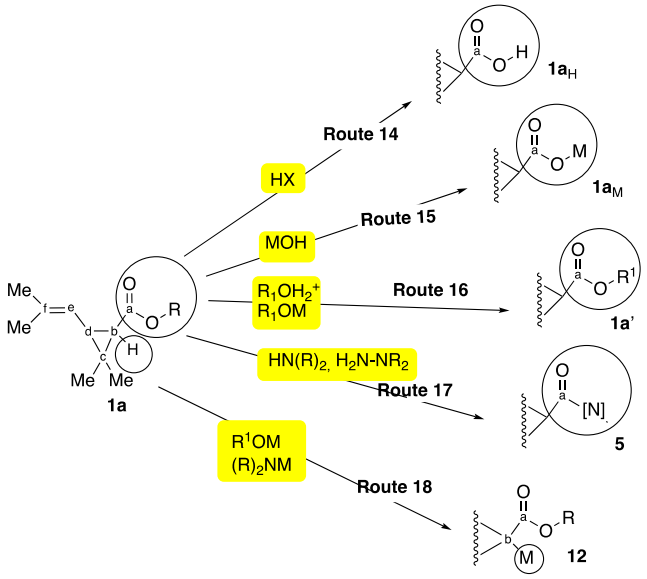
Scheme 9. Different behavior of each of *trans*-chrysanthemic acid enantiomers towards chiral reagents.

1.2.2. Identification of functional groups present on chrysanthemic acid and its lower esters. As already pointed out, chrysanthemic acid (**1a**$_H$) and its lower esters **1a**$_R$ concentrate on on their ten carbon atom framework a high reactivity due to the functionalities present that include the cyclopropane ring.

1.2.2.1. Synoptic view of reactions performed on chrysanthemic acid (1a$_H$) and its esters 1a that do not affect the cyclopropane moiety. Chrysanthemic acid (**1a$_H$**) and alkyl chrysanthemates **1a**$_R$ react in many instances the same way as compounds possessing carboxylic acid- (Scheme 10), ester- (Scheme 11) and trisubstituted alkene-moiety (Scheme 13).



Scheme 10. Synoptic view of reactions involving the carboxy-group of chrysanthemic acid.



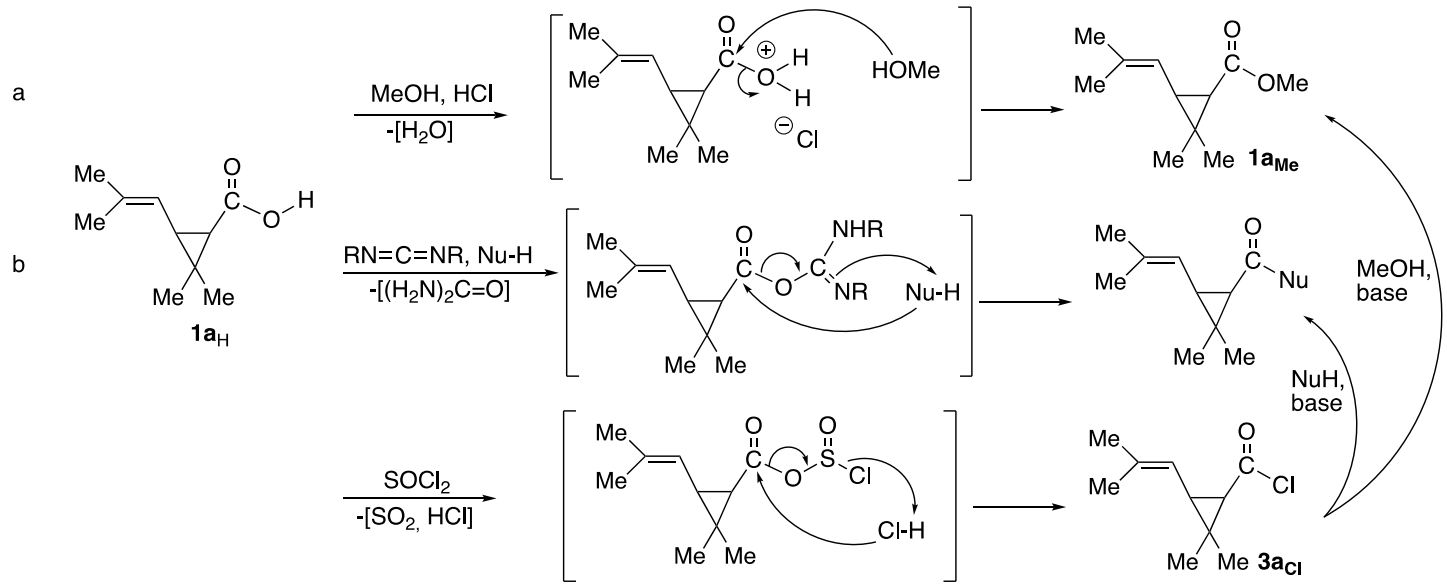
Scheme 11. Synoptic view of reactions involving the carboxy-group of chrysanthemic esters.

1.2.2.1.1. Reactions involving the carboxyl group of chrysanthemic acid. The reactions that affect the carboxyl groups have been mainly carried out on the carboxylic acid moiety (Scheme 10). They proceed by exchange either of the hydrogen (Scheme 10, Route 1, Route 3, Route 4a) or of the hydroxyl group (Scheme 10, Routes 2, 4b, 5, 6, 7). Among these reactions, esterification plays an important role and various methods that applied to each situation, especially those that can be industrialized, have been published especially in the patent literature. Some transformations including esterification have been carried out in multistep processes involving metal chrysanthemates **1a**$_M$ (Scheme 10, Route 9) or chrysanthemoyl chloride (**3**) as intermediates (Scheme 10, Route 10,11,12). Reduction to ketones **8** (Scheme 10, Route 7) and alcohols **9** using metal hydrides, Grignard reagents or enolates have been published (Scheme 10, Route 8). The synthesis of chrysanthemal (**7**) is best achieved in a two-steps sequence that involve the intermediate formation of chrysanthemol (**9a**) and its further oxidation (Scheme 10, Route 8 + Route 14).

Several of these reactions performed on chrysanthemic acid (**1a**$_H$) have been successfully extended to other cyclopropane carboxylic acids such as cypermethrinic (**1b**$_H$) and deltamethrinic (**1c**$_H$) acids and does not affect their dihalogeno-vinyl moiety. Some will be disclosed side by side to that of chrysanthemic acid (**1a**$_H$).

Transformation of hydroxyl group present on these vinylcyclopropane carboxylic acids to a better leaving group is a key process that allows the substitution of the hydroxyl group to various other groups (Scheme 10, Routes 2, 4b, 5, 6, 7) since direct transformation is prevented by thermodynamic and kinetic barriers. For this purpose, activation of the hydroxyl group can be achieved transiently using (I) acid catalysis (Scheme 12, entry a) or (ii) carbodiimides, that involves the intermediate formation of an imidate (Scheme 12, entry b) or (iii) thionyl chloride that involves the intermediate formation of a sulfinate among others (Scheme 12, entry c).

In the latter case the reaction delivers chrysanthemoyl chloride that can be isolated, purified and in turn used towards several nucleophiles. This sequence performs in two separate steps the substitution of the hydroxyl group of chrysanthemic acid. The transformation that has been widely used involves the intermediate formation of an acylium that is stable enough to be substituted (Scheme 10, Routes 10,11,12; Scheme 12) whereas cyclopropyl carbinyl cations, as it will be discussed later, are unstable and usually possess a high propensity to rearrange by cyclopropane ring opening.



Scheme 12. Model reactions used to "activate" the carboxyl-group of chrysanthemic acid.

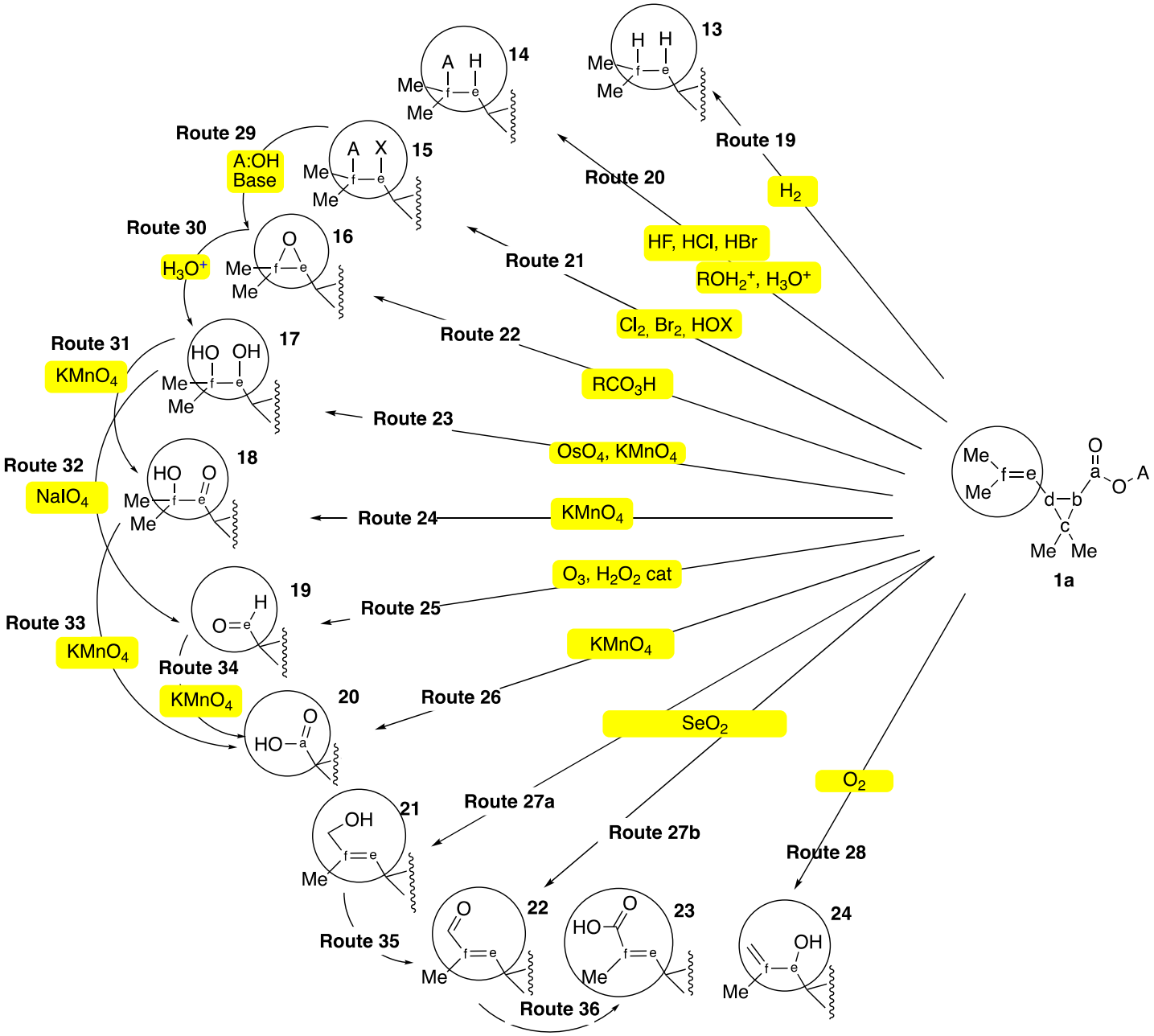
1.2.2.1.2. Reactions involving the carboxyl group of chrysanthemic esters. Esters have been transformed to chrysanthemic acid in acidic media (Scheme 11, Route 14), through saponification and acidification of the resulting salts (Scheme 11, Route 15) or on reaction with lipases. Reaction with an alcohol in acidic or basic media favors transesterification (Scheme 11, Route 16). The latter is particularly efficient if the exchanged alcohol is volatile and can be expelled from the medium to draw the equilibrium in the wanted direction. Reaction with amines and hydrazines allow under mild conditions the alkoxy/amino exchange (Scheme 11, Route 17). Finally, reactions of esters with metal amides or alcoholates allow regioselective metalation at [Cb] (Scheme 11, Route 18) a reaction particularly difficult with chrysanthemic acid that is in fact first transformed to the related metal carboxylates. Depending upon the conditions, the metalation produce epimerized alkyl carboxylates either as the *cis*-chrysanthemate under kinetically controlled conditions or as a *trans*-chrysanthemate under thermodynamically controlled conditions as will be discussed later.

Synthesis of esters[14] is one of the key reactions in the field of pyrethroids. It has been effectively achieved from the vinylcyclopropane carboxylic acid (**1**$_H$) or from their "lower esters" **1**$_R$. In the former case the transformation usually involves the substitution of their hydroxyl group by the alkoxy group of an alcohol usually after its "activation" as transient intermediate (OH/OR; Route 4b) or through an isolable intermediate, the most common one being the related acid chloride (OH/Cl, Route 2; then Cl/OR, Route 9b). Otherwise, esterification has been achieved by alkylation of the carboxylic acid in neutral or acidic media (Scheme 10, Route 4a) or after "activation" through the corresponding metal carboxylates (Scheme 10, H/M Route 1 then M/R Route 9a). Furthermore, the synthesis of methyl chrysanthemate is usually carried out for synthetic purpose with diazomethane on small scale (Scheme 10, Route 4a) or through the acid chloride for other "lower esters" including ethyl esters (Scheme 10, Route 2 + Route 9b). The more elaborated esters screened for their biological activity, including pyrethroids, have been routinely synthesized through the latter route (Scheme 10, Route 2 + Route 9b) although greener routes (Scheme 10, Route 4b or Scheme 11, Route 16) are being used especially industrially. They use cost effective approaches involving benign catalysts possessing high turnovers that produce as little by-products as possible.

As far as the stereochemistry of the esters is concerned, it should be noticed that usually the substitution reaction involving organic halides or tosylates proceeds by net inversion of configuration at the alkyl part when

performed by Route 9a (Scheme 10) and by retention of the configuration at the carbon bearing the hydroxyl of the alcohols when performed by the Routes 4b or 9b (Scheme 10).[14]

1.2.2.1.3. Reactions involving the isobutenyl moiety of chrysanthemic acid and of its lower esters. The transformation of the isobutenyl moiety has been usually carried out on lower esters of chrysanthemic acid **1a**$_R$ rather than on chrysanthemic acid (**1a**$_H$) avoiding thus competitive reaction of their carboxyl group especially those implying the *cis*-stereoisomers that tend to produce lactones (Scheme 8, entry b).



Scheme 13. Synoptic view of reactions involving the isobutenyl-group of chrysanthemic acid.

These reactions are of three types:

(i) addition reactions that occur across [Ce=Cf] double bond of alkyl chrysanthemates (Scheme 13, route 19,20,21,22,23) such as catalytic dihydrogenation (reduction, Scheme 13, route 19); hydration (same oxidation level, Scheme 13, route 20); dihalogenation or hydroxyhalogenation (oxidation, Scheme 13, Route 21),

epoxidation (oxidation, Scheme 13, Route 22), dihydroxylation (oxidation, Scheme 13, Route 23) or formation of ketoalcohols (over-oxidation, Scheme 13, Route 24),

(ii) reactions that oxidatively cleave the [Ce=Cf] bond such as ozonolysis followed by reductive treatment leading to hemicaronates **19** (Scheme 13, Route 25) or followed by oxidative cleavage leading to caronic monoesters **20** or using permanganates under drastic conditions: Scheme 13, Route 26)

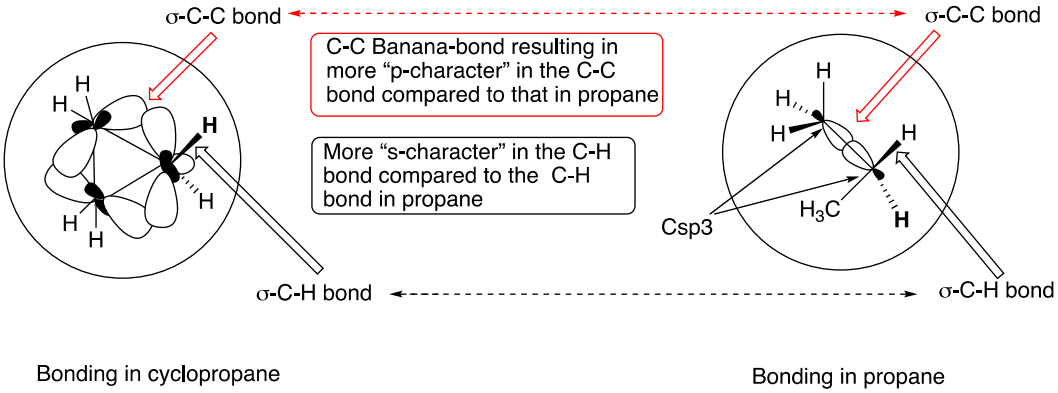
(iii) reactions that affect the methyl groups on the isobutenyl moiety through an ene reaction such as those involving selenium dioxide (Scheme 13, Route 27) or singlet oxygen (Scheme 13, Route 28).

Interestingly, in electrophilic addition reactions Markovnikoff's rule usually applies,[15,16] although, as will be discussed in the next section, other events can compete.

1.2.2.2. Reactions affecting the cyclopropane moiety. We have provided in the previous sections a series of reactions that tends to show that chrysanthemic acid (**1a**$_H$) and its esters **1a**$_R$ behave as other compounds that possess on their backbones a carboxy or an alkenyl functional group, the reactions of which do not interfere. The reality is slightly different since the cyclopropane moiety by itself is a reactive entity due to the strain introduced in the structure by the presence of a three membered ring and the exceptional nature of the internal [C−C] bonding that also affects the external bonding.

Accordingly, the cyclopropane ring in chrysanthemic acid transfers electronic information from the [C=C] double bond to the [C=O] double bond, playing a role similar to that of the [C=C] double bond. It adds various reagents that disrupt the cycle and release the strain (1,3-addition reaction) in a process that parallels the 1,2-addition of the same reagents across the [C=C] double bond of alkenes.

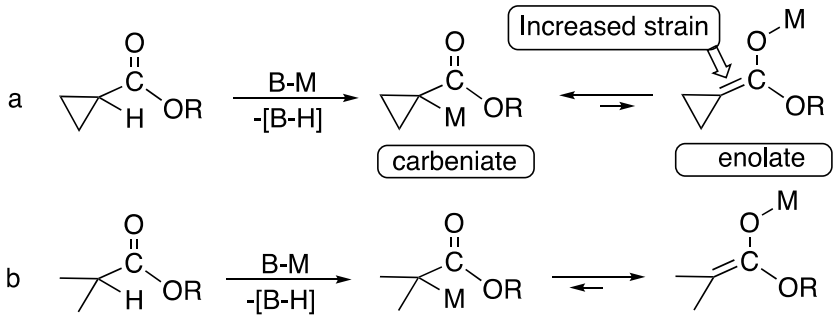
1.2.2.2.1. Structural features of the cyclopropane and their implication in modulating the reactivity of the cyclopropane moiety. As a consequence of the strain[17] involved by the presence of three sp^3 carbon atoms in a three-membered ring, the bonding in the cyclopropane ring is unusual. It has been proposed to involve "bent bonds"[18] or "banana-bonds", a type of sigma bond in which the overlap of the atomic orbitals of each carbon is no longer linear in between the two carbon atoms as it would be in propane or in an idealized equatorial triangle but out of the cyclopropane, ring (Scheme 14).[19] Those orbitals possess more p-character than for example that of carbon-2 in propane (Scheme 14) and confer to the related bond a reactivity closer to that of the pi-bond of a C=C bond in an alkene. As a consequence of this increase of the p-character of those orbitals, the two remaining *exo*-orbitals of the same carbons have an increased percentage of s-character (Scheme 14).



Scheme 14. Bonding in cyclopropane versus propane and its implication in the difference of reactivity

Accordingly, the acidity of cyclopropane should be higher than that of propane. Metalation of alkyl cyclopropane carboxylate takes advantage of the favorable inductive effect of this group but suffers for the over stabilization by delocalization of the charge in the enolate due to the excess of strain introduced during that

process (Scheme 15, compare entry a to entry b). In any case, metalation alpha to the carboxylate takes place more efficiently than that at the allylic position of alkyl chrysanthemates **1a**$_R$.



Scheme 15. Factors influencing the reactivity of cyclopropyl esters and isopropyl esters towards bases (B−M).

The presence of the "unsaturated" alkenyl and carboxyl moieties in chrysanthemic acid (**1a**$_H$) and its esters **1a**$_R$ offers the possibility of the [Ca−Cb] "banana bonds" of the cyclopropane to be delocalized through conjugation over these two moieties as disclosed in Figure 4 and that influence the reactivity of the compounds globally.

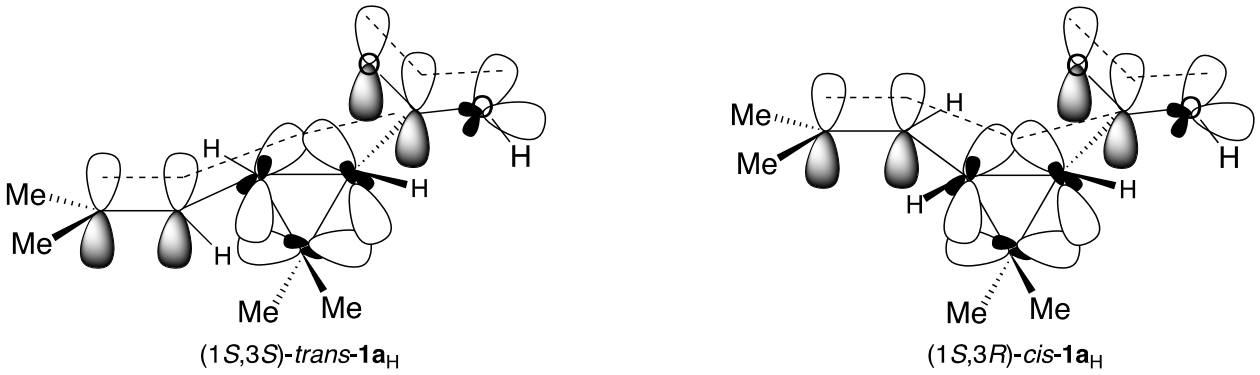


Figure 4. Modelling orbitals belonging to pi- and banana bonds in *trans*-/*cis*-chrysanthemic acid.

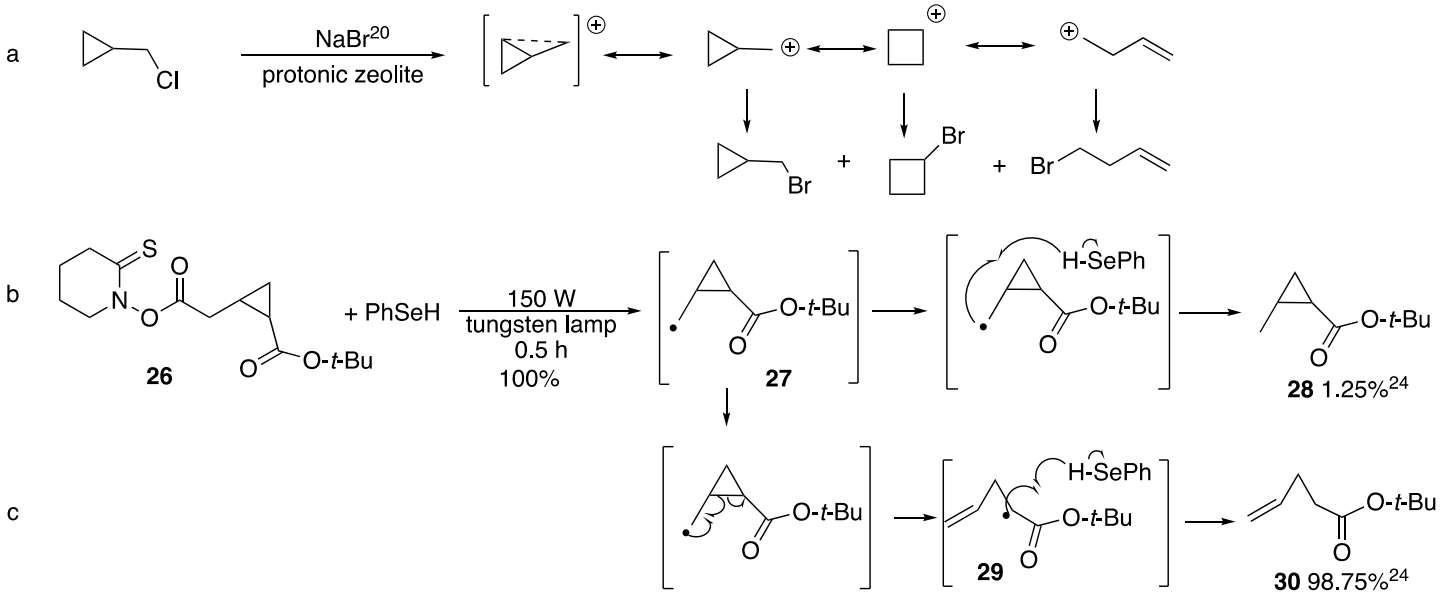
In fact, the cyclopropane ring is rarely directly affected by reagents since they usually react on the functional groups attached to it. This could be due to the presence of the gem-dimethyl group at C-2 as well as the groups attached to each of the other carbons of the ring that hinders the approach to the cyclopropane ring. Photochemical and thermal processes that do not require reagents however efficiently cleave the cyclopropane ring (Scheme 8, entry a). Anyhow, such cleavage produces radical or ionic intermediates that proceed further in rearranging, react with exogeneous reagents or react internally to re-generate the cyclopropane ring owing their proximity.

1.2.2.2.2. Synthesis and reactivity of intermediates possessing a cyclopropyl carbinyl moiety. Another interesting reactivity of compound possessing a cyclopropyl moiety lies in the unusual reactivity of cyclopropyl carbinyl compounds bearing a leaving group there. Thus, ethanolysis of cyclopropyl carbinyl benzene sulfonates is 14 times as rapid as that of the related allylic benzene sulfonate. The resulting products involve the intermediate formation of cyclopropyl carbinyl cations that easily interconvert with the cyclobutyl or homoallylcarbinyl cations that lead to a series of related compounds on which the strain present on the starting

material is in some way released. These features exemplified in Scheme 16, entry a)[20] leads to the concept of anchimeric assistance and that of "nonclassical ion" disclosed first by J.D. Roberts,[21] widely supported by H.C. Brown[22] and visualized spectroscopically by G.A. Olah (Scheme 16, entry a).[23]

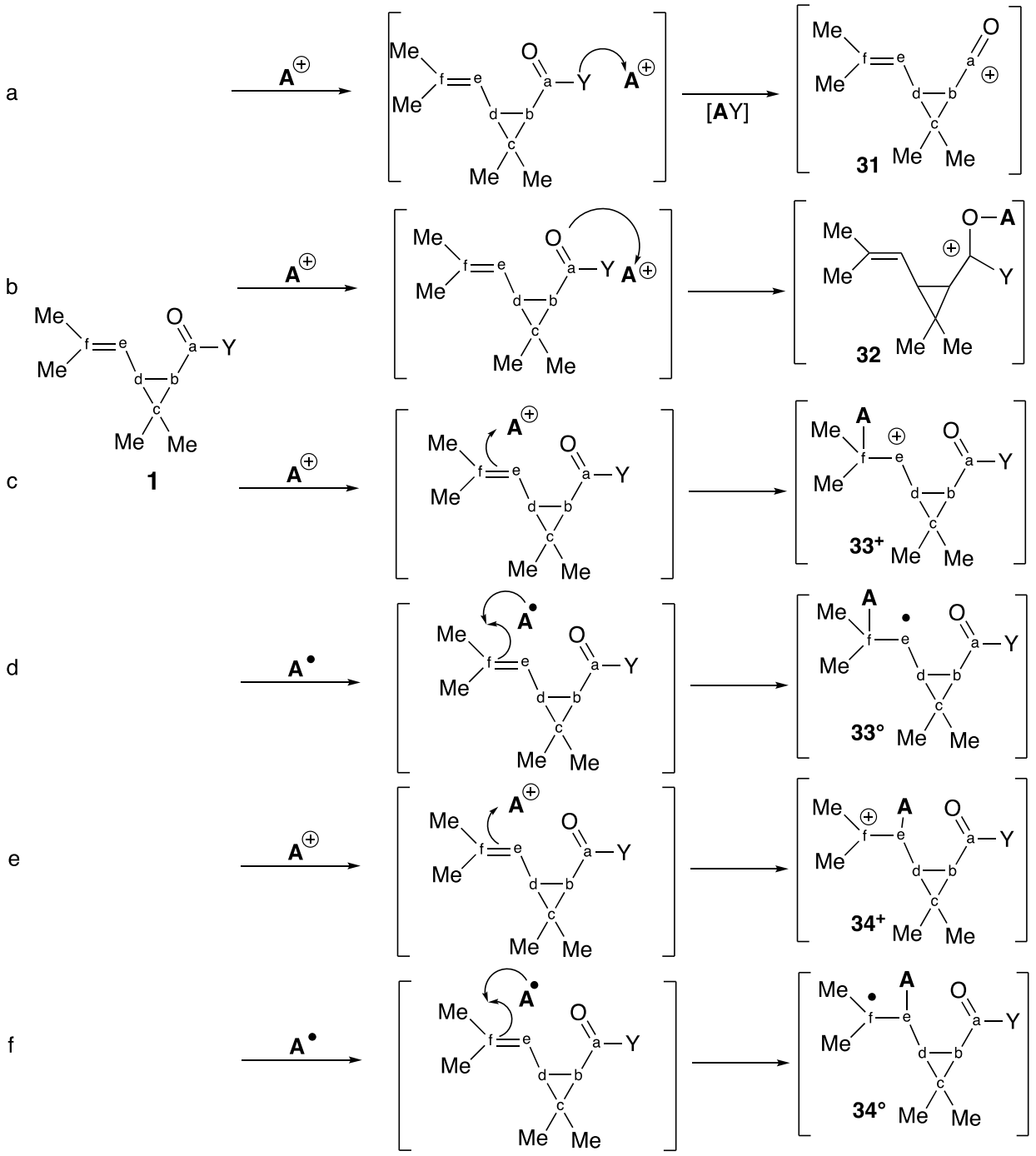
This is not the only type of reactions involving cyclopropylcarbinyl derivatives that exhibit unusual reactivity.

It has been for example described that [[((*trans*-2-(tert-butoxycarbonyl)cyclopropyl)methyl)carbonyl]oxy]-2(1*H*)-pyridinethione (**26**) on irradiation with a tungsten lamp (150 W; 0.5h), in the presence of phenylselenol, produces *tert*-butyl 4-pentenoate (**30**) in almost quantitative yield (Scheme 16, entry c).[24] The reaction involves the intermediate formation of the cyclopropylcarbinyl radical (CPC) (**27**) that exhibits a very high propensity to produce the isomeric radical (**29**) resulting from the cyclopropane ring opening, then trapped by phenylselenol to produce (**30**) (Scheme 16, entry b).[24] CPC radical ring opening to the 3-butenyl radical is the archetypal fast radical reaction with a rate constant at 25 °C of 1 x 10^8 s^{-1}. It has been used to time competing reactions as a "radical clock".[24] It has been also described that the presence of a carboxyl group in beta-position favors the cleavage of the bond of the cyclopropane ring that finally produce an homoallyl radical located on the carbon alpha to the carboxyl group as (**29**) with an increased ring opening rate constants of 7 and 12 10^{10} s^{-1} for the (*trans*-2-(ethoxycarbonylcyclopropyl) methyl radical and the *trans*-2-(*tert*-butoxycarbonylcyclopropyl)methyl radical, respectively (Scheme 16, entry c).[24]



Scheme 16. Ionic and radical model reactions of cyclopropylcarbinyl derivatives.[20,23,24]

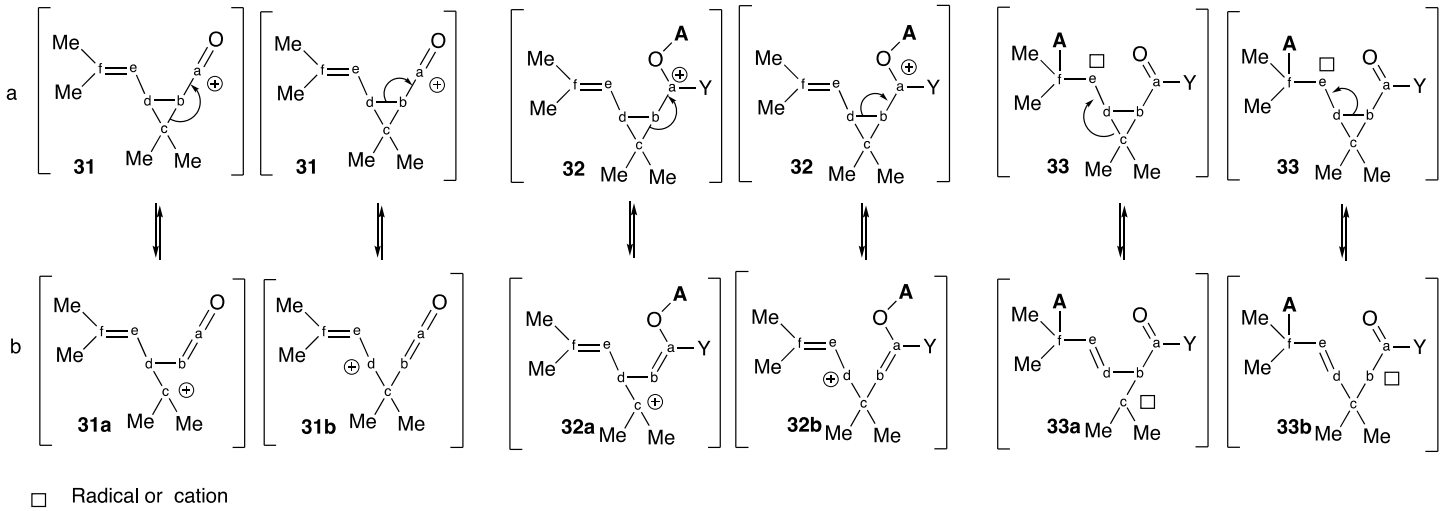
Such type of cyclopropyl carbinyl cation and radical can be produced from chrysanthemoyl derivatives on activation of their (i) carbamoyl moiety by a suitable Lewis acid on the halogen of chrysanthemoyl chloride leading to the thiomehyl group of chrysanthemoyl methylthiolate (Scheme 17, entry a) or (ii) on addition of Brønstedt acids (Scheme 17, entry b) or a halogen radical across the [C=C] double bond of its isobutenyl moiety (Scheme 17, entry c).



Scheme 17. Synoptic view of ionic and radical reactions acting on the alkenyl or carboxyl group of chrysanthemic derivatives.

Cationic or radical species can also react on the [Cf=Ce] double bond by forming the [Ce−A] bond instead of the that [Cf−A] generating **34** bearing at [Cf] the well stabilized tertiary carbocation (Scheme 17, entry e) or carbon radical (Scheme 17, entry f). Each of the cyclopropylcarbinyl moiety intermediates **31**, **32**, **33** is then able to release the accumulated strain by cleavage (Scheme 18) of either the:
(i) [Cc−Cb] bond to generate **31a** and **32a** possessing a cation at [Cc],
(ii) [Cc−Cd] bond to generate **33a** possessing a cation or a radical at [Cc],
(iii) [Cb−Cd] bond to generate either

(a) **31b** and **32b** possessing a cation at [Cd] or
(b) **33b** bearing a cation or a radical at [Cb].



Scheme 18. Synoptic view of reactions involving a cyclopropyl carbinyl intermediates and leading to the cleavage of the cyclopropane ring of chrysanthemic derivatives.

Each of these intermediates has a different stability and the related energy levels are not equally populated. Note, among others, that [Cc] bears two methyl groups able to stabilize in **31a**, **32a** and **33a** either a carbocation or a radical. This is also the case of [Cd] in **31b** and **32b** on which those two species are located on an allylic carbon. The propensity of [Cb] to stabilize a radical has been supported by the results reported above (Scheme 16, entry c).[24]

All these species lead to open chain compounds by trapping the carbocations with nucleophiles or lose a proton to produce a C=C double bond. Another possibility is to regenerate upon cyclization the three membered ring due to the proximity of the carbon bearing positive charge or a radical from the carbon to which it originates.

Competing formation of intermediates **34** over **33** is an interesting problem that will be discussed on specific examples in due course (Section 5).

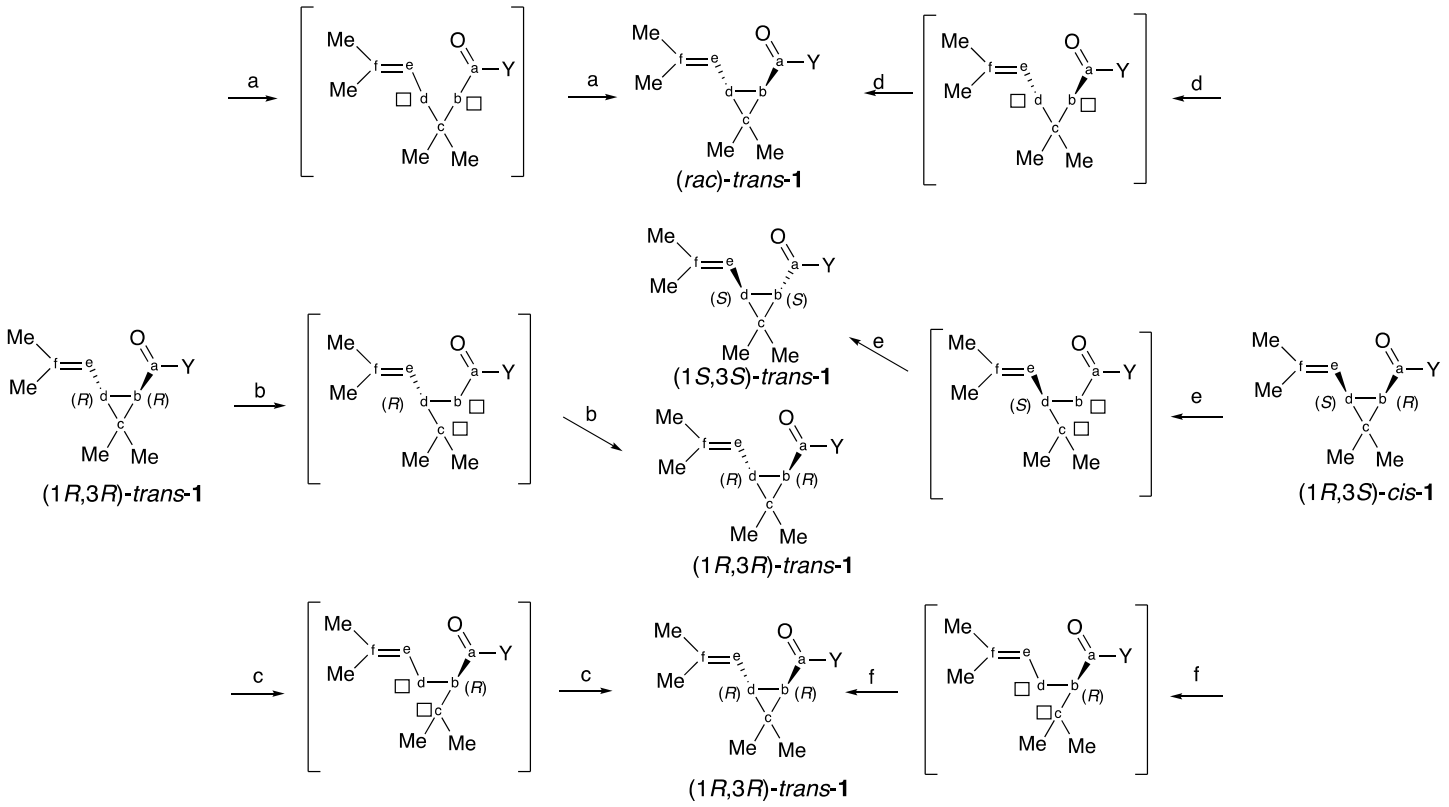
The description in Scheme 18 implying equilibria is quite naive and merits further comment. As general trend and due to the equilibria, the formation of *trans*-**1a** is clearly favored over that of *cis*-**1a** and therefore this feature mainly affects the *cis*-stereoisomers and has a much lower impact on the *trans*-stereoisomers (Scheme 19).

The cleavage of each of the bonds of the three membered cycle has a different impact on the stereochemistry of the cyclopropane derivatives that result from the reactions reported above (Scheme 19).

The cleavage of the [Cb−Cd] bond destroys at the same time both chiral centers (Scheme 19, entry a) and delivers mainly *trans*-chrysanthemic acid and/or related compounds as racemates.

The cleavage of the [Cb−Cc] or [Cc−Cd] destroy the stereochemistry present at [Cd] (Scheme 19, route b, route e) or [Cb] (Scheme 19, route c, route f), respectively, whereas stereochemistry present at [Cb] in the former case and [Cb] in the latter is preserved and directs the stereochemistry of the resulting cyclopropane derivative by favoring formation the enantiomerically pure *trans*-cyclopropane derivatives.

The impact of the relative absolute and relative stereochemistry of cyclopropane ring cleavage/ring regeneration is disclosed in Scheme 19. Specific examples will be disclosed in Section 6. Use of these results in the industrial syntheses of bioactive pyrethroids will be discussed in Chapter IVb.



Scheme 19. Stereochemical consequences of reactions implying cyclopropane ring opening (Squares refer to orbitals of undefined species resulting from the cleavage of a bond that are either empty or filled by one or two electrons to reach every time neutrality. They accommodate either radical- or ionic processses).

We will restrict our presentation to the reactivity of the vinylcyclopropane carboxylic acid and their esters that are related to pyrethroids and we will disclose it as topics related to the synthesis of types of functional group attached to the vinylcyclopropyl carbonyl framework. In some cases we will include some examples involving permethrinates that exhibit similar reactivity.

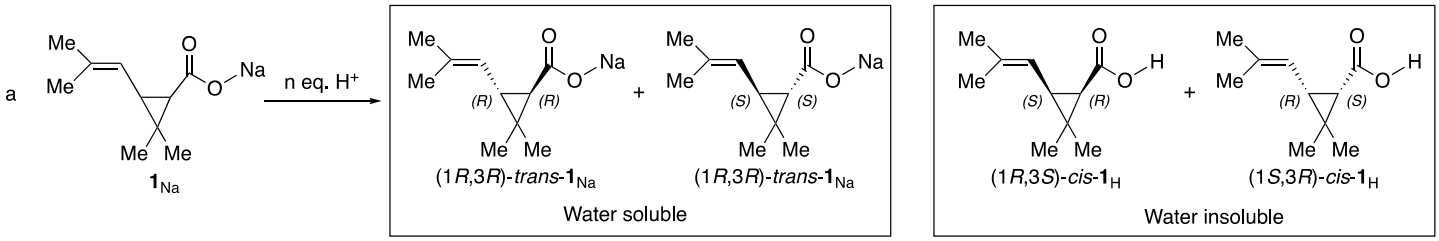
2. Reactions Involving the Carboxyl Group of Vinylcyclopropane Carboxylic Acids and Their Esters

2.1. Synthesis of metal and ammonium vinylcyclopropane carboxylates

2.1.1. Synthesis of metal vinylcyclopropane carboxylates from carboxylic acids (Scheme 10, Route 1): Application to the separation of the cis/trans-diastereoisomers. Metal vinylcyclopropane carboxylates are routinely synthesized from cyclopropane carboxylic acids and aqueous or ethanolic solution of sodium or potassium hydroxides.[25,26] When the solid salt is needed, the removal of the solvent has been achieved by distillation of the solvent and of the water concomitantly formed (aq. NaOH, reflux and distillation of water).[25] Silver *trans*-chrysanthemate has been generated on reaction of chrysanthemic acid with silver oxide.[27]

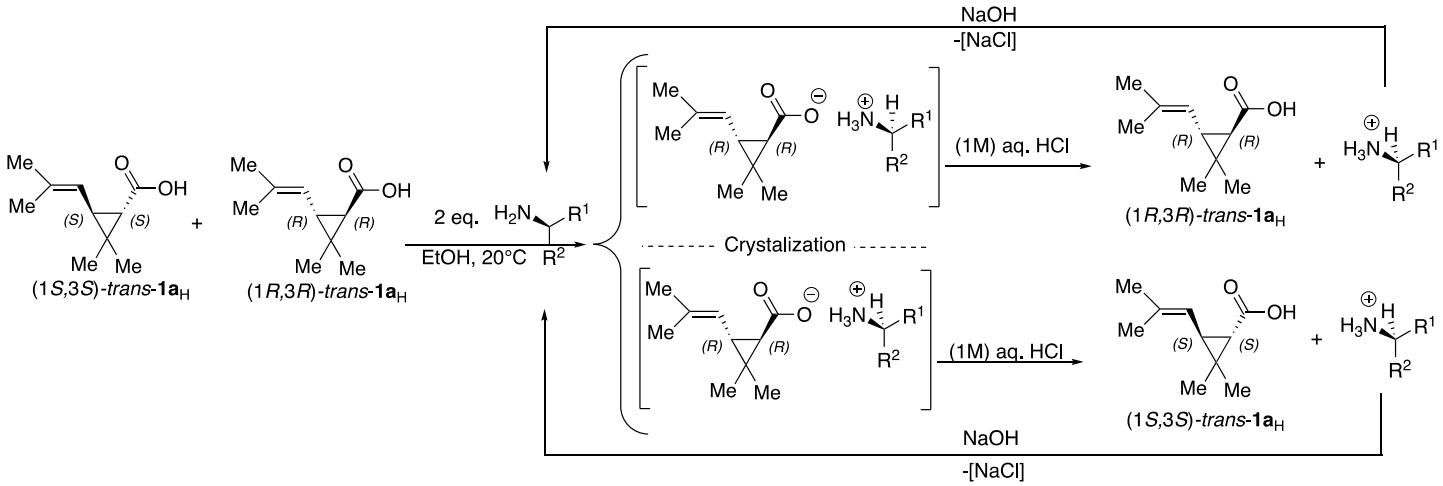
It has been found that *cis*-chrysanthemic acid is more acidic than its *trans*-diastereoisomer and this feature has been used as one of the effective methods to separate the *cis*- from its *trans*-stereoisomer as racemates (Scheme 20) as well as on cis/*trans*-mixtures of enantiomerically pure (1*R*,3*R*)-*trans*- and (1*R*,3*S*)-*cis*-chrysanthemic acid. The separation has been successfully extended to cis/*trans*-mixtures of cypermethrinic

(**1b**$_H$) and deltamethrinic (**1c**$_H$) acids.[28,29] Such separation has been effectively achieved by formation of the corresponding sodium salt that is soluble in water and selective acidification using for example acetic acid or carbonic acid (bubbling CO_2 in water) that leads to the precipitation of *cis*-chrysanthemic acid.[28,29]



Scheme 20. Different behavior of *cis*- and *trans*-chrysanthemic acid towards acids and bases.[28,29]

2.1.2. Synthesis of ammonium vinylcyclopropane carboxylates from the corresponding carboxylic acids. Application to the resolution of related racemates using enantiopure amines. Vinylcyclopropane carboxylic acids react with amines to produce the corresponding ammonium salts (Scheme 21). Performing this reaction with chiral amines on racemic mixtures of *trans*- or *cis*-diastereoisomers has allowed isolation of each of the two *trans*-enantiomers or each of the two *cis*-enantiomers by fractional crystallization of their respective diastereoisomeric ammonium salts (Scheme 21). This process named resolution of racemates[30] is still the most widely used in industry to obtain enantiomerically pure chrysanthemic acid. It is exemplified on a racemic mixture of *trans*-chrysanthemic acid (**1a**$_H$) in Scheme 21.



Scheme 21. Different behavior of *trans*-chrysanthemic acid enantiomers towards chiral amines.

Thus (1*R,*1*S*)-*trans*-chrysanthemic acid *trans*-(**1a**$_H$) has been efficiently resolved into its two enantiomers using, *inter alia* quinine,[31,32] 1-phenylethylamine,[31,32] L-lysine[33] (*S*)-1-phenyl-2(*p*-tolyl)ethylamine,[34] or even more conveniently with the D-threo base derived from a precursor of chloramphenicol [(1*R*,2*R*)-1-(4-nitro-phenyl)-2-dimethylaminopropane diol] (Figure 5). The latter conditions have been used by the Roussel-Uclaf company on an industrial scale (Figure 5) .[35,36,37]

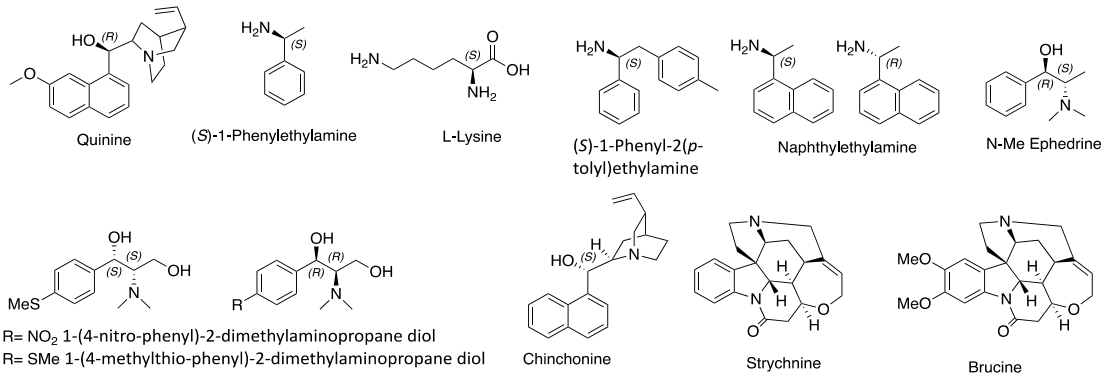
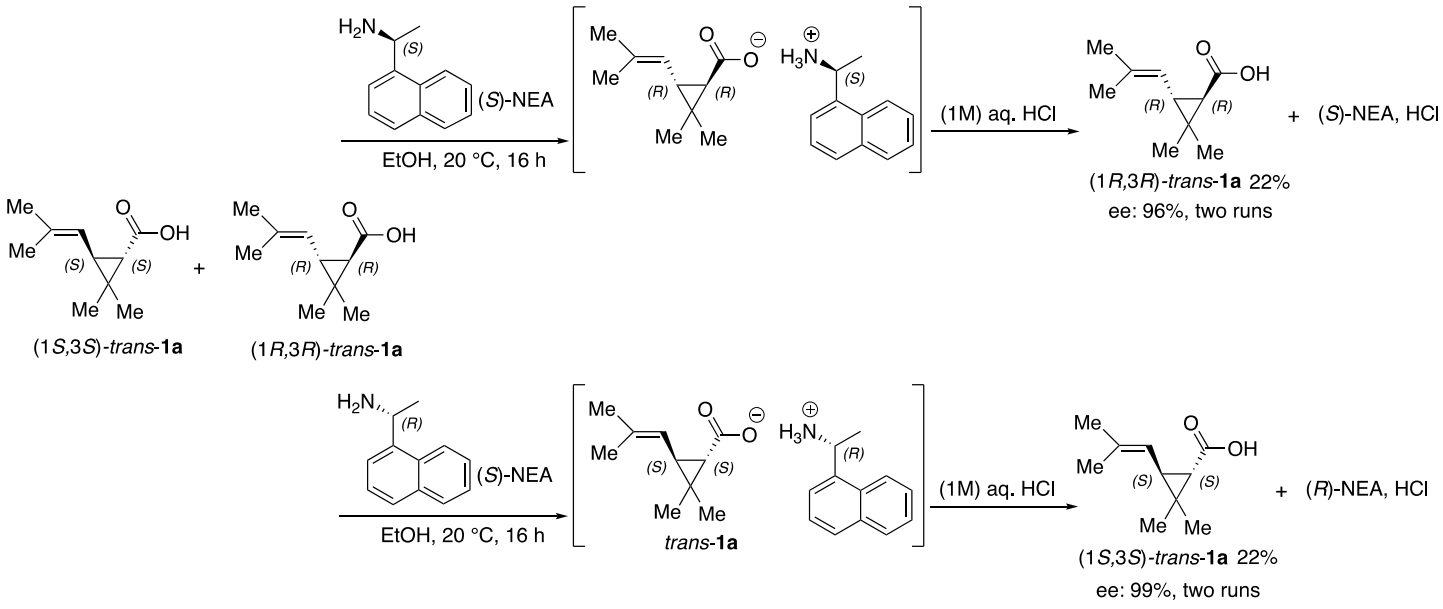


Figure 5. Structure of some enantiopure amines used in separation of racemic mixtures of chrysanthemic acid.

It has been also reported[38] that both enantiomers of *threo*-dimethylamino-1-[4-(methylthio)phenyl]propane-1,3-diol (MTDP, Figure 5) are effective resolving agents for *trans*-chrysanthemic acid *trans*-(**1a**$_H$) on an industrial scale but revealed to be "blind" towards the *cis*-enantiomers.[38] They work well on racemic and/or scalemic *trans*/*cis* mixtures, isopropyl ether being the solvent of choice that does not need the presence of co-solvents to allow the separation of diastereoisomers.[38] MTDP enantiomers are low cost, non-toxic, safe, and easily available from important precursors of thiamphenicol through a single straightforward reaction. After the resolution, they can be recovered almost quantitatively and reused without any loss of their chiral integrity.[38] Cinchonine, strychnine, brucine proved to be less efficient for the same purpose.[31]

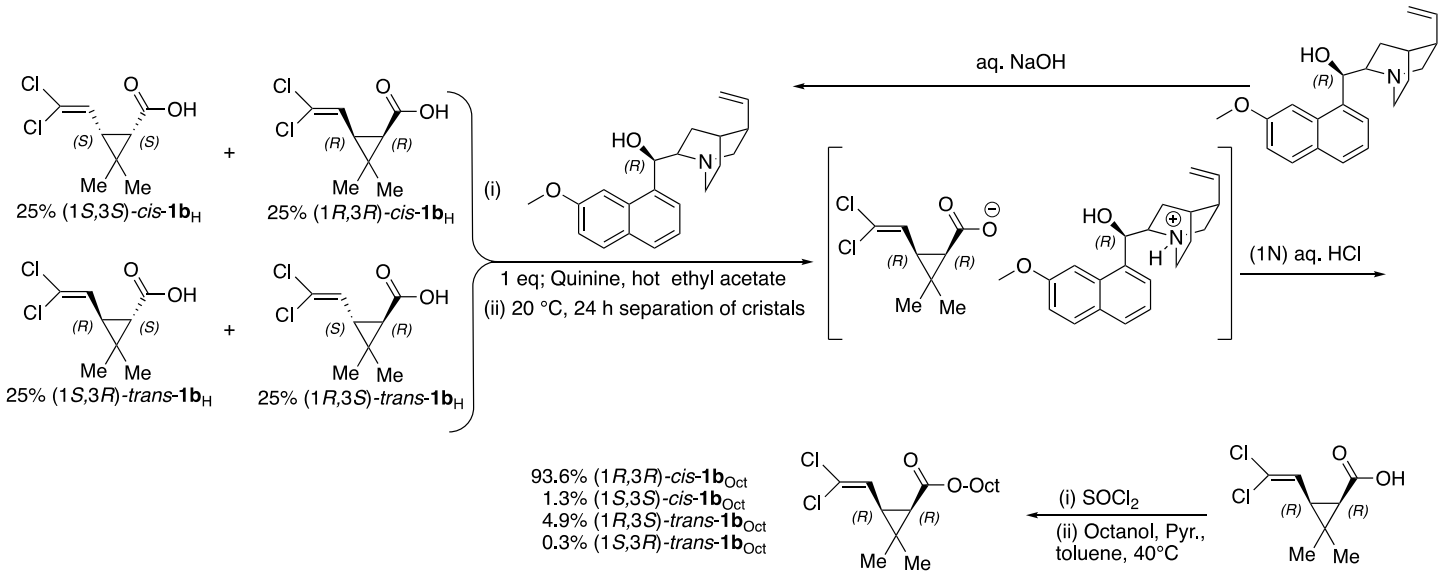
As a specific example, it has been recently reported[11] that (*S*)-naphthylethylamine (Figure 5) reacts with racemic *trans*-chrysanthemic acid in ethanol (20 °C, 17 h) to produce a crystalline ammonium salt (Scheme 22).[11] The latter on reaction with 1M aqueous HCl solution delivers the enantiopure chrysanthemic acid (1*R*,3*R*)-(**1a**$_H$) in 22% yield (two consecutive runs) with excellent enantiomeric excess (96%) and that the antipodal acid (1*S*,3*S*)-(**1a**$_H$) is generated from the same mixture using instead (*R*)-naphthylethylamine.[11]



Scheme 22. Recent example of resolution of *trans*-chrysanthemic acid with naphthylethylamine enantiomers.[11]

Otherwise resolution of (*d,l*)-*cis*-chrysanthemic acid has been achieved through (*l*)-quinine,[32,39] 1-phenylethylamine,[32] as well as through *l*-*N*-methylephedrine.[40]

It has been also reported that 1/1 racemic mixtures of *cis*/*trans*-cypermethrinic acid (**1b**$_H$) can be resolved by quinine in acetonitrile[37] or ephedrine in acetonirile[41] to deliver *cis*-cypermethrinic acid (1*R*,3*R*)-*cis*-(**1b**$_H$) almost as the single stereoisomer required to produce the most active cypermethrin insecticide (Scheme 23). The crystalline quinine salt has been transformed on reaction with excess of thionyl chloride, distillation of the excess and reaction with octanol in the presence of pyridine, to octyl cypermethrinate (**1b**$_{oct}$) that has been subjected to chromatographic analysis (Scheme 23).[5]



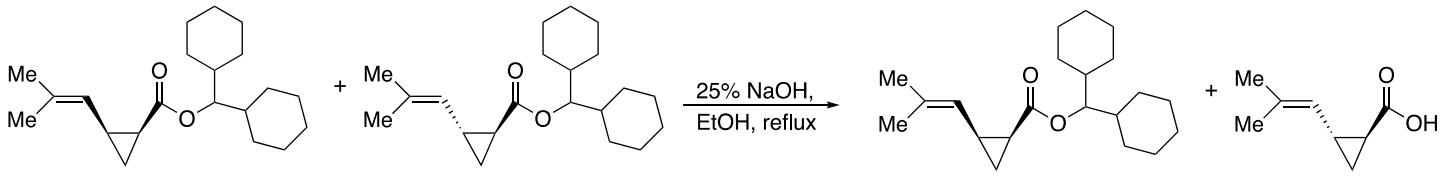
Scheme 23. Separation of a single enantiomer of cypermethrinic acid from a mixture of the four stereoisomers and control of its stereochemical purity. [5,41]

2.1.3. Synthesis of metal vinylcyclopropane carboxylates and carboxylic acids from the corresponding carboxylic esters (Scheme 11, Route 15): Application to the isolation of the "natural" enantiomer. Saponification of vinylcyclopropane carboxylic esters is an efficient route to the corresponding metal carboxylates **1**$_M$ and after acidification to vinylcyclopropane carboxylic acid **1**$_H$. Saponification of alkyl chrysanthemates derived from primary and secondary alcohols has been used as a key step for the structure elucidation of pyrethrins including pyrethrin I (**1a**$_a$) (Scheme 1).[42] It is usually achieved with 2N aqueous solution of sodium or potassium hydroxides in refluxing methanol for 1.5-4 h (See below, Scheme 62).[43-47] Saponification of ethyl chrysanthemate (*trans*/*cis*: 90/10) has been also performed using 5 equivalents of potassium hydroxide in aqueous ethanol (EtOH/H_2O; 5/1) at 135°C for 3 h and delivers stereoselectively chrysanthemic acid (86%, *trans*/*cis*: 90/10).[11] Even under these drastic conditions, saponification is faster than epimerization that would have led to *cis*/*trans* epimerization.

As general trend, cyclopropyl esters in which the carboxy group is *cis*- to the vinyl group such as chrysanthemic *cis*-**1a**$_R$ and *cis*-deltamethrinic **1c**$_R$ esters, are less prone to hydrolysis and more stable in the environment than their *trans*-isomers.[48-50]

This feature seems to be particularly efficient on dicyclohexylmethyl esters. [48,49] It has been for example reported that dicyclohexylmethyl *trans*-2,2-didesmethyl chrysanthemate is selectively saponified on refluxing a

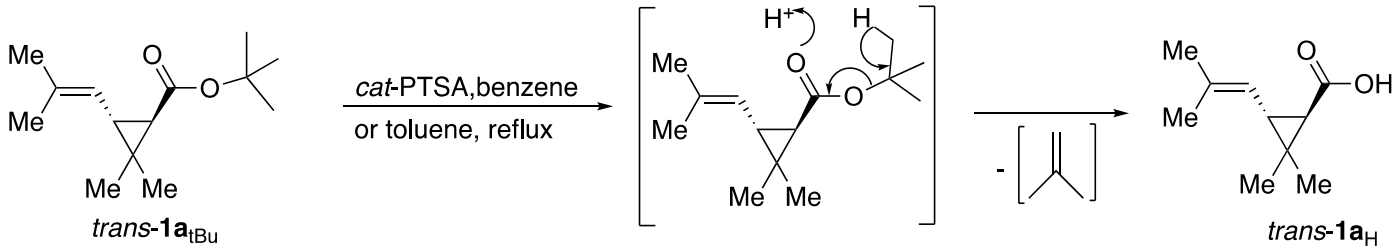
cis/*trans*-stereoisomeric mixture of dicyclohexylmethyl 2,2-didesmethyl chrysanthemate with an ethanolic solution of sodium hydroxide (Scheme 24).[48,49]



Scheme 24. Exceptional different behavior towards saponification of *cis*- and *trans*- dicyclohexylmethyl vinylcyclopropane carboxylates.[48,49]

It has also been used to purify diastereoisomeric *cis*/*trans*-mixtures of ethyl (**1a**$_{Et}$) or methyl (**1a**$_{Me}$) chrysanthemates by selective saponification of their *trans*-isomers isomers.[50] Thus a 35/65 *cis*/*trans*-mixture of methyl chrysanthemate (**1a**$_{Me}$) has been reacted[50] with a slightly substoichiometric amount (related to the *trans*-stereoisomer) of a 25% aqueous solution of sodium hydroxide (85 °C, 4 h). The alcohol generated by the saponification is removed by distillation and the aqueous residue after extraction with hexane delivers, after acidification, pure *trans*-chrysanthemic acid (80%) whereas evaporation of hexane delivers a *cis*/*trans* mixture of esters (**1**$_{Me}$), in which *cis*-**1**$_{Me}$ prevails.[50]

t-Butyl (**1a**$_{tBu}$) and *t*-amyl (**1a**$_{tAm}$) chrysanthemates are resistant to basic hydrolysis. It has been for example reported that ethyl chrysanthemate (**1a**$_{Et}$) is selectively hydrolyzed[51] from a mixture of ethyl chrysanthemate (**1a**$_{Et}$) and *t*-amyl chrysanthemate (**1a**$_{tAmyl}$) on reaction with potassium hydroxide in ethanol at reflux and *t*-amyl chrysanthemate **1a**$_{tAm}$ is recovered unchanged.[51] Similarly ethyl *t*-butyl *cis*-caronate (**20**$_{tBuET}$) on reaction with K_2CO_3 is regioselectively transformed to mono *t*-butyl *cis*-caronate (see below, Scheme 33, entry b).[52,53] Dealkylation of *t*-butyl chrysanthemate **1a**$_{tBu}$ requires a different treatment. It has been achieved under pyrolysis at 220°C to deliver isobutylene as a co-product (Scheme 25).[54] The reaction takes place at much lower temperature (100°C) if carried out in the presence of an acid such as 1N hydrochloric acid,[27] or catalytic amount of *p*-toluenesulfonic acid (PTSA) in benzene[55-57] or toluene[59] (reflux for about 2 h) (Scheme 25)[55-58]

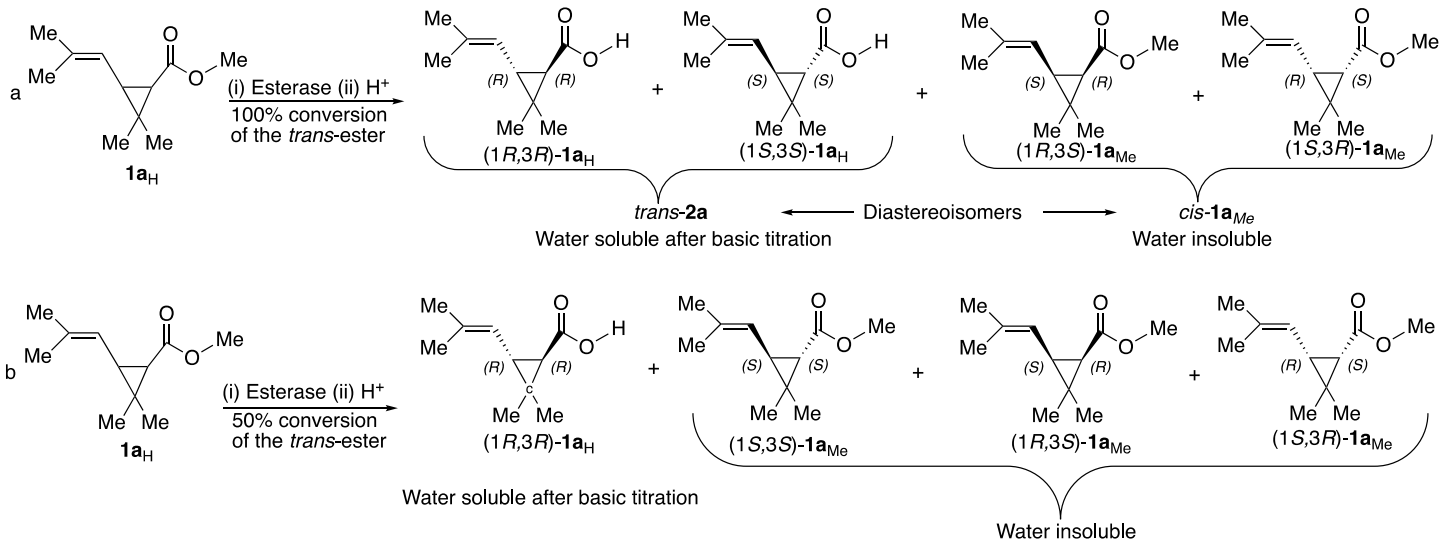


Scheme 25. Acid catalyzed transformation of a *t*-butyl ester to the corresponding carboxylic acid.[51,58,59]

This dealkylation reaction has been successfully extended to *t*-butyl diflurovinylcyclopropane carboxylate[60] (**1f**$_{tBu}$) and *t*-butyl pyrethrate[57]**1d**$_{tBu}$. It has been used as a key step in the multistep transesterification reaction discussed below, which proved far better when groups sensitive to bases are present in the starting material. It has been used in one of the syntheses of resmethrin (**1a**$_{e}$) (see below Scheme 63, entry a),[58] fluorethrin (**1f**$_{e}$) (see below Scheme 64)[60] and in the synthesis of several pyrethric esters (**1d**$_{R}$).[57]

The conditions reported above allow separation of the *cis* from the *trans*-cyclopropane carboxylates but not for one enantiomer from a racemate. Enzymatic hydrolysis allows this discrimination at 50% conversion and

allows the stereoselective isolation of (1*R*,3*R*)-*trans*-chrysanthemic acid (1*R*,3*R*)-*trans*-(**1a**$_H$) in almost quantitative yield (Scheme 26, entry b).[61]



Scheme 26. Saponification of stereoisomeric mixtures of methyl chrysanthemate with lipases. Effect of the % conversion.[61]

Otherwise, porcine liver esterase, as other reagents, saponifies more efficiently and under very mild conditions produces a racemic mixture of methyl *cis*-chrysanthemate *cis*-(**1a**$_{Me}$) from a mixture of containing all four stereoisomers (Scheme 26, entry a). Similar effects have been disclosed for monomethyl caronate (**20**$_{Me}$).[61]

Typically, the enzymatic hydrolysis has been performed on 200 mmol scale of racemic *cis*/*trans*-mixtures of methyl chrysanthemate by porcine liver esterase [PLE, 70 units (standard ethyl butyrate = 0.7mg/g substrate)]

Stereoselective production of (1*R*,3*R*)-*trans*-chrysanthemic acid ((1*R*,3*R*)-*trans*-(**1a$_H$**) from a racemic mixture of ethyl *trans*-chrysanthemate *trans*-(**1a**$_{Et}$) or a stereoisomeric mixture of ethyl *cis,trans*-chrysanthemate cis/*trans*-(**1a**$_{Et}$) [(1*R*,3*S*))-*cis*/(1*S*,3*R*)-*cis*/(1*R*,3R)-*trans*/(1*S*,3*S*)-*trans* ratio 2.5:2.5:47.5:47.5] has been 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.[62] The hydrolytic activity of the recombinant *E. coli* cells for ethyl chrysanthemate reached 605 μmol of chrysanthemic acid per min/g of dry cells, which is approximately 2,500-fold higher than that of *A. globiformis* cells.[62]

2.2. Synthesis of vinylcyclopropane carboxylic acid chlorides (Scheme 10, Route 2)

The synthesis of chrysanthemoyl chloride (**3a**$_{Cl}$) from the different stereoisomers of chrysanthemic acid (**1a**$_H$) has attracted wide interest. It has been used as "the" precursor of the related anhydrides (Scheme 10, Route 10; Section 2.6.), esters (Scheme 10, Route 9b; Section 2.4.1.2.4.), amides (Scheme 10, Route 10; Section 2.5.) and hydrazides (Scheme 10, Route 12; Section 2.6.), and as a precursor of rearranged products implying the insertion of one atom on their backbone between the cyclopropane ring and carbonyl of their carboxy group (Scheme 10, Route 13; Section 2.11.). Various stereoisomers or mixtures of stereoisomers of chrysanthemoyl chlorides have been furthermore cleanly racemized on reaction with Lewis acids already at -10 °C (Scheme 17, Route A; Section 5.4.2.).

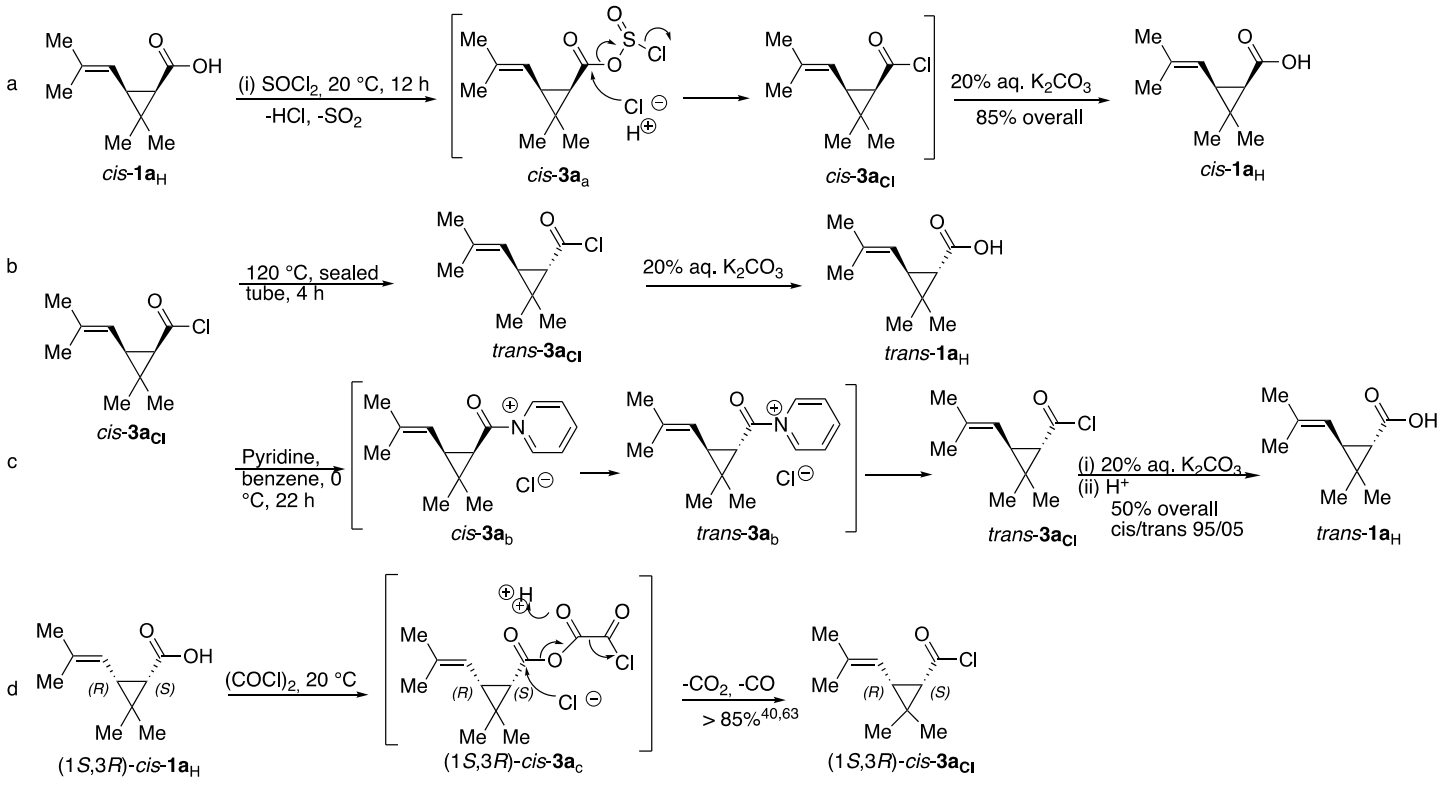
2.2.1. Synthesis of vinylcyclopropane carboxylic acid chlorides using thionyl or oxalyl chlorides. The transformation of chrysanthemic acid (**1a**$_H$) to chrysanthemoyl chloride (**3a**$_{Cl}$) has been routinely achieved with

thionyl chloride due to its great availability and low cost (Scheme 27, entry a[43-45,57,64-67,68] and more rarely using instead oxalyl chloride (Scheme 27, entry d).[40,69]

In the former case, it has been suggested to use thionyl chloride purified using a well-established protocol. It involves two subsequent distillations from quinoline, then from linseed oil to avoid the presence of hydrochloric acid that possesses a high propensity to add competitively to the C=C double bond of the vinylcyclopropane moiety (see related results below in Scheme 40). The reaction has been successfully carried out on *trans*-chrysanthemic acid neat,[63,70] in light petroleum ether, pentane or hexane,[3, 8,64,66,67,71-73] or HMPA (1 eq., -10 °C, 85%).[56] The reaction has been also achieved in the presence of an amine or a carbonate and more often in pyridine-benzene (20 °C, 2 h).[52]

To avoid the presence of hydrochloric acid, the transformation has been in some cases carried out on the corresponding metal chrysanthemate **1a**$_M$. For example, *trans*-chrysanthemic acid (1*R*,3*R*)-*trans*-(**1a**$_H$) has been transformed to the corresponding acid chloride (1*R*,3*R*)-*trans*-(**3a**$_{Cl}$) on sequential reaction with sodium methoxide in pentane, evaporation of the methanol and reaction of the resulting sodium salt (**1a**$_{Na}$) with a slight excess of oxalyl chloride in ether (20 °C, 1.5 h).[74]

It has been also reported [63] that the reaction of thionyl chloride on *cis*-chrysanthemic acid (**1a**$_H$) occurs with high stereocontrol (20 °C, 12 h, Scheme 27, entry a).[63,65,75] *cis*-Chrysanthemoyl chloride *cis*-(**3a**$_{Cl}$) is however isomerized to its *trans*-stereoisomer *trans*-(**3a**$_{Cl}$) on heating at 120°C (Scheme 27, entry b)[63] or even at much lower temperature, if the reaction is instead carried out in the presence of pyridine.[63] The intermediate formation of the *cis*-pyridinium chloride is suspected to favor this side reaction (Scheme 27, entry c)[63] and therefore the use of pyridine in the esterification process should be carefully monitored.[63]

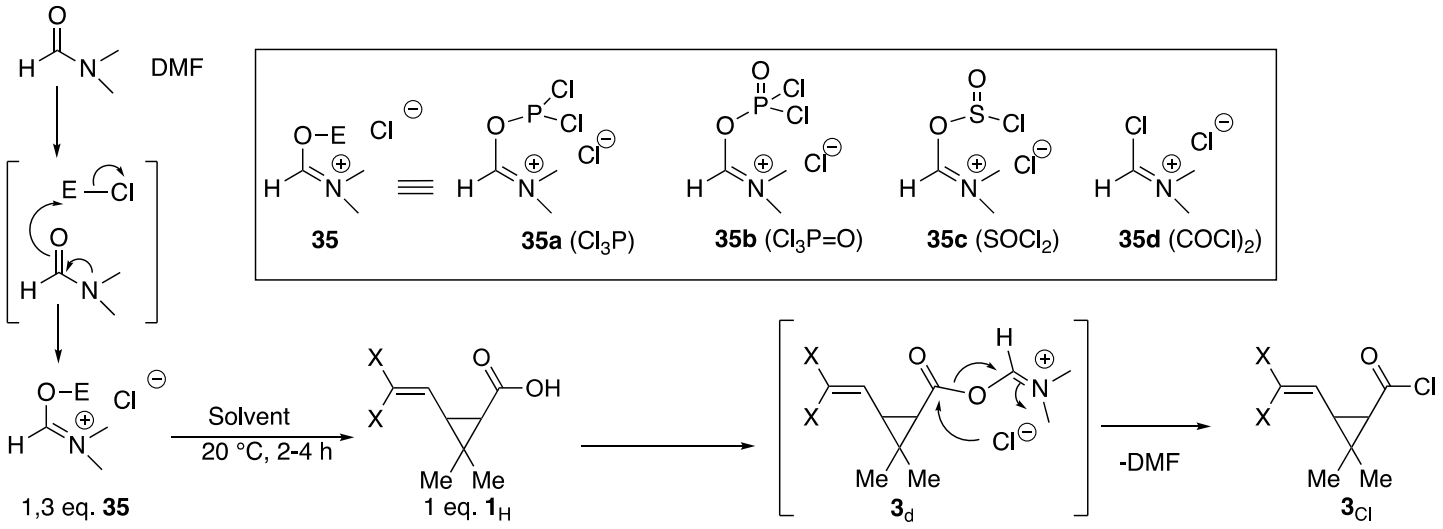


Scheme 27. Synthesis of chrysanthemoyl chlorides using thionyl- and oxalyl-chlorides.[40,54,63]

2.2.2. Synthesis of vinylcyclopropane carboxylic acid chlorides using activated *N,N* dimethyl formamide. It has been mentioned[76] that isomerization often affects the transformations in the *cis*-series including that of *cis*-

cypermethrinic acid (**1b**$_H$) and that the few percent of the acid chloride *trans*-(**3**$_{Cl}$) (5-10%) concomitantly produced leads to impure pyrethroids.[76]

Inexpensive and valuable solutions have been proposed to avoid such inconvenience.[76] It has been found[76] for example, that the reagents **35**, generated on mixing N,N-dimethyl formamide with thionyl chloride, phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride or oxalyl chloride at around -10°C for less than one hour, the structures of which are expected to be close to that of the Vilsmeier reagent,[77,78] avoids such epimerization (Scheme 28).[76]



E-Cl	Solvent	X		Yield
$POCl_3$	Neat	Cl	*cis*-**1b**$_H$	*cis*-**3**$_{Cl}$ 95%
$POCl_3$	Hexane	Br	*cis*-**1c**$_H$	*cis*-**3**$_{Cl}$ 82%
$POCl_3$	Neat	Me	*trans*-**1a**$_H$	*trans*-**3**$_{Cl}$ 95%
$SOCl_2$	CCl_4	Cl	*trans*-**1b**$_H$	*trans*-**3**$_{Cl}$ 95%
$SOCl_2$	Neat	Cl	*cis*-**1b**$_H$	*cis*-**3**$_{Cl}$ 94%
$(COCl)_2$	Hexane	Cl	*trans*-**1b**$_H$	*trans*-**3**$_{Cl}$ 61%
PCl_3	Neat	Cl	**1b**$_H$	——— 97%
PCl_5	Neat	Cl	*cis*-**1b**$_H$	*cis*-**3**$_{Cl}$ 94%

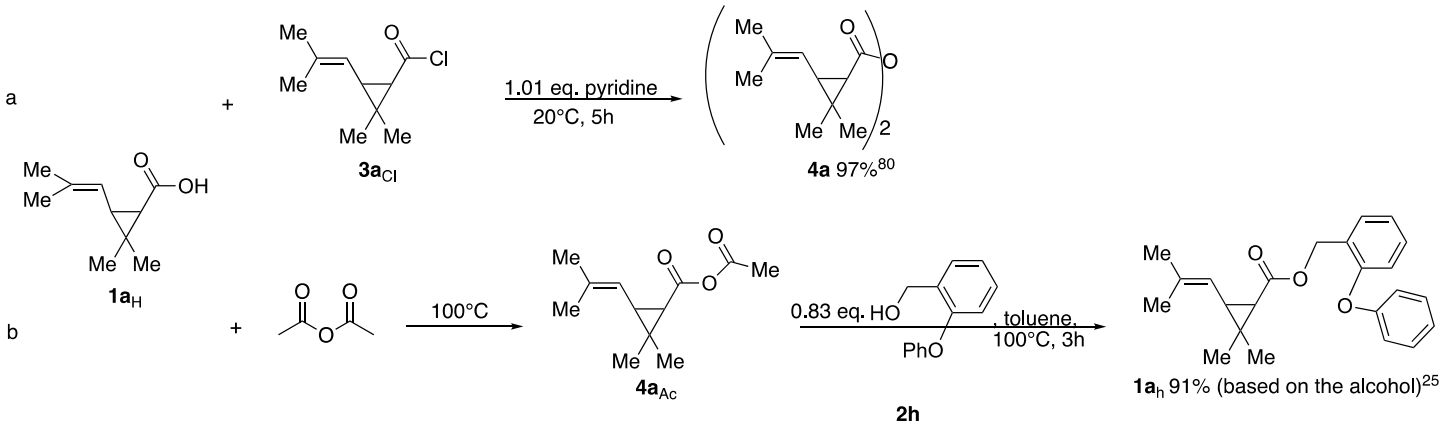
Scheme 28. Synthesis of vinylcyclopropane carboxyloyl chlorides using Vilsmeier type reagents.[76]

Reagent **35** efficiently reacts with each of the stereoisomers of chrysanthemic acid (**1a**$_H$), cypermethrinic acid (**1b**$_H$) and deltamethrinic acid (**1c**$_H$) neat, in hexane or in carbon tetrachloride to produce completely stereoselectively and in less than two hours at room temperature, the corresponding acid chlorides (*trans*-**3a**$_{Cl}$, *trans*-**3c**$_{Cl}$, *cis*-**3b**$_{Cl}$, *cis*-**3c**$_{Cl}$) in almost quantitative yields even on large scale (Scheme 28).[76,79] Best results have been obtained when slight excess of DMF is reacted sequentially with equimolecular amounts of one the reagents listed above, especially thionyl chloride, then the vinylcyclopropane carboxylic acid **1**$_H$. The upper phase of the two, which contains the acid chloride **3**$_{Cl}$ is separated by decantation and used as it is for the next step.

2.3. Synthesis of vinylcyclopropane carboxylic anhydrides (Scheme 10, Route 3)

Anhydrides **4** derived from chrysanthemic acid (**1a**$_H$) have been scarcely used. (1*S*,3*S*)-*trans*-chrysanthemic anhydride (**4a**) has been synthesized on reaction of the corresponding (1*S*,3*S*)-*trans*-chrysanthemoyl chloride (1*S*,3*S*)-*trans*-(**3a**$_{Cl}$) with (1*S*,3*S*)-*trans*-chrysanthemic acid (1*S*,3*S*)-*trans*-(**1a**$_H$) in pyridine (1 eq. each, 1.01 eq.

pyridine, 20 °C, 5 h, 97% yield, Scheme 29, entry a).[80] The mixed chrysanthemoyl anhydride (**4a**$_{Ac}$) bearing an acetoxy moiety has been synthesized by exchange reaction of (**1a**$_{H}$) with acetic anhydride in toluene at high temperature (Scheme 29, entry b).[25]

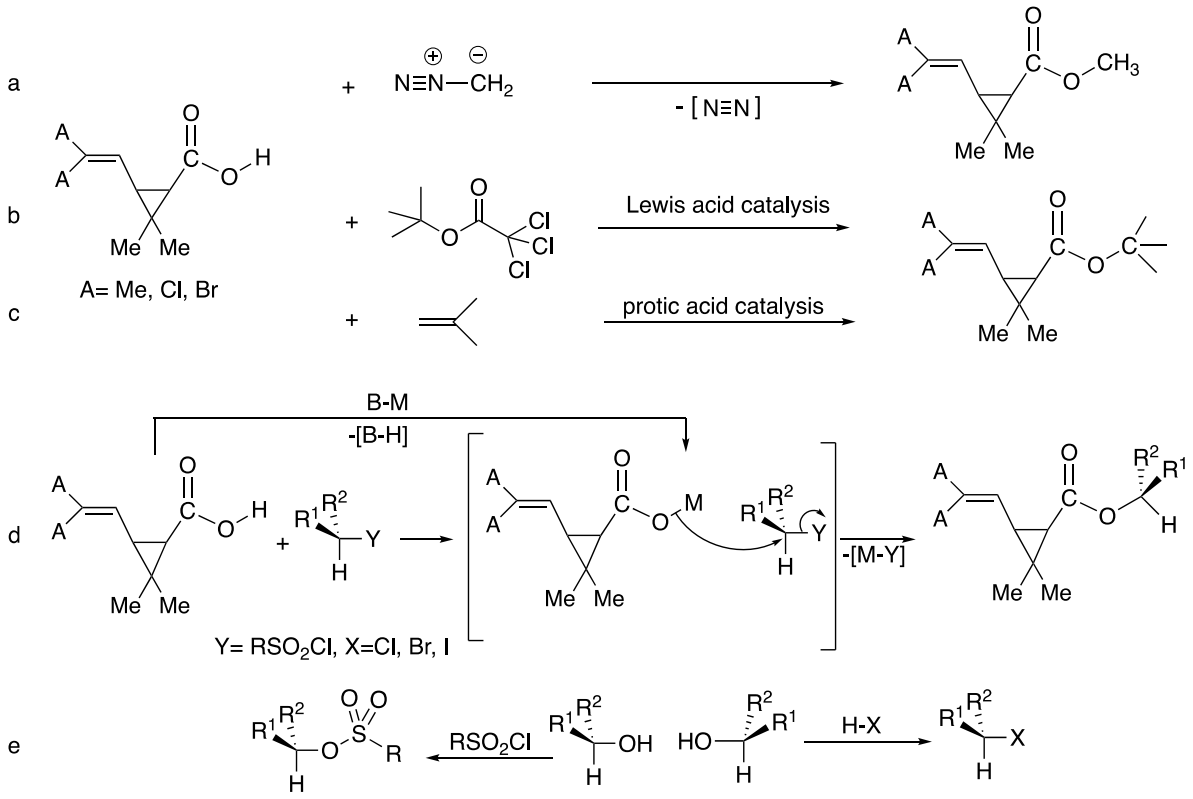


Scheme 29. Synthesis of anhydrides from chrysanthemic acid and further application.[25,80]

2.4. Synthesis of vinylcyclopropane carboxylic esters

2.4.1. Synthesis of vinylcyclopropane carboxylic esters from the corresponding carboxylic acids. 2.4.1.1. Synthesis of vinylcyclopropane carboxylic esters from the corresponding carboxylic acids by alkylation reaction (formal H/R exchange, Scheme 10, Route 4a, Route 9a). Esterification by alkylation of chrysanthemic acid offers the advantage to start with readily available and stable compounds. It is achieved by substitution on an alkyl group bearing a good leaving group (Scheme 30, entries a,b,d) or by addition across the [C=C] double bond of an alkene (Scheme 30, entry c). The reaction involves either the carboxylic acid and an acid (Scheme 30, entries b,c) or the carboxylate produced from the vinylcyclopropane carboxylic acid and a base, generated before the alkylation reaction or *in-situ* during the substitution reaction (Scheme 30, entries b,c). In the case of diazoalkanes, the basic entity is built in as well as the leaving group in the ylide structure and alkylation proceeds in neutral media (Scheme 30, entries b,c).

Esterification using this strategy is only valuable for the synthesis of alkyl cyclopropane carboxylates derived from lower alcohols (Scheme 30). For example, alkylation with alkyl halides and sulfonate is usually unsuitable with tertiary ones and but is particularly efficient when involving primary benzylic and allylic halides and sulfonates. It usually takes place with inversion of configuration at the substituted carbon atom (Scheme 30, entry e). This has an impact for the esterification leading to (*S*)-bioallethrin (*S*)-(**1a**$_b$) as will be discussed in the next subsection.



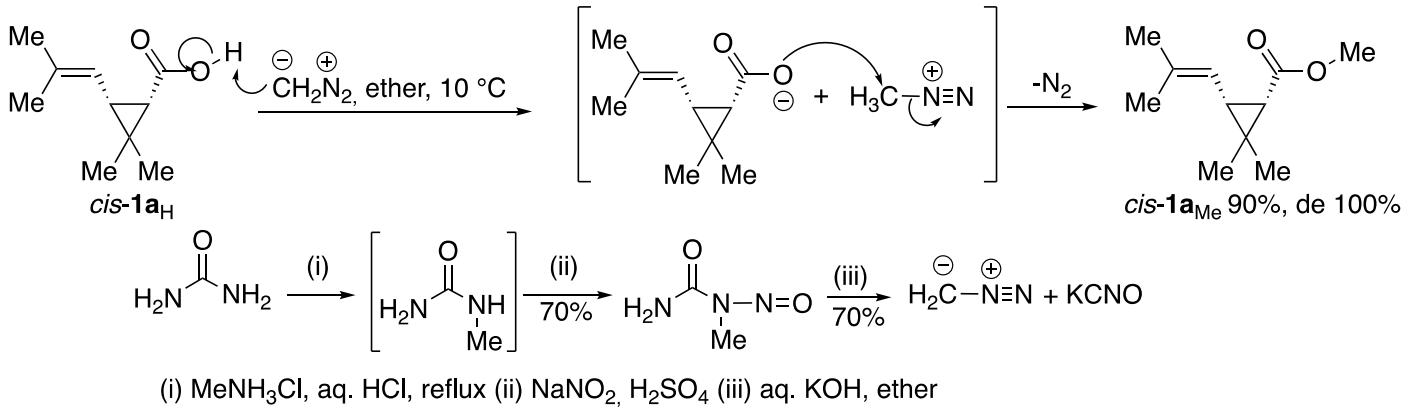
Scheme 30. Synoptic view of some esterification methods of vinylcyclopropane carboxylic acids.

2.4.1.1.1. Alkylation of vinylcyclopropane carboxylic acids with diazomethane: Synthesis of methyl esters. Alkylation of chrysanthemic acid [31,51,72,81-83] (Scheme 31) with diazomethane[84,85] is probably the most efficient synthetic method to produce their methyl esters especially for analytical purposes.

The reaction is usually carried out in ether at around 10 °C with 10% excess of diazomethane and the excess rapidly destroyed by addition of acetic acid. Its advancement can be followed by looking at fading the yellow color of the original solution of diazomethane in ether on addition of the solution of the vinylcyclopropane carboxylic acid in the same solvent. At the same time bubbles of nitrogen are concomitantly released.

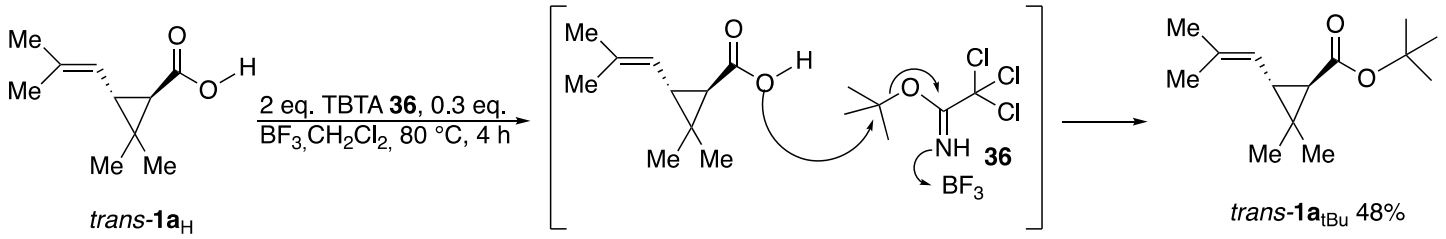
Care must be taken to avoid large excess of reagent since it has been once reported[31] that diazomethane used in excess adds across the [C=C] double bond of methyl chrysanthemate and leads, through an 1,3-dipolar cycloaddition,[86] to a pyrazoline which decompose at 130 °C with vigorous evolution of nitrogen.

Although several diazo compounds are known, the reaction at least in this context has been exclusively published with diazomethane. Diazomethane is an unstable substance it has to be prepared before use among other, from *N*-nitrosomethyl urea (prepared as disclosed below) and aqueous potassium hydroxide and dried over potassium hydroxide pellets.[84,85] Care must be taken to avoid evaporation of ether reported to lead to explosions and to fire.[84,85]



Scheme 31. Synthesis of methyl chrysanthemate from the acid using diazomethane and one of its synthesis.[51]

2.4.1.1.2. Lewis acid catalyzed transalkylation of vinylcyclopropane carboxylic acids: Synthesis of *t*-butyl esters. 2,2,2-Trichloroacetimidate (**36**) (TBTA, 2eq.) reacts with *trans*-chrysanthemic acid *trans*-(**1a**$_H$) in the presence of boron trifluoride as Lewis acid catalyst to deliver *t*-butyl chrysanthemate *trans*-(**1a**$_{tBu}$) in modest yield (Scheme 32).[46]

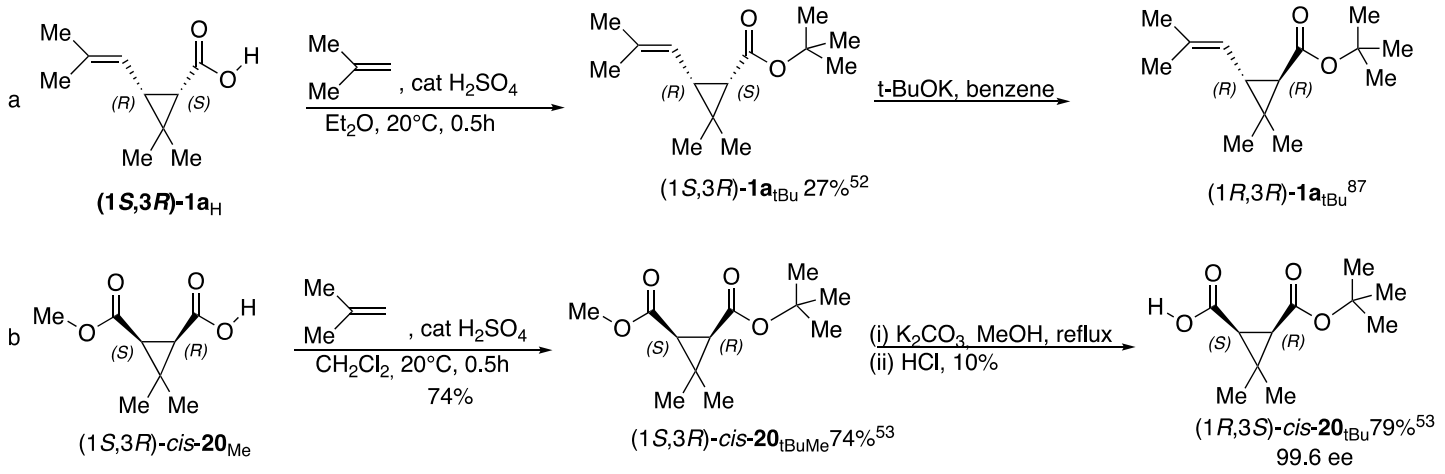


Scheme 32. Synthesis of *t*-butyl chrysanthemate from the acid using 2,2,2-trichloroacetimidate.[46]

2.4.1.1.3. Alkylation of vinylcyclopropane carboxylic acids with olefins in acidic media: Synthesis of *t*-butyl esters. Cyclopropane carboxylic acids have been sometime reacted with isobutylene in protic media. Although the reaction proceeds under quite drastic condition it allows the formation of *t*-butyl esters. These offer the advantage of being poorly affected by basic/nucleophilic reagents and easily transformed back to the carboxylic acids in acidic media or by thermolysis.[54]

The reaction involving (1*S*,3*R*)-*cis*-chrysanthemic acid *cis*-(**1a**$_H$) leads to the corresponding *t*-butyl ester *cis*-(**1a**$_{tBu}$) in poor yields (Scheme 33, entry a) probably due to competing intramolecular addition of the carboxylic group on the proximal isobutenyl group that competitively leads to the formation of the lactone (**25**) (Scheme 8, entry b).[53] This is no longer the case of mono methyl (1*S*,3*R*)-*cis*-caronate (**20**$_{Me}$) which delivers the mixed methyl, *t*-butyl diester (**20**$_{tBuMe}$) in reasonably high yield under related conditions (Scheme 33, entry b).[53]

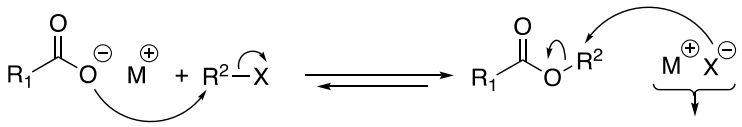
The main interest related to the use of *t*-butyl esters instead of other lower esters comes from
(i) a more efficient *cis*- to *trans*-epimerization of chrysanthemates under basic conditions (Scheme 33, entry a)[87] that relates to the bulkiness of the *t*-butyl group,
(ii) an easier differentiation of by gas chromatography and by ^{1}H-NMR[27] at the difference of the related mixtures of methyl or ethyl esters,
(iii) an easy transformation to the corresponding carboxylic acids under thermal or acidic conditions that differs from the usual conditions used with methyl or ethyl esters instead (basic media then acid treatment),



Scheme 33. Synthesis of *t*-butyl cyclopropane carboxylates using isobutylene under acidic conditions.[52,53,87]

The synthesis of the bicylic [4.1.0] lactone (**25**) also relates to that section as an intramolecular version of the esterification of carboxylic acid from alkenes has been efficiently achieved using boron trifluoride etherate (benzene, 20 °C, 12 h, Scheme 8, entry b)[88,89] or zinc dichloride (ethylene dichloride, 80 °C, 19 h).[90]

2.4.1.1.4. Alkylation of vinylcyclopropane carboxylic acids by alkyl halides through their metal or ammonium carboxylates*.* Alkylation of vinylcyclopropane carboxylic acids involving alkyl halides is another strategy to access the corresponding esters. This reaction is an unusual one since often alkylation of carboxylates leading to esters is in equilibrium with the dealkylation of esters producing back the metal carboxylates and the alkyl halides (Scheme 34).[91] This reverse reaction has been even successfully used as a synthetic method for dealkylation of esters.[91] This reaction which usually occurs via an S_N2 process, takes place on methyl or ethyl esters is best achieved using an excess of metal halides and is particularly useful with esters that possess a hindered carbonyl group.

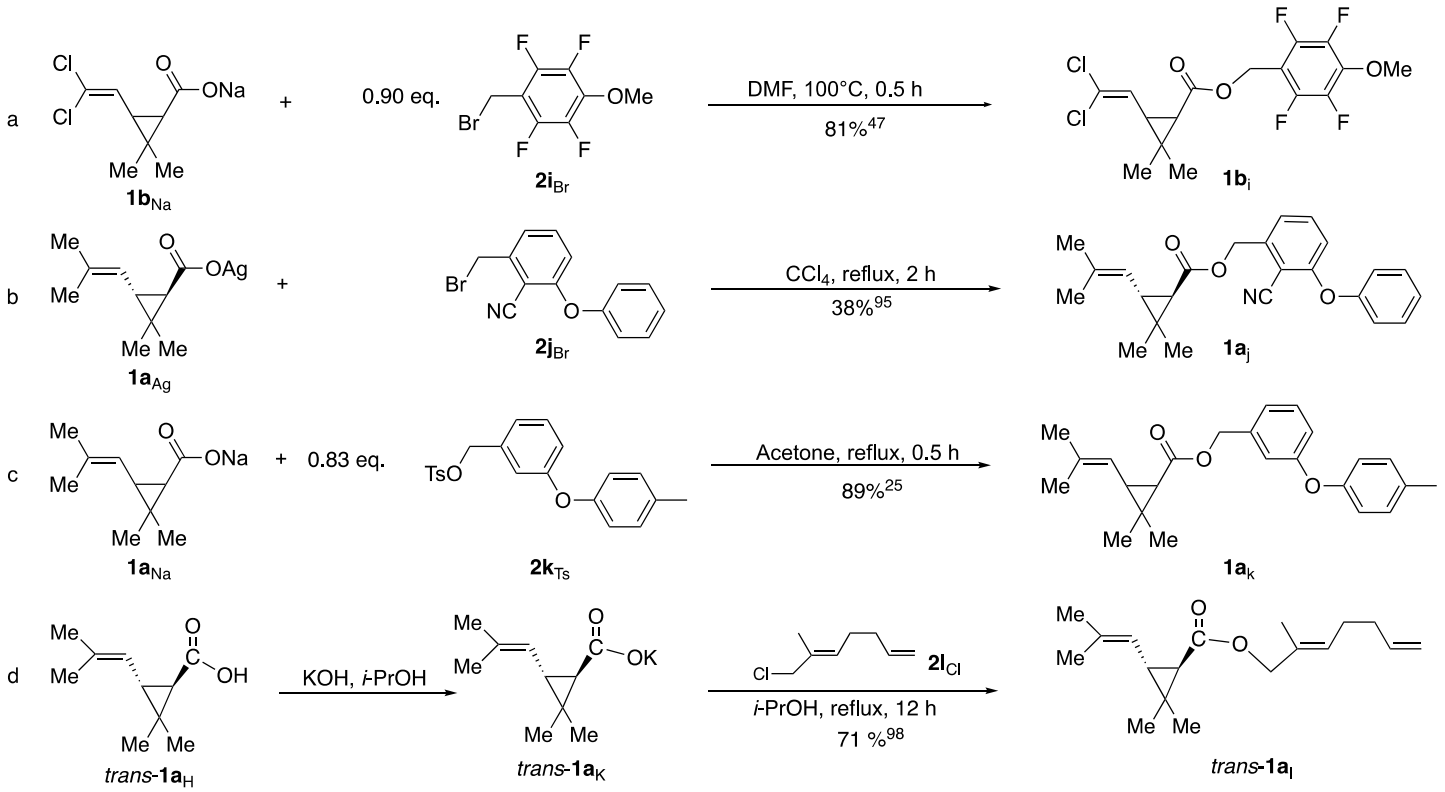


Scheme 34. Generic route to ester from metal carboxylates and alkyl halides and sulfonates.[91]

A solution to such problem is to withdraw the equilibrium in favor of the formation of the ester through its precipitation or precipitation of the salts concomitantly produced, according to Le Chatelier's principle.[92-94] For that purpose the silver carboxylate **1a**$_{Ag}$ has been reacted in place of an alkali metal salt, expecting that precipitation of the silver halide will withdraw the equilibrium.[35] The results disclosed in Scheme 35, entry b,[71,95] unfortunately does not provide an improvement although the costs dramatically increase. This reaction has been however successfully extended to the synthesis of methyl[71] and *t*-butyl[27] chrysanthemates.

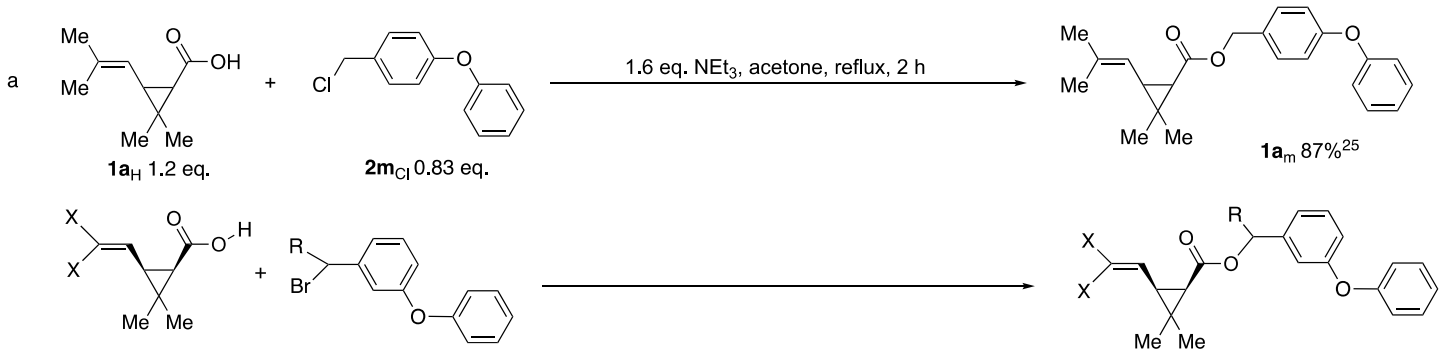
Interestingly however, the esterification reaction has been successfully applied to the synthesis of several pyrethroids from chrysanthemic acid (**1a**$_H$) as well as cypermethrinic acid (**1b**$_H$) and deltamethrinic acid (**1c**$_H$). The vinylcyclopropane carboxylates needed for the process have been prepared independently (Section 2.1.1.) by reaction of the acid with a base (Scheme 35)[47,71,95] or *in-situ* in the presence of triethylamine (Scheme 36, entry a).[25] The reaction proved particularly well suited to produce benzylic or allylic esters on alkylation with

benzyl-[25,47,71,90,95, 96] or allyl-[98] halides (Scheme 35, entries a,b,d, Scheme 36) or sulfonates (Scheme 35, entry c) as well as with allethronyl mesylate (see below, Scheme 38, entry b,c).[26,97]



Scheme 35. Synthesis of benzyl- and allyl-vinylcyclopropane carboxylates from their metal salts and related halides and sulfonates. [47,71,95,98]

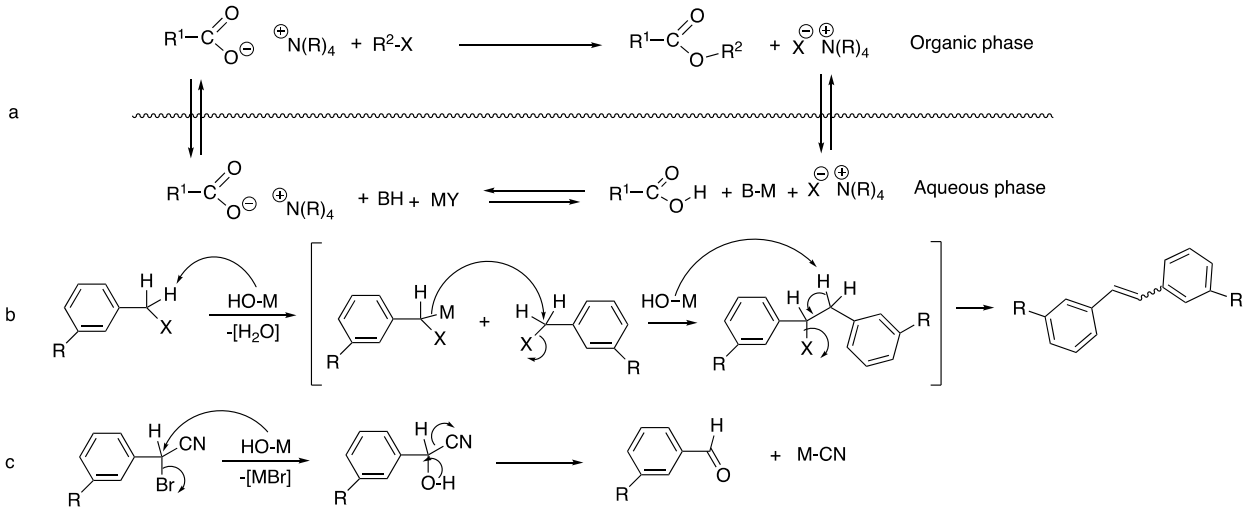
The reaction carried out with potassium carbonate under phase transfer catalysis[99,100] such as tetrabutyl ammonium bromide (TBAB) in dichloromethane proved highly efficient (Scheme 36, entries b-e).[25,96]



b	(1*R*,3*R*)-*cis*-**1c**$_H$	X; Br	R: CN	**2d**$_{Br}$ 0.91 eq.	0.5 eq. K_2CO_3, 0.01 eq. TBAB, H_2O-CH_2Cl_2, 40 °C, 10 h	(1*R*,3*R*)-*cis*-**1c**$_d$ 100 %[96]
c	*trans*-**1c**$_H$	X; Br	R: CN	**2d**$_{Br}$ 0.91 eq.	0.5 eq. K_2CO_3, 0.01 eq. TBAB, H_2O-CH_2Cl_2, 40 °C, 10 h	*trans*-**1c**$_d$ 100 %[96]
d	**1b**$_H$	X; Cl	R CN	**2d**$_{Br}$ 0.91 eq.	0.5 eq. K_2CO_3, 0.01 eq. TBAB, H_2O-CH_2Cl_2, 65 °C, 10 h	**1b**$_d$ 100 %[96]
e	**1b**$_H$	X; Cl	R: H	**2c**$_{Br}$ 0.91 eq.	0.5 eq. K_2CO_3, 0.05 eq. TBAB, H_2O-CH_2Cl_2, 85 °C, 48 h	**1b**$_c$ 96 %[96]

Scheme 36. Synthesis of 3-phenoxylbenzylcyclopropane carboxylates from acid and related halides.[25,96]

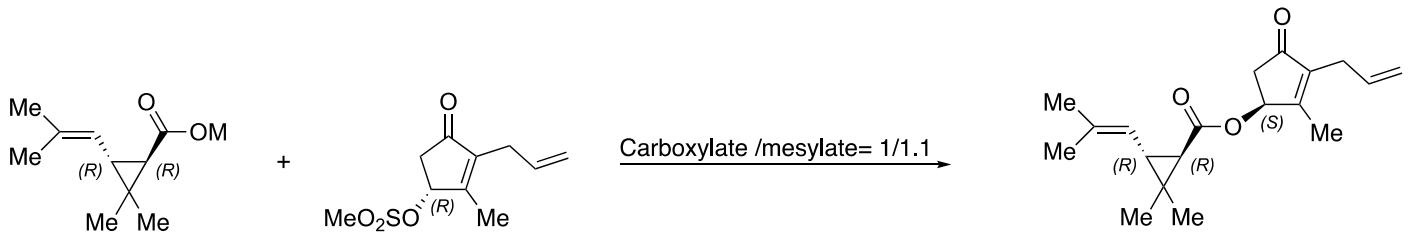
The latter conditions offer the advantages to separate the basic aqueous phase from the organic one containing the carboxylic acid and the alkyl halide (Scheme 37, entry a) [101-103] avoiding thus the interaction of the base with the alkyl halide that otherwise would have promoted (i) the coupling of benzyl halides that would had led to stilbene type derivatives (Scheme 37, entry a) or (ii) the transformation of alpha-bromo benzylcyanide to the corresponding cyanohydrin then to the metal cyanide and the aromatic aldehyde (Scheme 37, entry c).[104]



Scheme 37. Usefulness of phase transfer catalysis over classical synthetic methods of benzyl cyclopropane carboxylates.

The results reported[96] in Scheme 36, entries e and d, clearly show that the benzylic bromide possessing a cyano group (**2c**$_{Br}$) on the benzylic carbon is far more reactive than it analog (**2d**$_{Br}$) missing the cyano group there (Scheme 36, compare entry d to e).[105] Note that this strategy allows the synthesis of deltamethrin (*S*,1*R*,3*R*)-*cis*-(**1c**$_d$) resulting from the reaction of enantiopure (1*R*,3*R*)-*cis*-deltamethrinic acid (1*R*,3*R*)-*cis*-(**1c**$_H$) with the racemic alpha-cyano benzyl bromide (**2c**$_{Br}$) (Scheme 36, entry b).

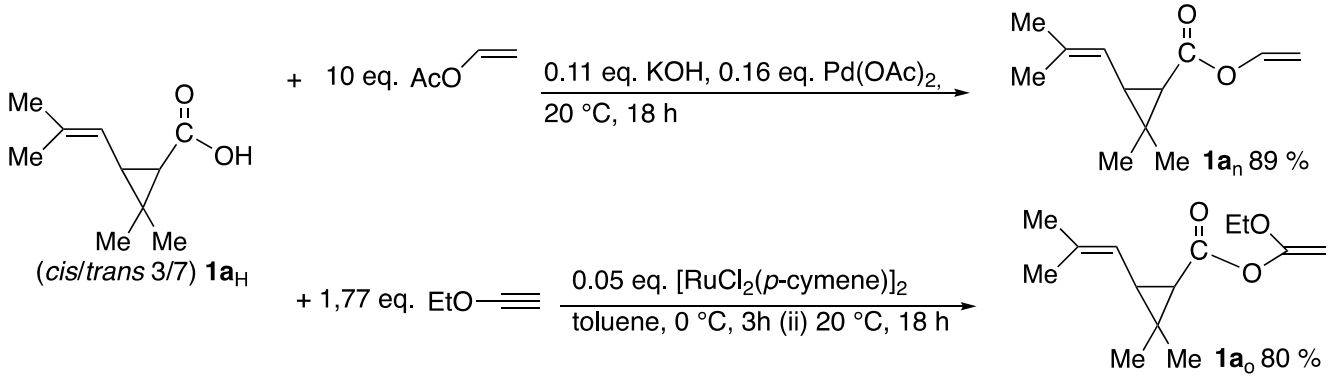
The reaction has been successfully extended to the synthesis of enantiomerically pure (*S*)-bioallethrin (*S*,1*R*,3*S*)-(**1a**$_b$) from enantiomerically pure alkali (1*R*,3*S*)-*trans*-chrysanthemates and enantiomerically pure (*R*)-allethronyl mesylate (Scheme 38, entries b,c) produced from allethrolone and sulfene (not mesyl chloride. See Chapter II[10]).[97,106,107] The alkylation proceeds with complete retention of configuration of the chrysanthemoyl moiety but complete inversion of the configuration at the allethronyl allylic asymmetric center (Scheme 38, entry b).[97,26] Note that the substitution reaction proceeds in good yield in polar aprotic solvents and proved much faster in HMPA (Scheme 38, entry a) than in DMSO (Scheme 38, entry b).[26,97]



a	(1*R*,3*R*)-*trans*-**1a**$_{Na}$	(*R*)-**2b**$_{Ms}$	M= Na HMPA, 20 °C, 0.2 h 77%	Allethrin (*S*,1*R*,3*R*)-**1a**$_b$
b	(1*R*,3*R*)-*trans*-**1a**$_K$	(*R*)-**2b**$_{Ms}$	M= K DMSO, 20 °C, 24 h 77%	Allethrin (*S*,1*R*,3*R*)-**1a**$_b$

Scheme 38. Synthesis (*S*)-allethrin from metal chrysanthemates and allethronyl methyl sulfonate.[25,26]

2.4.1.1.5. Synthesis of vinyl chrysanthemates from chrysanthemic acid. Vinyl chrysanthemates **1a**$_n$, **1a**$_o$ that have found application in enzymology, have been prepared in high yields from chrysanthemic acid by formal substitution reaction implying vinyl acetate catalyzed by palladium diacetate in basic media (Scheme 39, entry a)[108] or addition to ethoxyacetylene implying a ruthenium catalyst (Scheme 39, entry b).[108]



Scheme 39. Synthesis of vinyl chrysanthemates from chrysanthemic acid.[108]

2.4.1.2. Synthesis of vinylcyclopropyl esters from the corresponding carboxylic acids by alkoxylation reaction (formal OH/OR exchange, Scheme 10, Route 9b). The reactions affecting the hydroxyl group of chrysanthemic acid (**1a**$_H$) and its dihalogenovinyl analogs (**1b**$_H$) and (**1c**$_H$) are the more efficient ones to produce vinylcyclopropyl esters from the related acids. They take advantage of the aptitude of their carbonyl group to formally stabilize a positive charge on the acyl moiety favoring under suitable conditions a substitution reaction. This substitution involves the transformation of hydroxyl group to a better leaving group either by:

(i) transient activation using for example an acid catalyst when it is compatible with the process. In such case however the reaction is under equilibrium and removal of the co-product, usually water, is required to allow the reaction to go to completion,

(ii) formation of an intermediate that irreversibly activates the hydroxyl group favoring its substitution and leading to a stable by-product. Activation by carbodiimides **37** is one of the leading examples although other reagents will be reported in this section,

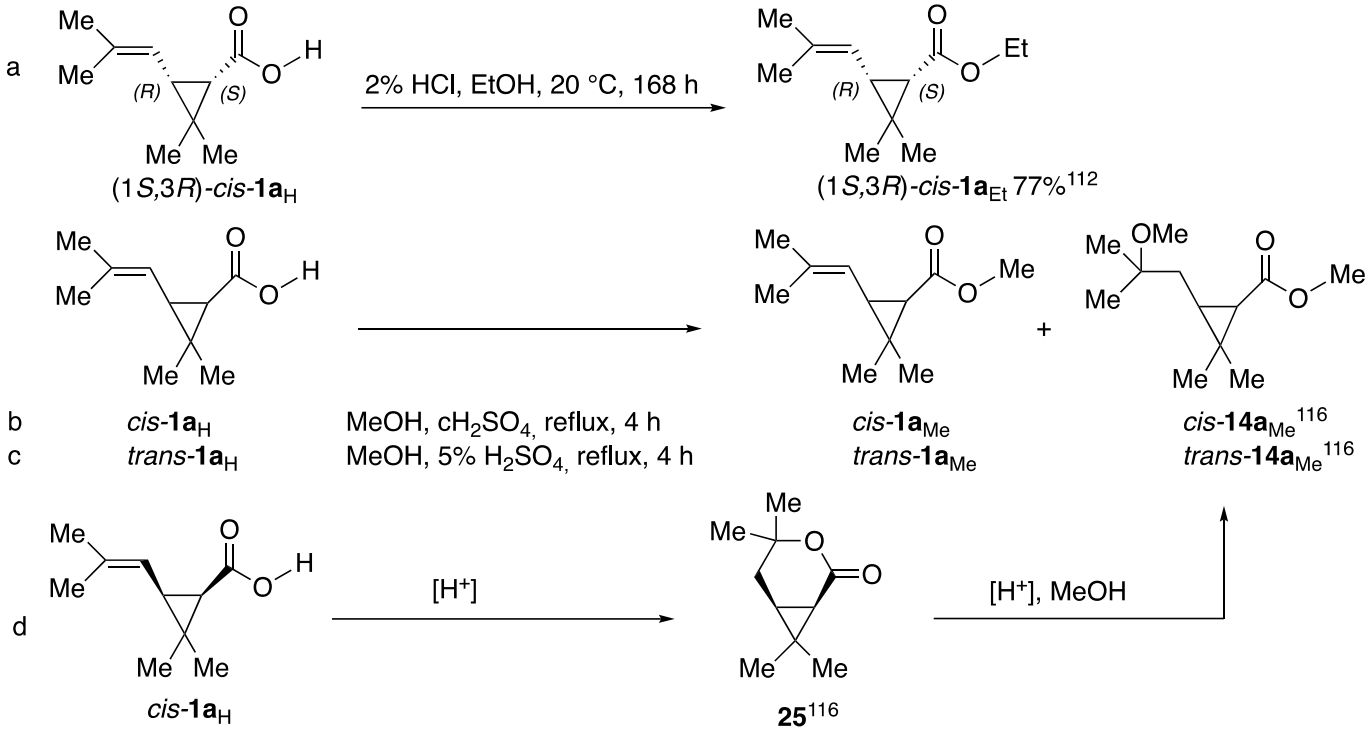
(iii) producing an isolable and even purifiable, stable intermediate that bears a good leaving on which several reagents are able to react. Although this strategy involves as an extra step the formation of acid chlorides **3**$_{Cl}$ and to a lower extend anhydrides **4**, that are the typical stable intermediates, it has been widely used especially for the synthesis of almost all the types of esters.

2.4.1.2.1. Reaction of vinylcyclopropane carboxylic acids with alcohols catalyzed by protic acids. The condensation of vinylcyclopropane carboxylic acids with alcohols under acid catalysis, the Fischer esterification reaction,[109] is one of the most valuable synthetic method to esterify carboxylic acids and has been used to access vinylcyclopropane carboxylic esters.[110,111] Since the reaction proceeds under equilibrium the formation of the esters is best achieved by displacing the equilibrium by withdrawing the water formed out of the medium.[92-94] However, conditions should be as mild as possible to avoid competing addition of the alcohol across the alkenyl moiety or cyclopropane ring opening.

The reaction of (1*S*,3*R*)-*cis*-chrysanthemic acid (**1a**$_H$) with methanol and ethanol performed at 20 °C in the presence of hydrochloric acid as a catalyst is extremely slow (1 week) and delivers the corresponding esters (1*S*,3*R*)-*cis*-**1a**$_{Me}$ and (1*S*,3*R*)-*cis*-**1a**$_{Et}$ with high stereocontrol (Scheme 40, entry a).[31,112-114] Faster reactions have

been achieved with methanol in refluxing dichloromethane as the solvent, in a biphasic system aimed to expell water. It has been used to produce methyl *trans*-chrysanthemate (**1a**$_{Me}$) in up to 82% yield.[90,115]

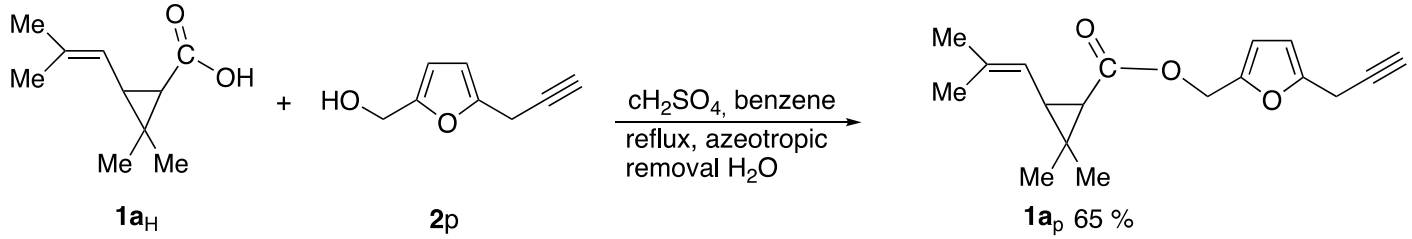
Esterification's of primary and secondary "lower" alcohols have been also performed using sulfuric acid that plays both the role the acid catalyst and the water sequestering agent (Scheme 40).[51]



Scheme 40. Reaction of vinylcyclopropane carboxylic acids with alcohols catalyzed by protic acids.[112,116]

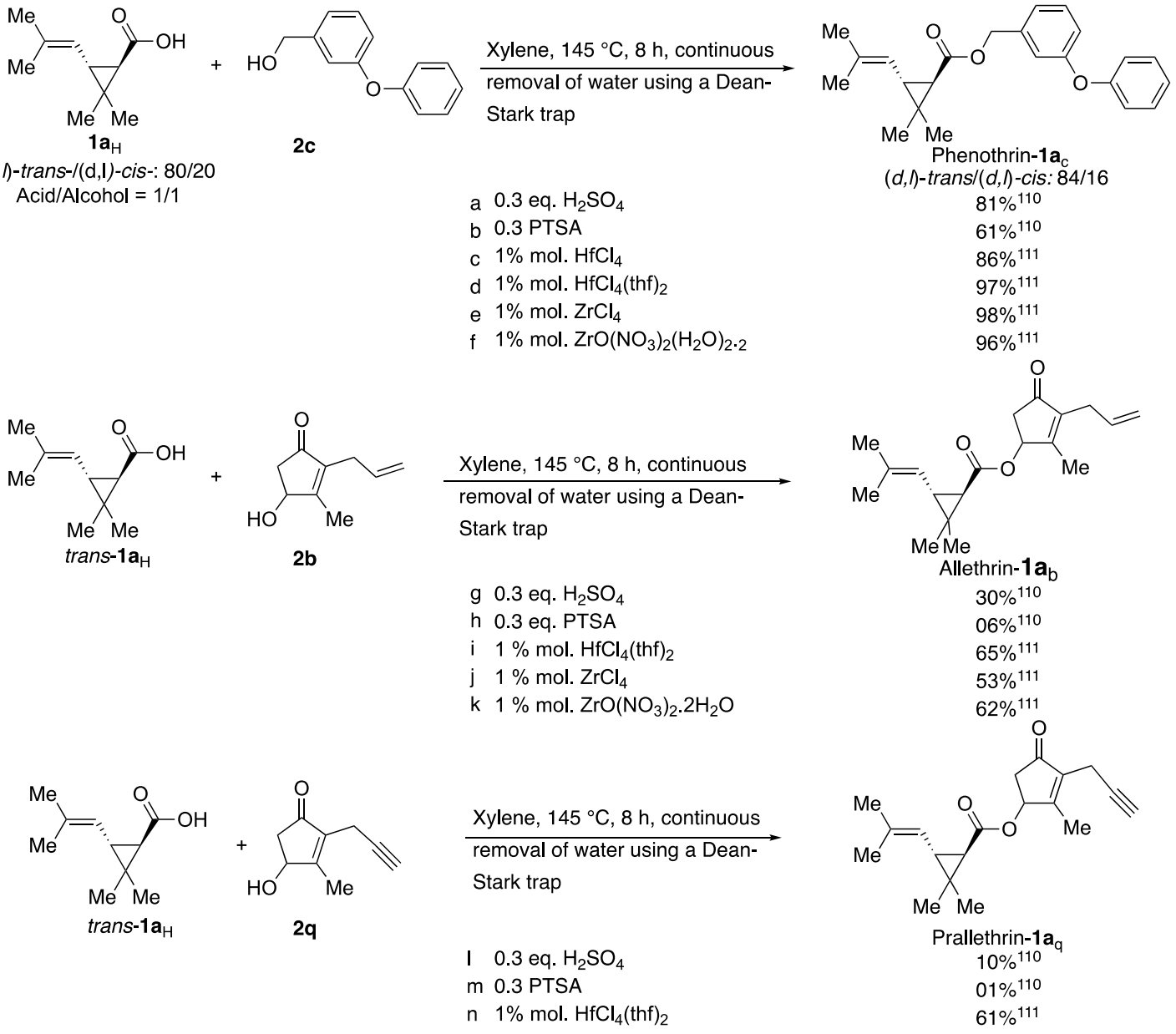
Accordingly, methyl *cis*-chrysanthemate *cis*-(**1a**$_{Me}$) (Scheme 40, entry b)[116] and its *trans*-(**1a**$_{Me}$) stereoisomer (Scheme 40, entry c)[11,116] have been produced in good yields from the corresponding stereoisomeric chrysanthemic acid *cis*-(**1a**$_H$) and *trans*-**1**$_H$ but contaminated with the corresponding methyl ether **14a**$_{Me}$ resulting from addition of methanol across their [C=C] double bonds (Scheme 40 entries b,c). The amount of *cis*-**14a**$_{Me}$ from *cis*-**1a**$_H$ has been found to be higher than that of *trans*-**14a**$_{Me}$ from *trans*-**2a**, suggesting that the former could have come from the intermediate formation of a bicyclic lactone (**25**) (Scheme 40, entry d).[11]

These conditions involving sulfuric acid and azeotropic removal of water have been applied to the synthesis of the furfuryl ester **1a**$_p$ from chrysanthemic acid (**1a**$_H$) and 5-propargyl furfuryl alcohol **2**$_p$ (Scheme 41).[117,118]



Scheme 41. Acid catalyzed esterification of chrysanthemic acid with functionalized furfurol.[117,118]

We have collected in Scheme 42 esterification reactions, performed under various conditions, and involving chrysanthemic acid (**1a**$_H$) and different alcohols **2a**$_R$ leading to pyrethroids.



Scheme 42. Comparison between protic and Lewis acids catalysts for the synthesis of phenothrin, allethrin, and prallethrin insecticides from chrysanthemic acid.[110,111]

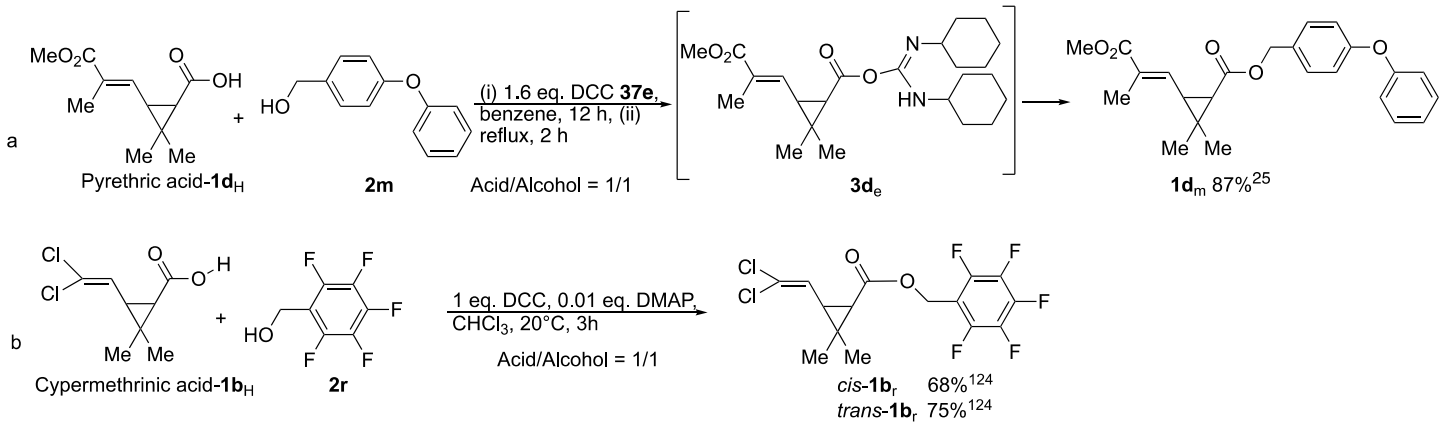
These results clearly show that these conditions are not optimum for the synthesis of the whole family of pyrethroids. Although the synthesis of phenothrin insecticide (**1a**$_c$) has been successfully achieved at 145 °C from **1a**$_H$ and stoichiometric amounts of 3-phenoxy benzyl alcohol (**2c**) using sulfuric acid (Scheme 42, entry a) or PTSA (Scheme 42, entry b) as catalyst and a Dean-Stark trap for continuous water removal, some *cis*/*trans*-isomerization seems to have taken place concomitantly in the process.[110] This processes cannot be efficiently extended to alcohols possessing more elaborated structures such as allethrolone (**2b**) and prallethrolone (**2q**) that is expected to produce allethrin (**1a**$_b$) and prallethrin (**1a**$_q$) (Scheme 42, entries g,h,l,m)[110] especially when PTSA is used as catalyst (Scheme 42, entries h,m).[110]

2.4.1.2.2. Reaction of vinylcyclopropane carboxylic acids with alcohols catalyzed by Lewis acids. Pyrethroids have been synthesized[110,111] in much higher yields by replacing Brønstedt-acids by Lewis-acids such as hafnium(IV) or zirconium(IV) salts as originally described by H. Yamamoto.[119] The original work performed[119] on a series of carboxylic acid and alcohols, especially with 4-phenylbutyric acid and benzyl alcohol with the commercially available and particularly stable $HfCl_4(thf)_2$ as catalyst, has been performed at reflux of toluene with continuous removal water. It proceeds in 1.5 h with 10% of catalyst and in much longer time (12 h) with only 1%.[110]

The work disclosed by the Sumitomo Company uses the same catalyst [$HfCl_4(thf)_2$] but at higher temperature (xylene, 150 °C) that allows to carry the reaction in shorter time (only 8 h; Scheme 42, entries d,I,n) and leads, in reasonably high yields, to phenothrin (**1a**$_c$), allethrin (**1a**$_b$), and prallethrin(**1a**$_q$) from 3-phenoxy benzyl alcohol (**2c**) (Scheme 42, entry d), allethrolone (**2b**) (Scheme 42, entry i) and prallethrolone (**2q**) (Scheme 42, entry n)[110] and chrysanthemic acid (**1a**$_H$). This reaction has been successfully extended to the synthesis of a stereoisomeric mixture of deltamethrin. [35,120]

Uncomplexed hafnium(IV)chloride, zirconium(IV)chloride and zirconium(IV)oxynitrate hydrate have been also successfully used for synthesis of these three pyrethroids (Scheme 42, entry c,e,f,j,k,n)[110,111] but we have not been able to find related results involving *cis*-chrysanthemic acid. Selection of the catalyst however requires not only comparison of the experimental conditions and the yield of pyrethroids but also the cost of the catalyst. At one time for example industrial cost for [$HfCl_4(thf)_2$] was 40 € per kg whereas zirconium(IV)oxynitrate hydrate complex costed only 0.2 € per kg (Iwakura, K; Souda, H., *Sumitomo chemical company*, personal communication).

2.4.1.2.3. Reaction of vinylcyclopropane carboxylic acids with alcohols involving the in-situ activation of their carboxy group. Esterification of vinylcyclopropane carboxylic acids has been also achieved with alcohols in the presence of reagents able to activate their carboxyl group such as dicyclohexyl carbodiimide **37e** (DCC)[121] or *p*-toluenesulfonyl chloride (TsCl) in the presence of N-methylimidazole.[122,123] Thus, pyrethric acid **1d**$_H$ has been successfully esterified with 4-phenoxy-benzyl alcohol (**2m**) (Scheme 43, entry a)[25] and cypermethrinic acid (**1b**$_H$) with perflurobenzyl alcohol (**2r**) (Scheme 43, entry b)[124] in the presence of dicyclohexyl carbodiimide (**37e**).

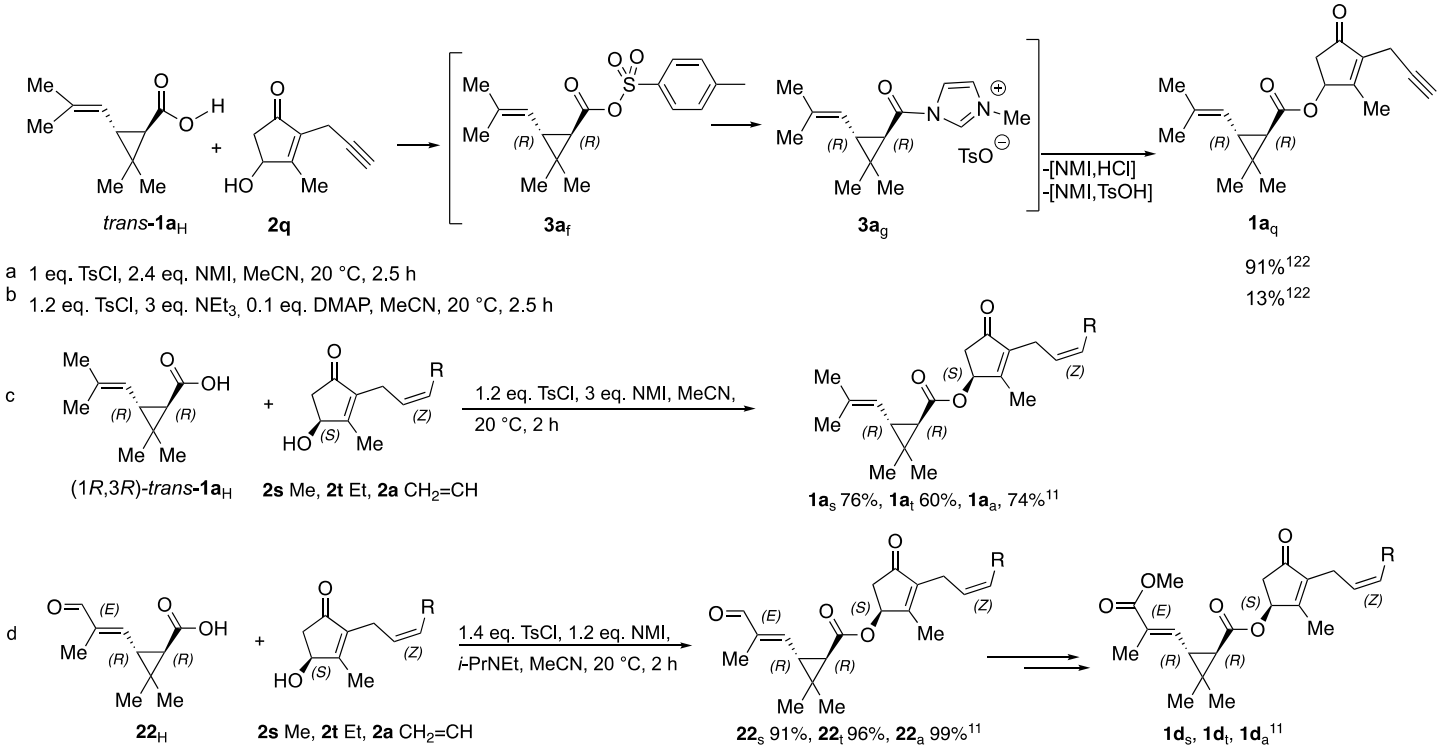


Scheme 43. Esterification of vinyl cyclopropane carboxylic acids involving benzyl alcohols and dicyclohexyl carbodiimide.[25,124]

Use of DCC in esterification reactions has been introduced by Steglich in 1978,[121] as a versatile method of esterification of carboxylic acids. It takes place even with bulky starting materials and accepts the presence of

various functional groups. It works under mild conditions (room temperature) and is particularly efficient when carried out in the presence of 4-dimethylaminopyridine (DMAP). It however delivers beside the ester an equimolar amount of dicyclohexylurea. Although the latter usually mostly precipitate out of the medium, it sometimes remains as trace amounts in the ester. However, the disposal of large quantities of the urea co-product constrains its use in production.

The tosyl chloride, *N*-methylimidazole (NMI) method proved to be particularly efficient for the synthesis of prallethrin (**1a**$_q$) (Scheme 44, entry a),[122] allethrin (**1a**$_b$), as well as scalemic natural (*S*,1*R*,3*R*)-cinerin I (**1a**$_s$), (*S*,1*R*,3*R*)-jasmolin I (**1a**$_t$) and (*S*,1*R*,3*R*)-pyrethrin I (**1a**$_a$) from prallethrolone (**2q**), allethrolone (**2b**), (*S*)-cinerolone (**2s**), (*S*)-jasmolone (**2t**) and (*S*)-pyrethrolone (**2a**) respectively (Scheme 44, entry c).[11] The reaction proceeds efficiently when a 1/1 mixture of the acid and the alcohol is reacted with at least two equivalents of NMI in acetonitrile. It usually delivers, in about two hours at room temperature, the ester in up to 70% yield with complete retention of configuration at each of the chiral center of the ester.[11] The presence of NMI is crucial for the success of the reaction that is expected to produce sequentially the acyl sulfonate (**3a**$_f$), *N*-methylimidazolium tosylate (**3a**$_g$) and the related chlorohydrate intermediates (Scheme 44, entry a).[122] In fact, it has been reported[122] that replacing NMI by triethylamine even in the presence of 4-dimethylaminopyridine (DMAP) leads to the formation of prallethrin (**1a**$_q$) in only 13% yield instead of 91% yield when NMI is used (Scheme 44, compare entries b to entry a).

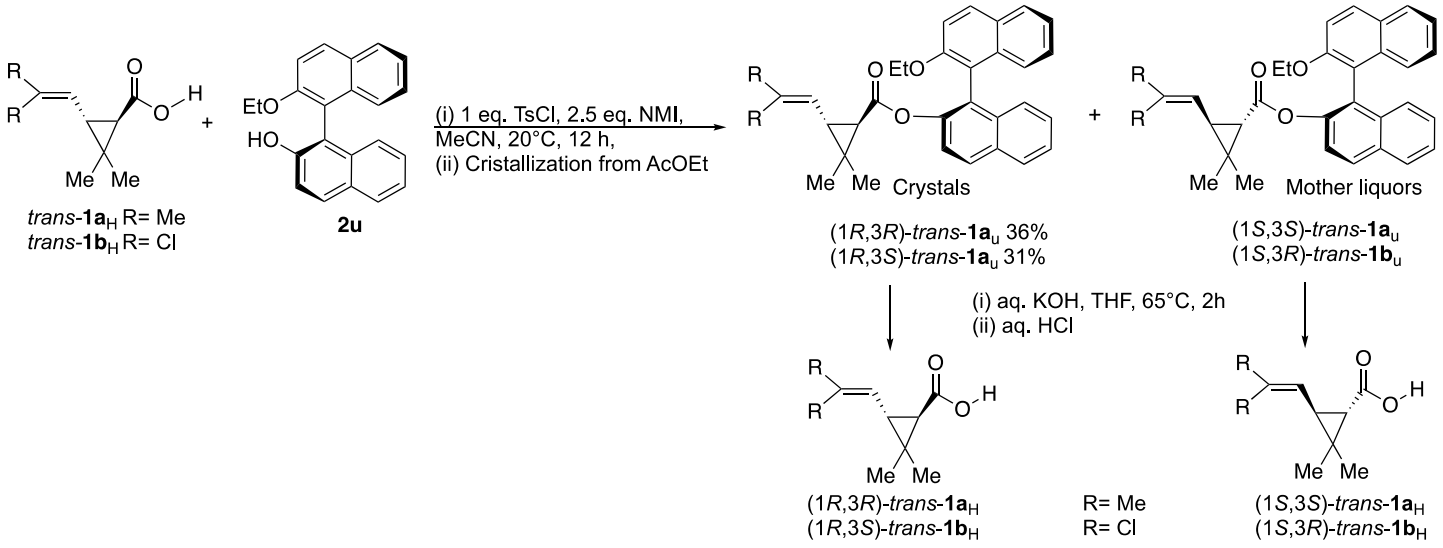


Scheme 44. Synthesis of pyrethrin I, pyrethrin II and analogues from related carboxylic acids and allethronyl alcohols using the tosyl chloride and *N*-methylimidazole (NMI) method.[11,122]

The reaction of the related yinyl cyclopropane carboxylic acid (**22**$_H$) bearing an unsaturated aldehyde on the side chain with scalemic cinerolone (*S*)-(**2s**), jasmolone (*S*)-(**2t**) and pyrethrolone (*S*)-(**2a**) in the presence of tosyl chloride and NMI leads to the related esters **22**$_s$, **22**$_t$ and **22**$_a$ (Scheme 44, entry d) that after oxidation produce (*Z*,*S*,1*R*,3*R*)-cinerin II (**1d**$_r$), (*Z*,*S*,1*R*,3*R*)-jasmolin II (**1d**$_s$) and (*Z*,*S*,1*R*,3*R*)-pyrethrin II (**1d**$_a$), respectively.[11] Lowering

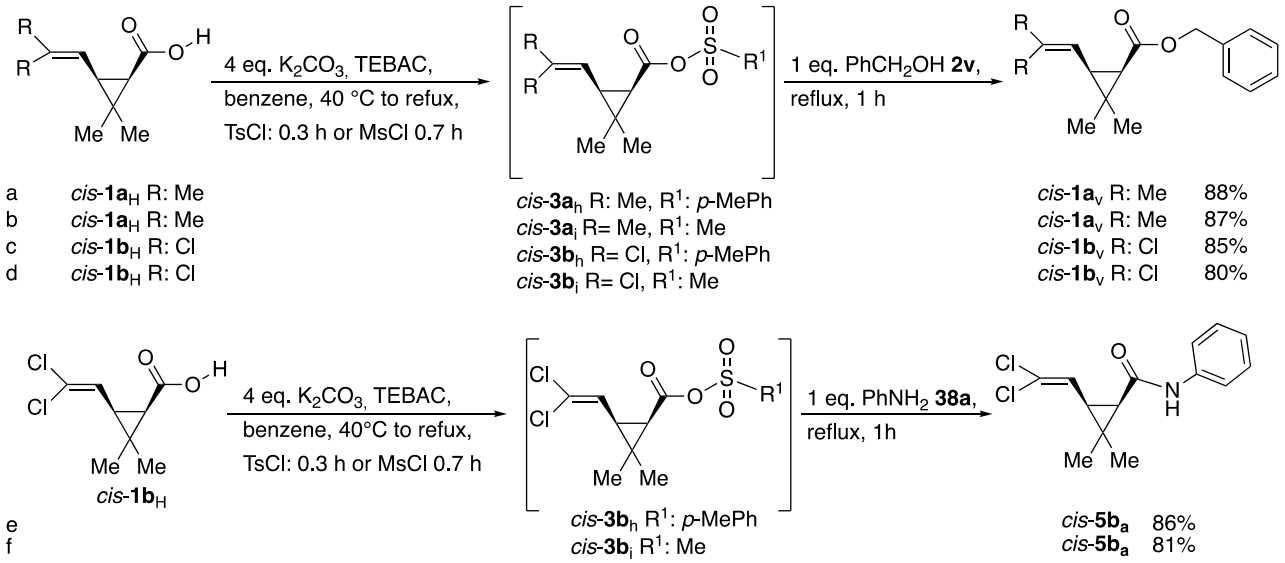
the amount of NMI and replacing the excess by the Hünig's base (*i*-Pr_2NEt, DIPEA) proved particularly rewarding (Scheme 44, entry d).[11]

Extension of this reaction to racemic mixtures of *trans*-chrysanthemic acid (*rac*)-(**1a**$_H$) as well as to *trans*-cypermethrinic acid (*rac*)-(**1b**$_H$) and enantiopure binaphthol derivative **2u** allows the synthesis of diastereoisomeric mixtures of *trans*-esters (**1a**$_u$) and (**1b**$_u$) (Scheme 45).[125] The latter have been successfully used for the resolution of racemic mixtures of these acids (Scheme 45).[125]



Scheme 45. Resolution of racemates of vinylcyclopropane carboxylic acid from binaphtyl derivatives using the tosylchloride and *N*-methylimidazole (NMI) method.[125]

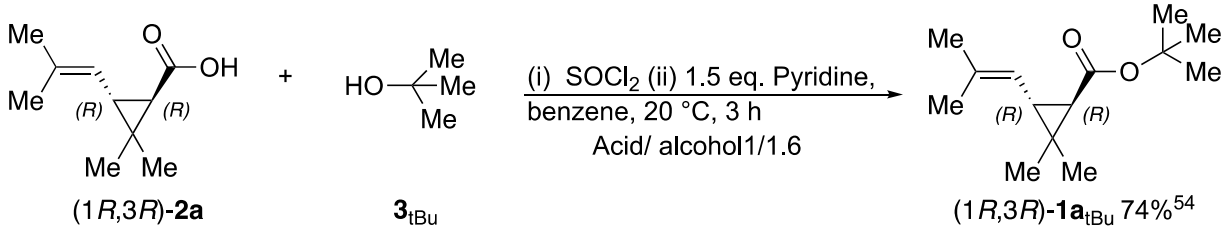
A related procedure[126] that involves phase transfer catalysis[99,100] and uses potassium carbonate and triethylbenzylammonium chloride (TEBAC) in place of NMI has been also reported (Scheme 46).



Scheme 46. Synthesis vinylcyclopropane carboxylic esters and amines from alcohols and amines using sulfonylchlorides under phase transfer catalysis.[126]

These conditions have been successfully extended to the synthesis of carboxylic amides from cypermethrinic acid (Scheme 46, entries e,f).[126]

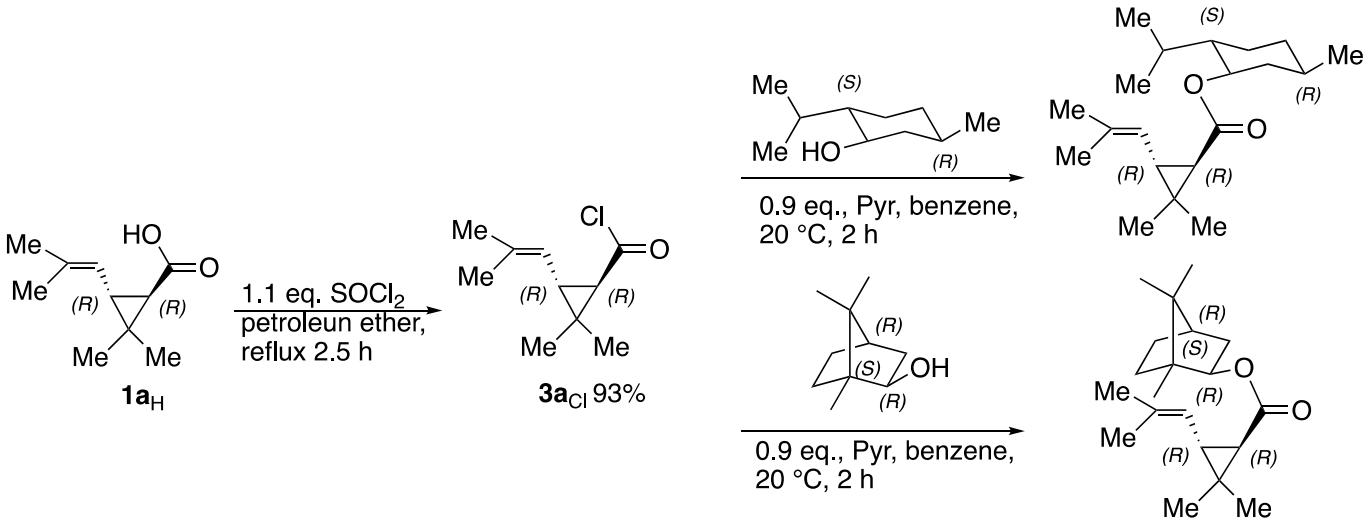
2.4.1.2.4. Synthesis of esters from carboxylic acid and alcohols implying the intermediate formation of acyl chlorides (Scheme 10, Route 9b). This synthesis of esters of vinylcyclopropane carboxylic acids involving the intermediate formation of the related acyl chlorides is by far the most widely used method to produce all the esters of vinylcyclopropane carboxylic acids. It has been used since the initial work on pyrethrins and has been used constantly since then to synthesize all the lower esters of chrysanthemic and permethrinic acids and related pyrethrins and pyrethroids as well.[127-129] The reaction is usually carried out in two steps and two pots in which the acid chloride is first synthesized from the vinylcyclopropane carboxylic acids and the resulting acid chlorides, after purification, usually distillation, is reacted with the alcohol. In rare cases, the transformation is carried out in one pot (Scheme 47). In these cases, the purification is omitted but the excess of reagent used in the first step is removed before the addition of the alcohol.[54,65]



(1*R*,3*R*)-**2a** **3**$_{tBu}$ (1*R*,3*R*)-**1a**$_{tBu}$ 74%[54]

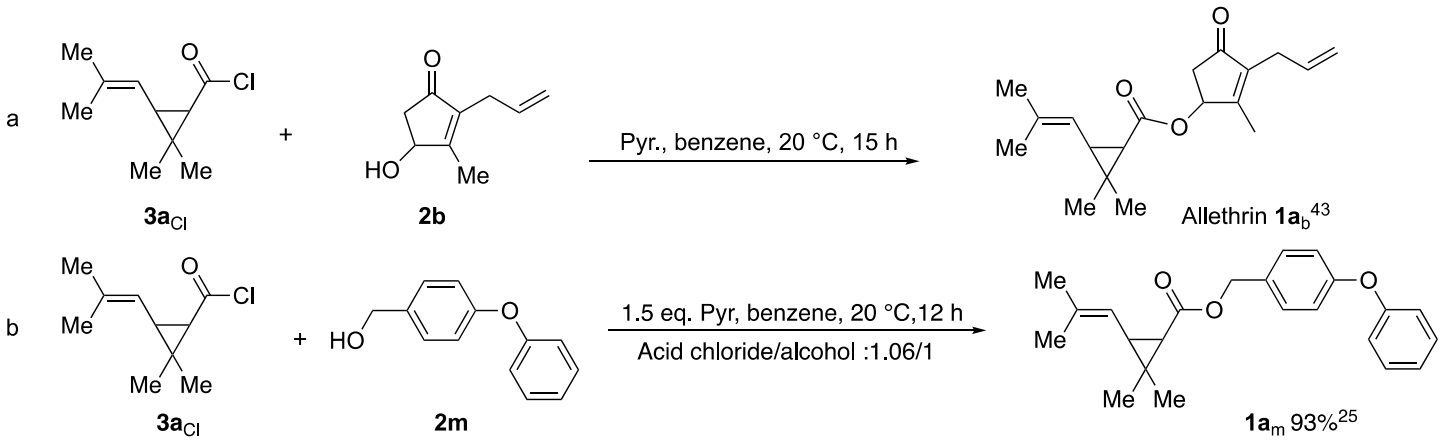
Scheme 47. One pot synthesis of *t*-butyl chrysanthemate from chrysanthemic acid and *t*-butanol.[54,65]

The reaction is often carried out in the presence of pyridine and benefits from the use of up to 10% of 4-dimethylaminopyridine (DMAP)[130,131] as catalyst. The two step transformation has been performed with *cis*- and *trans*-chrysanthemic acid (**1a**$_H$) through chrysanthemoyl chloride (**3a**$_{Cl}$) and involves among others methanol,[70, 66] *t*-butanol (Scheme 47),[54,65] *l*-menthol (75%),[52,64] *l*-borneol (78%),[52] *d*-fenchol (48%) (Scheme 48),[52] pyrethrolone[3] and cinerolone[3] precursors of pyrethrins, allethrolone (**2b**) precursor of allethrin-(**1a**$_b$) (Scheme 49, entry a),[43] and various benzylic alcohols such as the *p*-phenoxy-benzylalcohol (**2m**) (Scheme 49, entry b).[25]



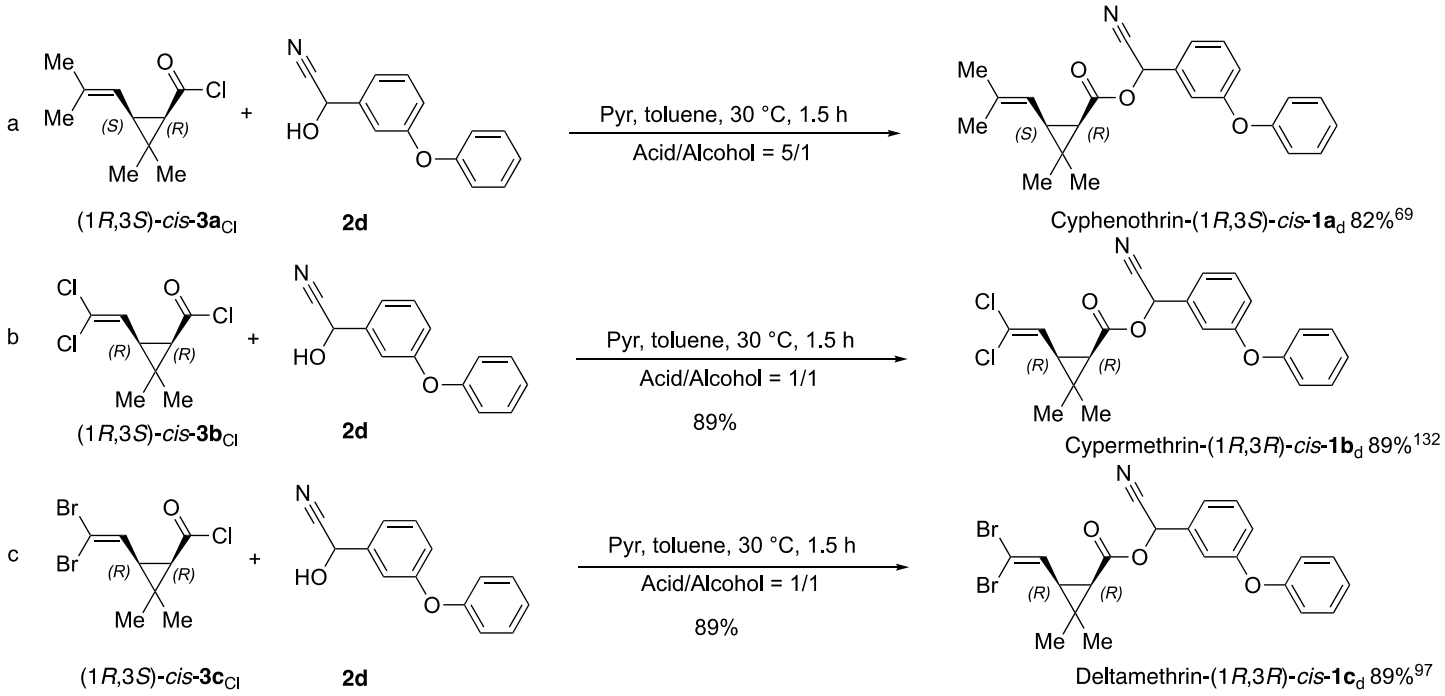
1a$_H$ **3a**$_{Cl}$ 93%

Scheme 48. Multi-steps synthesis of alkyl chrysanthemates from chrysanthemic acid.[25,52,64]



Scheme 49. Synthesis of alkyl chrysanthemates from chrysanthemoyl chloride and alcohols.[25,43]

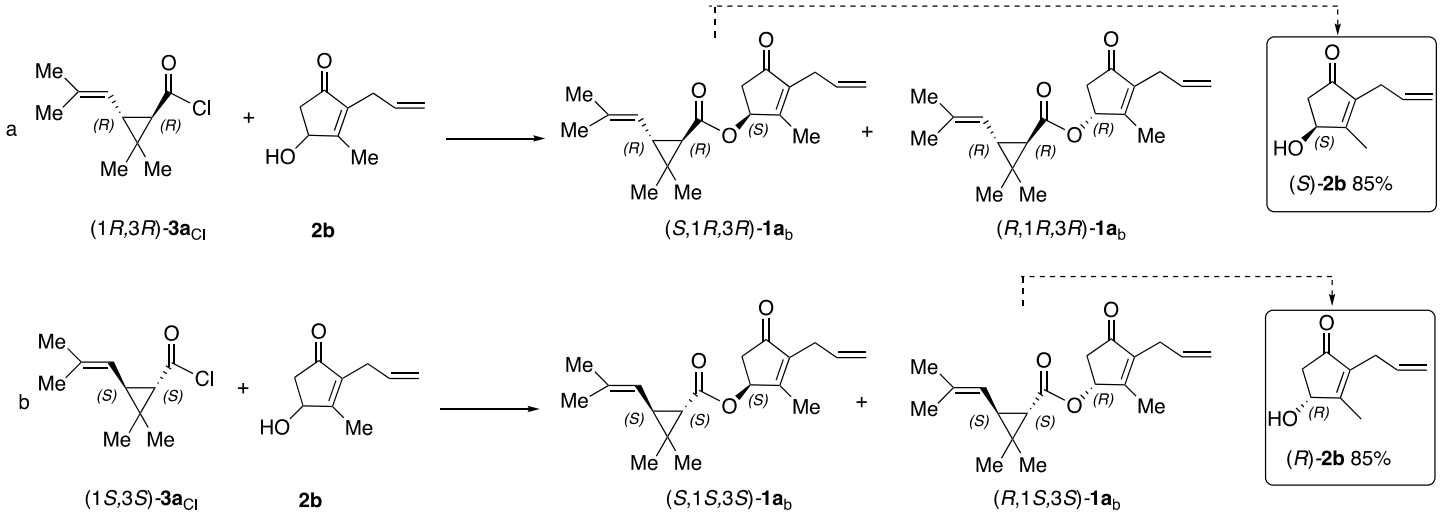
This transformation has been also applied to synthesize (1*R,*3*R*)-*cis*-cyphenothrin-(**1a**$_d$) (Scheme 50, entry a)[69] including its ^{14}C radiolabeled form,[69] (1*R,*3*R*)-*cis*-cypermethrin (**1b**$_d$) (Scheme 50, entry b)[69,132] and (1*R,*3*R*)-*cis*-deltamethrin (**1c**$_d$) (Scheme 50, entry c)[97] from 3-phenoxy mandelonitrile **2d** and chrysanthemoyl chloride (**3a**$_{Cl}$), cypermethrinoyl chloride (**3b**$_{Cl}$) and deltamethrinoyl chloride (**3c**$_{Cl}$) respectively (Scheme 50).



Scheme 50. Synthesis of alkyl vinylcyclopropane carboxylates from vinylcyclopropane carbonyl chloride and alcohols.[69,97,132]

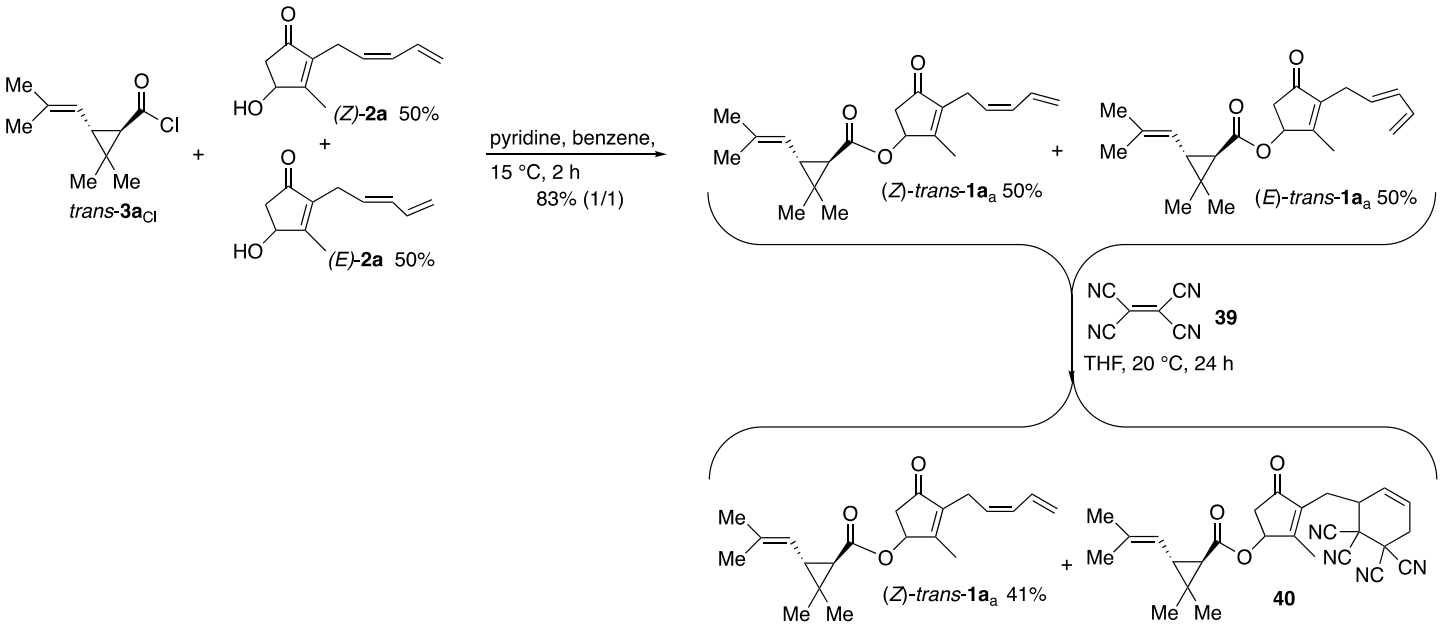
This method has been used for:

(i) isolation of each of the two enantiomers of allethrin (**1a**$_b$) from their racemic mixture through their stereoisomers (*S*,1*R*,3*R*)-(**1a**$_b$) (Scheme 51, entry a) and (*R*,1*S*,3*S*)-(**1a**$_b$) (Scheme 51, entry b), the hydrazones of which crystallize nicely from the media. [7,133]



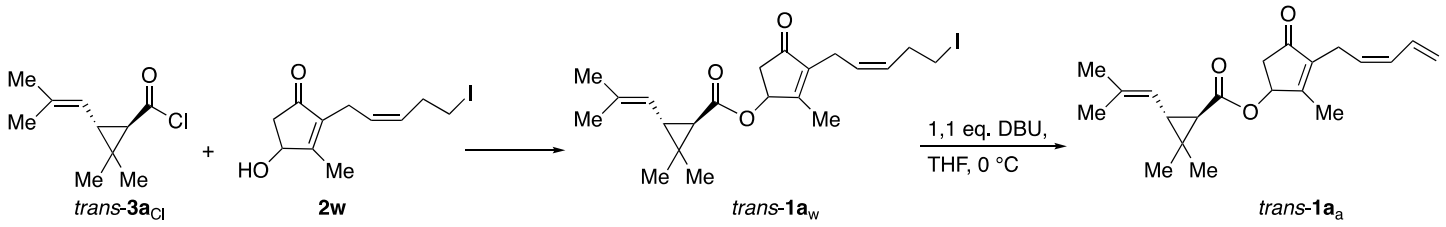
Scheme 51. Resolution of allethrolone through (1*R,*3*R)-trans*- and (1*S,*3*S)-trans*-chrysanthemic acid chlorides.[133]

(ii) separation of (*Z*)-pyrethrin (**1a**$_a$) from its (*E*)-stereoisomer (Scheme 52). Thus, *trans*-chrysanthemoyl chloride *trans*-(**3a**$_{Cl}$) has been reacted with an E/Z mixture of pyrethrolone (**2a**) and the racemic pyrethrin I (*Z*)-*trans*-(**1a**$_a$) has been separated from its (*E*)-stereoisomer through selective Diels-Alder reaction of the latter with tetracyanoethylene (**39**) in the mixture and removal of the resulting Diels-Alder adduct **40**. [7,134]



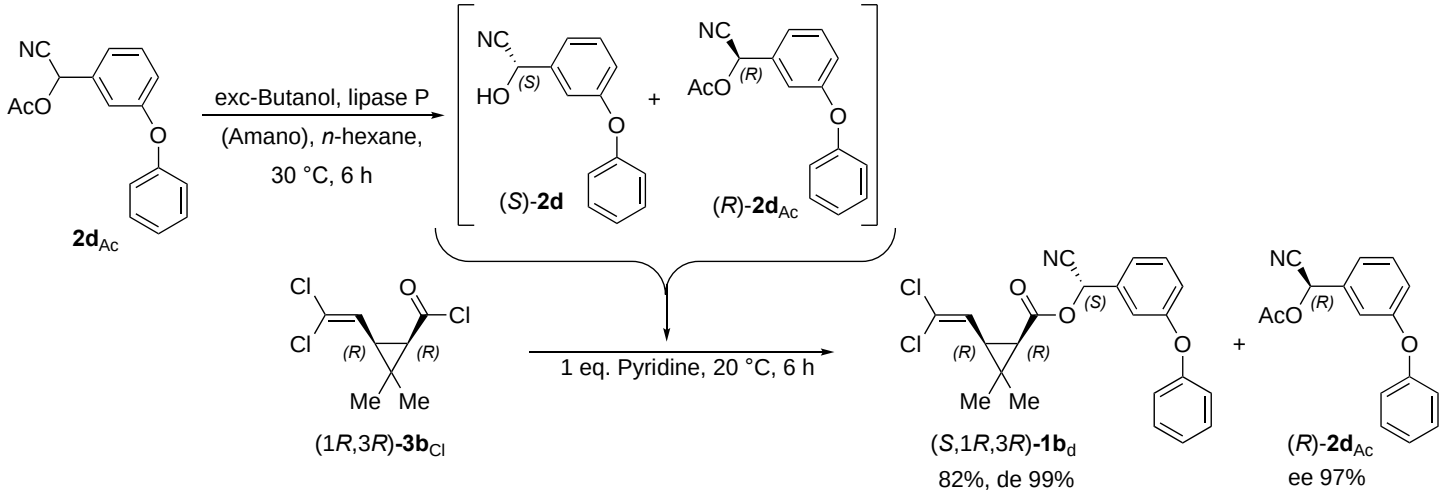
Scheme 52. Synthesis of pyrethrin from a cis/trans mixture of pyrethrolone.[134]

(iii) the synthesis of rac-pyrethrin I *trans*-(**1a**$_a$) from rac-*trans*-chrysanthemoyl chloride *trans*-(**3a**$_{Cl}$) and the rethrolone **2w** resulting from allethrolone (**2b**) by olefin cross-metathesis (Scheme 53).[135]



Scheme 53. Synthesis of cinerolone and pyrethrin from allethrolone by olefin cross-metathesis.[135]

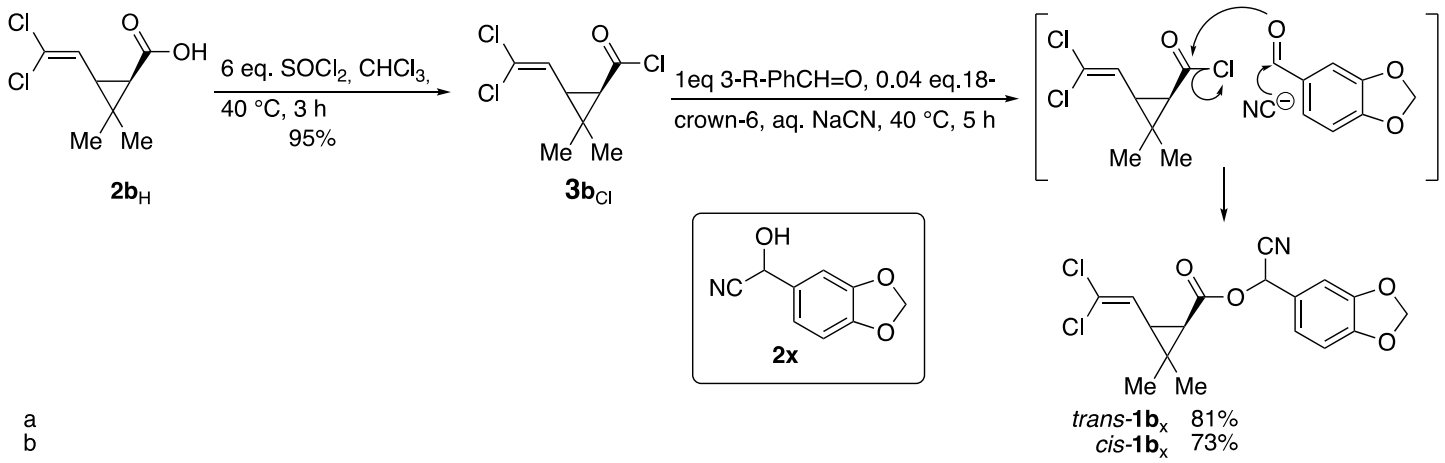
(iv) the synthesis of cypermethrin (**1b**$_d$) that has been successfully carried out (82% yield, ee 90%) on reaction of (*1R,*3*R*)-*cis*-cypermethrinoyl chloride (1*R*,3*R*)-*cis*-(**3b**$_{Cl}$) with a crude mixture of (*S*)-hydroxy-(3-phenoxyphenyl)acetonitrile (*S*)-(**2d**) and (*R*)-acetoxy-(3-phenoxyphenyl)acetonitrile (*R*)-(**2d**$_{Ac}$) resulting from enantioselective, lipase (native or immobilized) catalyzed transesterification, of racemic (*R,S*)-acetoxy-(3-phenoxyphenyl)acetonitrile (**2d**$_{Ac}$) with *n*-butanol in hexane (6 h, 49% conversion, Scheme 54).[10,136]



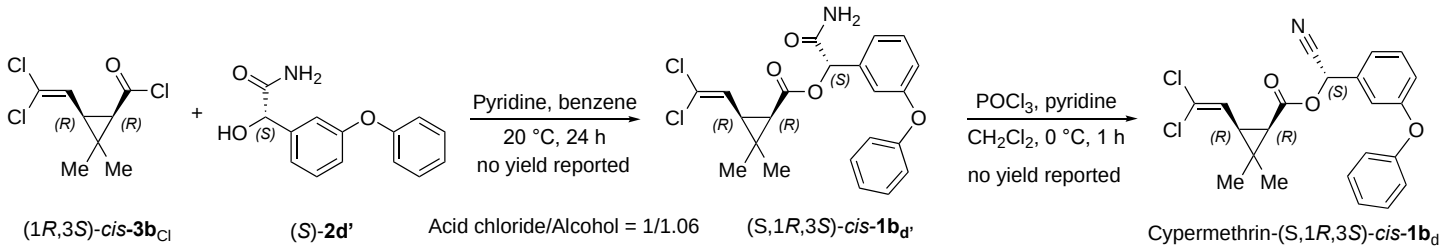
Scheme 54. Synthesis of enantiopure permethrinate from enantiopure cypermethrinoyl chloride and (*S*)-3-phenoxy mandelonitrile from the resolution of racemic 3-phenoxy mandelonitrile with lipase P.[136]

Related reactions involve (i) the one pot formation of octyl (1*R*,3*R*)-*cis*-cypermethrinate (1R,3R)-*cis*-(**1b**$_{Oct}$) from racemic mixture of *cis*/*trans*-cypermethrinic acid (**1b**$_H$) (Scheme 23)[41] (ii) the *in situ* synthesis of the ester **1b**$_x$ involving the *in situ* formation of the cyanohydrin **2x** on reaction of an aromatic aldehyde and potassium cyanide in the presence of the cypermethrinoyl chloride (**3b**$_{Cl}$) and a crown ether (Scheme 55). [124] Interestingly, the addition of the cyanide on the aromatic aldehyde is faster than its reaction on the cypermethrinoyl chloride (**3b**$_{Cl}$).

Alternatively, cypermethrin (**1b**$_d$) has been produced as an epimeric mixture of stereoisomers at the benzylic carbon or as the pure (*S*)-epimer there by dehydration of the corresponding carboxamidoester (*S,*1*R,*3*S*)-*cis*-**1b**$_{d'}$ with phosphorus oxychloride ($POCl_3$, pyridine, CH_2Cl_2, 0 °C, 1 h, Scheme 56).[137,138] This compound, which is much more stable than cypermethrin (**1b**$_d$), can be easily manipulated and purified before dehydration that occurs with complete integrity of the stereochemistry at the labile benzylic carbon.[137,138] Note that the substitution of the chlorine of cypermethrinoyl chloride *cis*-(**3b**$_{Cl}$) by the hydroxyl group of the alcohol selectively occurs in the presence of the primary amide group also present on (*S*)-(**2d'**).

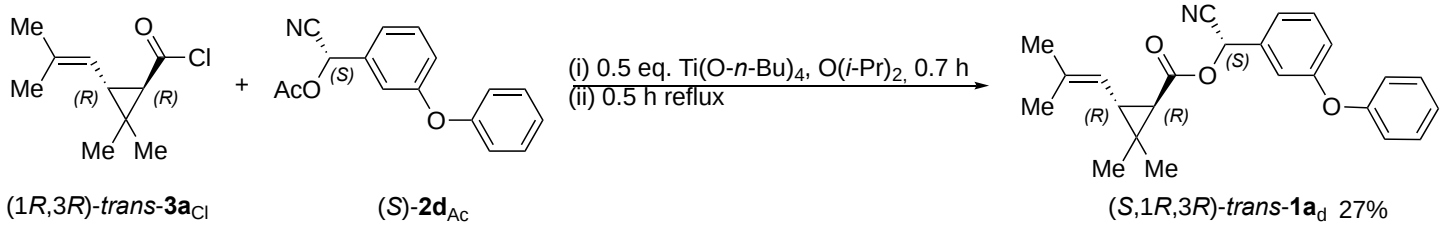


Scheme 55. One pot synthesis of permethrinate from cypermetrinic acid, aromatic aldehyde and sodium cyanide.[124]



Scheme 56. Synthesis of cypermethrin from cypermetrinic acid chloride and alpha-carbamido-3-phenoxybenzylalcohol.[137,138]

A related reaction involves the synthesis of cyphenothrin (S,1*R*,3*R*)-(**1a**$_d$) by titanium tetrabutoxide catalyzed exchange of the acetyl group of acetoxy 3-phenoxymandelonitrile (*S*)-(**2d**$_{Ac}$) with the acyl group of scalemic *trans*-chrysanthemoyl chloride (1*R*,3*R*)-(**3a**$_{Cl}$). This reaction that takes place in modest yield, occurs with complete retention of the configuration at the substituted benzylic carbon, (Scheme 57).[104] It offers an advantage over the reaction that involves instead the cyanohydrin (S)-(**2d**) and produce (**1a**$_d$) partly epimerized at its benzylic site.[104]



Scheme 57. Synthesis of cyphenothrin from chrysanthemic acid chloride and acetoxy 3-phenoxymandelonitrile.[104]

2.4.1.2.5. Synthesis of esters from carboxylic acid and alcohols through intermediate formation of anhydrides (Scheme 10, Route 9b). Only few examples of the esterification of alcohols with vinylcyclopropane carboxylic

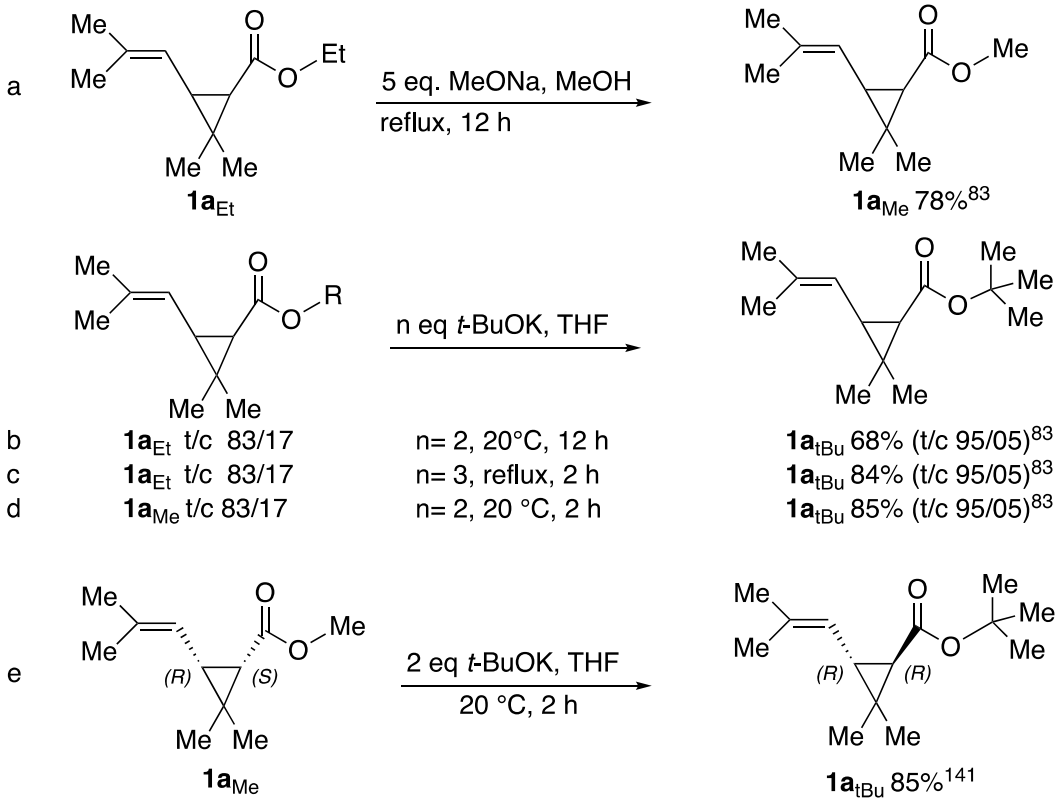
anhydrides have been disclosed. They are related to the reaction using acyl chlorides reported above but offer the advantage to be performed without the need for a catalyst (Scheme 29, entry b).[25]

2.4.2. Synthesis of vinylcyclopropane carboxylic esters from vinylcyclopropane carboxylic esters possessing a different alkoxy group.

2.4.2.1. Synthesis of vinylcyclopropane carboxylic esters by transesterification involving another vinylcyclopropyl ester and alcoholates (formal OR/OR' exchange, Scheme 11, Route 16). Most of the syntheses of the cyclopropane derivatives deliver vinylcyclopropane carboxylates belonging to the "lower ester" family and therefore transesterification is the privileged method to transform them to pyrethroids.

Transesterification has been efficiently achieved from ethyl (**1a**$_{Et}$) to methyl (**1a**$_{Me}$) chrysanthemates with more than stoichiometric amount of sodium methylate in methanol at reflux (Scheme 58, entry a) and from methyl (**1a**$_{Me}$) and ethyl (**1a**$_{Et}$) to *t*-butyl (**1a**$_{tBu}$) chrysanthemates on reaction with potassium *t*-butoxide in THF at room temperature (Scheme 58, entries b,d,e)[83] or at reflux (Scheme 58, entry c). [66,83,139,140] Anyhow, the reaction is much faster when carried out on methyl than on ethyl ester (Scheme 58, compare entries d to b,c).[83]

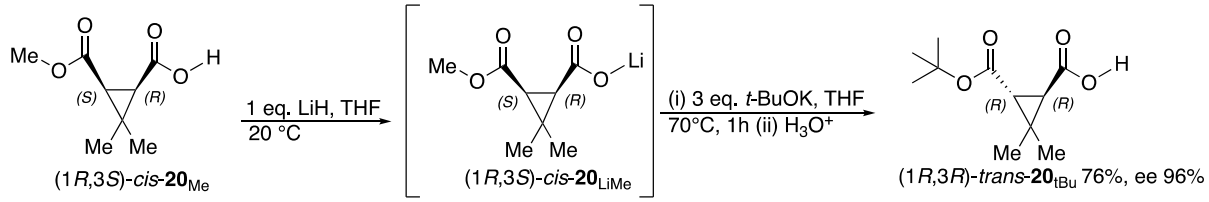
The reaction proceeds stereoselectively in the *trans*-series in which both the starting material and the product possess the same *trans*-stereochemistry. In the *cis*-series however isomerization concomitantly occurs.[83,139] The percentage of the *trans*-isomer is the highest in *t*-butyl chrysanthemate in which the interaction between the vicinal isobutenyl and carboxy groups is the highest since the *t*-butyl group is the bulkier of the 'lower alkyl" groups (Scheme 58, entry e).[141]



Scheme 58. Transesterification of alkyl chrysanthemates.[83,141]

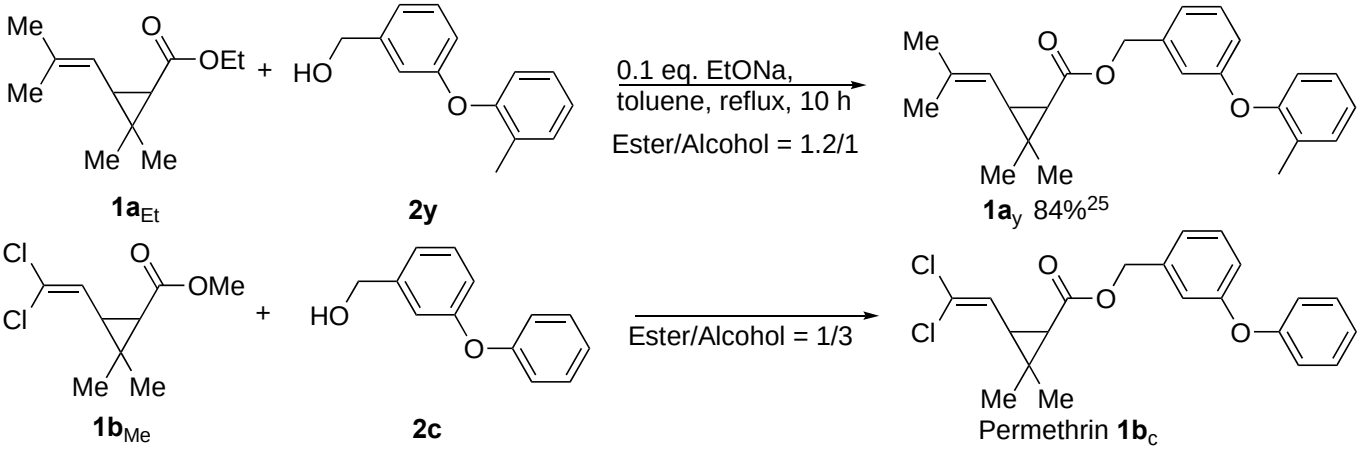
A related interesting regio and stereoselective transesterification leading to mono *t*-butyl caronate (1*R*,3*S*)-*cis*-(**20**$_{tBu}$) has been reported from mono methyl caronate (1R,3S)-*cis*-(**20**$_{Me}$) and potassium *t*-butoxide (Scheme 59).[53] The success of this process takes advantage of the propensity of the lithium salt tightly bonded to the related carboxylate that protect this group and avoid (i) the alkoxy group from scrambling from one to the other

carbonyl carbon on the cyclopropane leading to the formation of its enantiomer (1S,3R)-*cis*-(**20**$_{Me}$) (ii) competing metalation leading to epimerization to the more stable *trans*-stereoisomer (1*R*,3*R*)-*trans*-(**20**$_{tBu}$). The same transformation could not be achieved by replacing the lithium carboxylate (**20**$_{LiMe}$) by its potassium analogue (**20**$_{KMe}$).[53]



Scheme 59. Transesterification of methyl *cis*-caronate.[53]

Transesterification of ethyl chrysanthemate (**1a**$_{Et}$) with the benzyl alcohol **2y** has been achieved in the presence 0.1 eq. of sodium ethanolate at reflux (Scheme 60, entry a)[25] and that of methyl cypermethrinate (**1b**$_{Me}$) with an excess of 3-phenoxybenzyl alcohol (**2c**) has been carried out at 100 °C, in the presence of sodium in toluene, [58] lithium or potassium hydroxide (5-10%; Scheme 60, entries b-d), or potassium carbonate neat (Scheme 60, entry d).[142-145] Azeotropic removal of more volatile alcohols favors, as expected, the transformation (Scheme 60, compare entries b,e).[143] However little is known about the stereochemical course of these transformations.



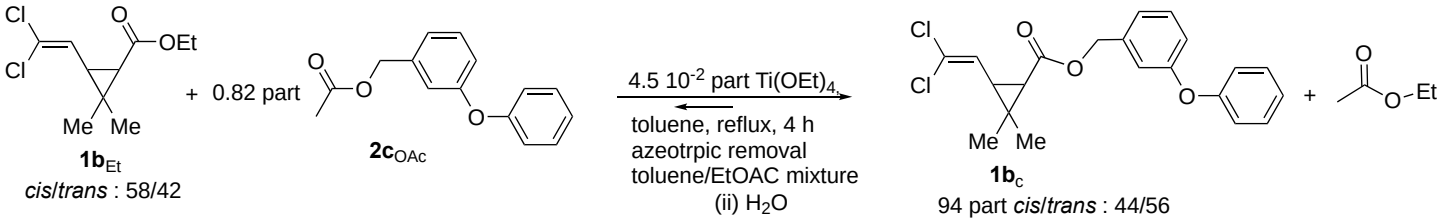
b	5% mol. $LiOH.H_2O$, neat	100°C, 12 h	98%[143]
c	10% mol. KOH, neat	100°C, 12 h	47%[143]
d	10% mol. K_2CO_3, neat	100°C, 12 h	94%[143]
e	10% mol. $LiOH.H_2O$, heptane azeotropic dist.	100°C, 3 h	98%[143]
f	5% mol. Ti(O*i*-Pr)$_4$, neat	90°C, 12 h	31%[143]
g	5% mol. Ti(O*i*-Pr)$_4$, neat	100°C, 12 h	91%[143]
h	5% mol. Sm(O*i*-Pr)$_3$, neat	100°C, 12 h	98%[143]

Scheme 60. Transesterification of methyl cypermethrinate and alcohols catalyzed by metal hydroxides, metal carbonates and metal isopropoxides.[25,143]

2.4.2.2. Synthesis of vinylcyclopropane carboxylic esters by transesterification with alcohols under Lewis acid catalysis. Transesterification has been also successfully achieved on catalysis with titanium or samarium

isopropoxides catalysts (Scheme 60, entries f-h),[111,143] Important temperature effects have been observed (Scheme 60, compare entry g to entry f).[143] Unfortunately very little is known about the stereochemical course of these transformations.

2.4.2.3. Synthesis of vinylcyclopropane carboxylic by transesterification with another ester under Lewis acid catalysis. A few examples of titanium tetraalkoxide catalyzed transesterification between two esters have been disclosed in the patent literature.[146] It is exemplified on ethyl cypermethrinate (**1b**$_{Et}$) and 3-phenoxybenzyl acetate (Scheme 61) that delivers permethrin (**1b**$_c$) in very high yield at the condition that the ethyl acetate co-produced is removed from the medium by distillation (Scheme 61).[146] The process has been reported to apply successfully to a large variety of vinylcyclopropane carboxylic esters including those derived from chrysanthemic acid and alpha-cyano and alpha-ethynyl 3-phenoxybenzyl alcohols.[146]

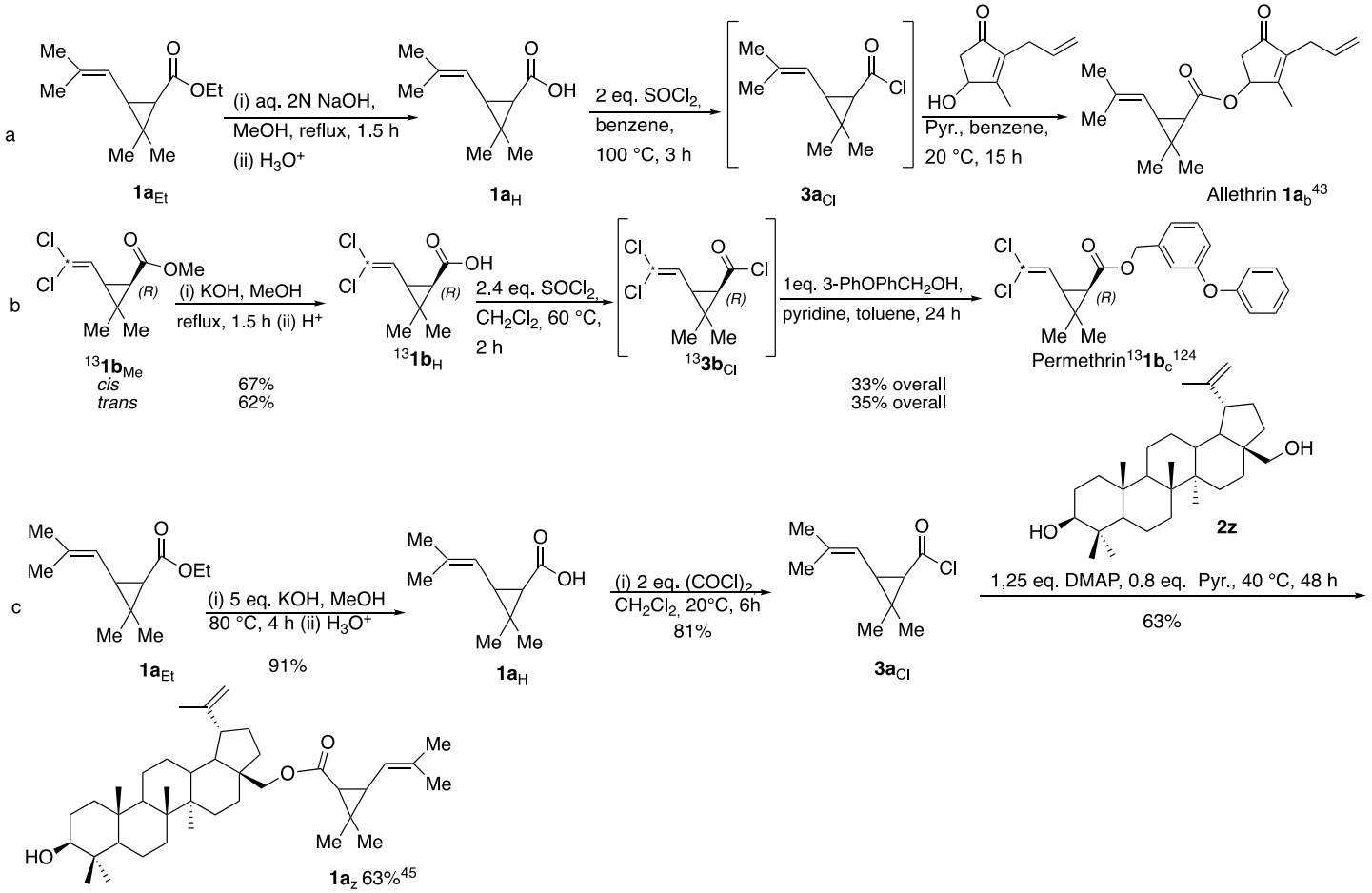


Scheme 61. Transesterification of ethyl cypermethrinate with a benzylic acetate (The amount of chemicals used is unclear).[146]

2.4.3. Multistep catalyzed transesterification reactions. As already pointed out, methyl, ethyl and *t*-butyl chrysanthemates **1a** and permethrinates **1b** and **1c** are usually the products of almost all syntheses of vinylcyclopropane carboxylates and therefore a transesterification is at least formally required to access pyrethrins and pyrethroids, especially the commercial ones. The one step transesterification involving (*S*)-allethrolone and (*S*)-3-phenoxy mandelonitrile is apparently difficult. Thus, the desired transformation has been routinely achieved via a multistep process that involves the intermediate formation of the corresponding acid chlorides and their reaction with the alcohol required to achieve the synthesis of the desired ester as already reported in Section 2.4.3.1. (Scheme 62, entry a). Most of the transformations involve at the first stage a saponification of methyl and ethyl vinylcyclopropane carboxylates and transformation of the resulting metal salts to the corresponding carboxylic acid on acidic treatment (Section 2.4.3.2., Scheme 63, entry b). A shorter approach involves the acid hydrolysis of *t*-butyl vinylcyclopropane carboxylates that directly delivers the carboxylic acid and allows a straightforward transformation (Section 2.4.3.2., Scheme 63, entry a) and an even shorter approach deals with direct transesterification reaction.

2.4.3.1. Multistep transesterification reactions involving the intermediate formation of a carboxylate. Using such strategy, the starting ester has been routinely saponified (NaOH, MeOH, reflux, 1 h), transformed to its acid chloride (thionyl chloride, pyridine-benzene[43,44,56,70] or oxalyl chloride in dichloromethane,[45] then reacted with the required alcohols to generate the pyrethroids (Scheme 62).[43,44,56,70,68]

The whole sequence has been used indistinctly (i) to transform ethyl chrysanthemate (**1a**$_{Et}$) to methyl chrysanthemate (**1a**$_{Me}$)[70] or *t*-butyl chrysanthemate (**1a**$_{tBu}$)[54] or (ii) to access allethrin (**1a**$_b$) on large scale from ethyl chrysanthemate (**1a**$_{Et}$) (Scheme 62, entry a),[43] or to produce a tiny amount of [^{13}C]-labeled *cis*- and *trans*-permethrin (^{13}**1b**$_c$) from the related labelled methyl cypermethrinate (^{13}C**1b**Me) (Scheme 62, entry b).[44]

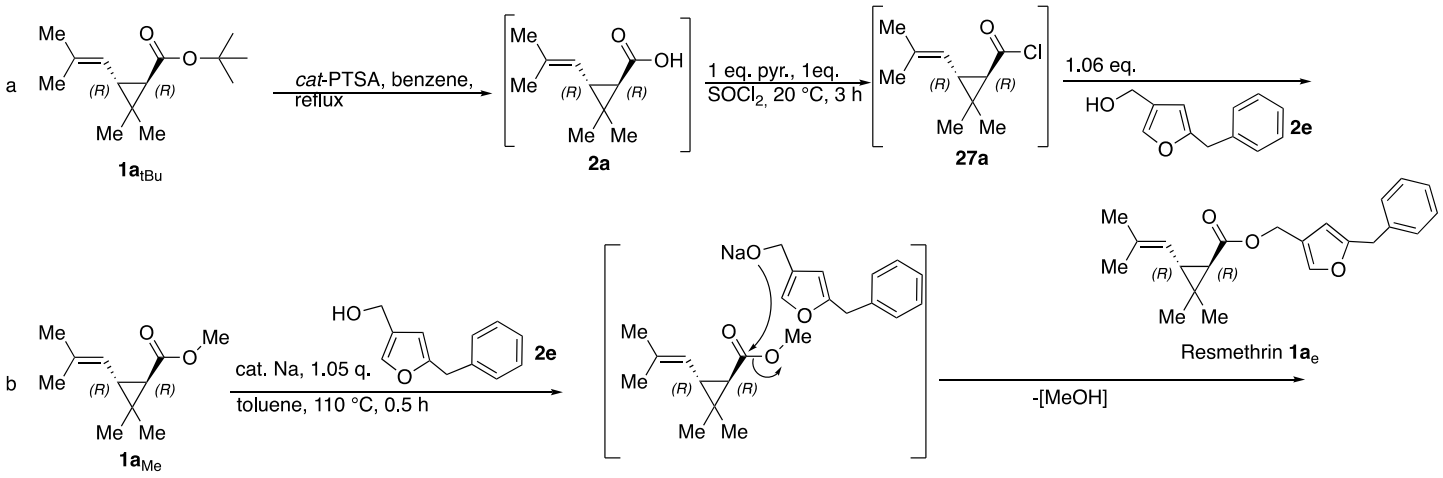


Scheme 62. Examples of multi-steps, multi-pots transesterification reactions involving acid chlorides.[43-45]

This transformation has been used, among others, for the synthesis of an ester of chrysanthemic acid (**1a**$_z$) derived from a steroidal diol **2z**. Esterification takes exclusively place on the neopentylic alcohol in the presence of a tertiary one (Scheme 62, entry c).[45]

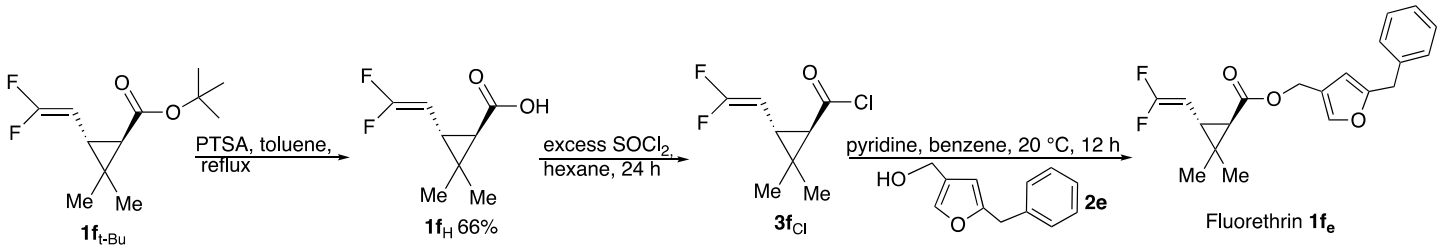
2.4.3.2. Multistep transesterification reactions involving the intermediate formation of a carboxylic acid. A much better approach uses *t*-butyl chrysanthemate as the precursor of such biologically active esters. It takes advantage of the acid catalyzed cleavage of the *t*-butyl moiety that allows one to achieve the whole transesterification in a single pot avoiding any intermediate extraction or purification.[55-57]

Thus, *t*-butyl chrysanthemate (**1a**$_{tBu}$) produces chrysanthemic acid on heating in the presence of *p*-toluenesulfonic acid (PTSA) (benzene, reflux, 2 h Scheme 63, entry a).[55-57,68] Addition of thionyl chloride in pyridine (20 °C, 2 h) then 5-benzyl-3-furfurylmethyl alcohol allows the efficient synthesis of resmethrin (**1a**$_e$) (Scheme 63, entry a).[55-57] This one-pot multistep approach has to be compared with the direct transesterification of methyl chrysanthemate that requires much higher temperature (Scheme 63, entry b).[55,57,68]



Scheme 63. Examples of multi-steps, single-pot transesterification reactions.[55,57]

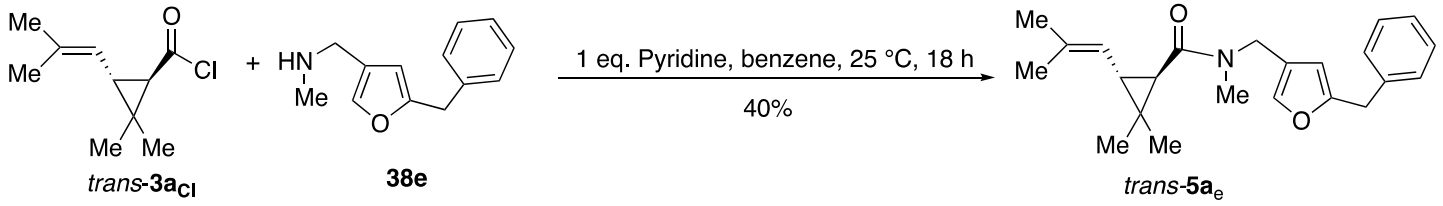
The acid catalyzed multistep transesterification reaction, reported above, proved far better anytime groups sensitive to bases are present in the starting material as for the synthesis of pyrethric esters[60] and fluorethrin (**1f**$_e$) (Scheme 64).[60]



Scheme 64. Examples of multi-step, single-pot transesterification reaction implying a *t*-butyl ester.[60]

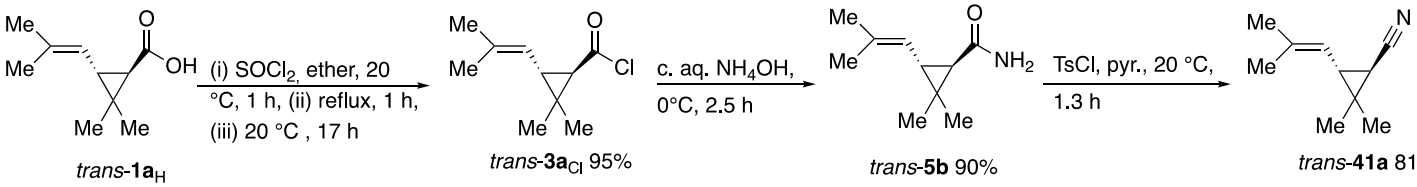
2.5. Synthesis of vinylcyclopropane carboxylic amides (Scheme 10, Route 5, Route 12)

The amidation reaction has been performed between chrysanthemic acid chloride *trans*-(**3a**$_{Cl}$) and 5-benzyl-3-furfuryl methylamine (**38e**), in the presence of a stoichiometric amount of pyridine, in order to compare the insecticidal property of the resulting amide *trans*-**5a**$_e$ to that of the related resmethrin pyrethroid (**1a**$_e$) (Scheme 65).[147]



Scheme 65. Synthesis of chrysanthemic amides from chrysanthemic acid chloride.[147]

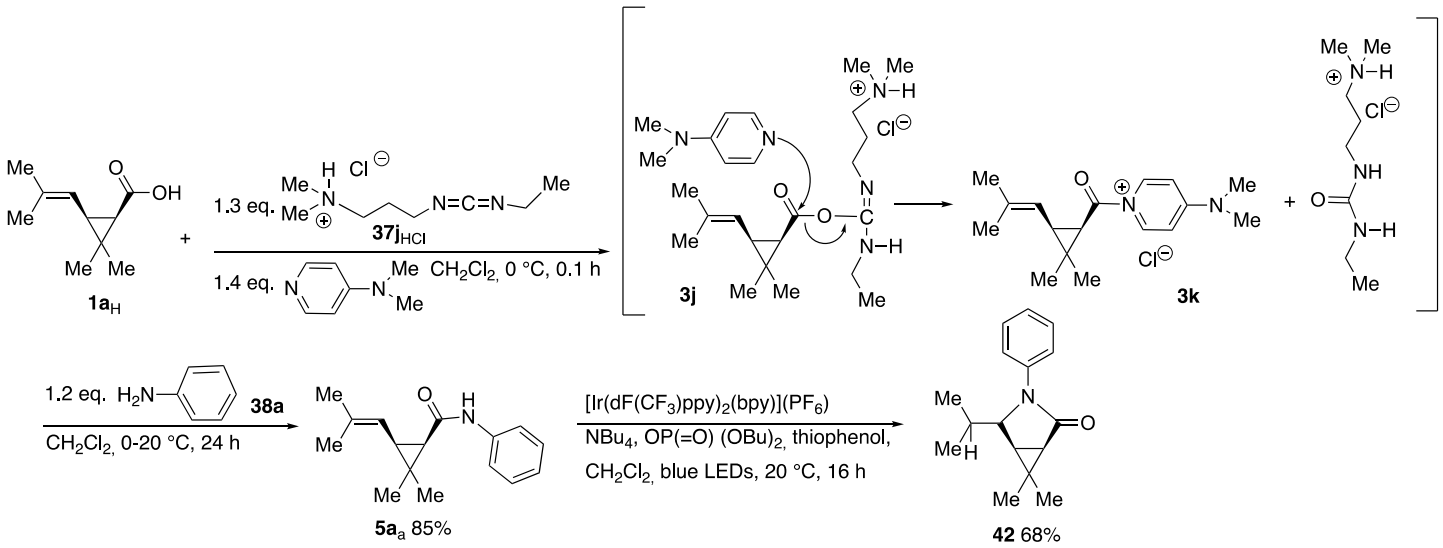
trans-Chrysanthemoyl chloride **3a**$_{Cl}$ has also been reacted with ammonia (Scheme 66)[148] and the resulting primary amide *trans*-**5b** has been then transformed to *trans*-chrysanthemonitrile 4**1a** after dehydration using *p*-toluenesulfonyl chloride (TsCl) and pyridine (Scheme 66).[148]



Scheme 66. Synthesis of chrysanthemic amides from chrysanthemic acid chloride. application to the synthesis of chrysanthemonitrile.[148]

Otherwise *cis*-chrysanthemic acid *cis*-(**1a**$_H$) (Scheme 67)[149] and *trans*-cypermethrinic acid *trans*-(**1b**$_H$) (Scheme 46, entries e,f)[126] have been transformed to amides[79,126] for example to the amide **5a**$_a$ on reaction with aniline (**38a**) after activation of their carboxyl group using (i) the water soluble *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl, (**37j**$_{HCl}$)) in the presence of DMAP (Scheme 67).[149] (**37j**$_{HCl}$) offers the advantage over dicyclohexyl carbodiimide (**37e**) (Scheme 43) to alllows easy removal of the urea by-product by water washing after the reaction[149] or (ii) tosyl- or mesyl chloride, in the presence of potassium carbonate and triethylbenzylammonium chloride (TEBAC) as the phase transfer catalyst (Scheme 46, entries e,f).

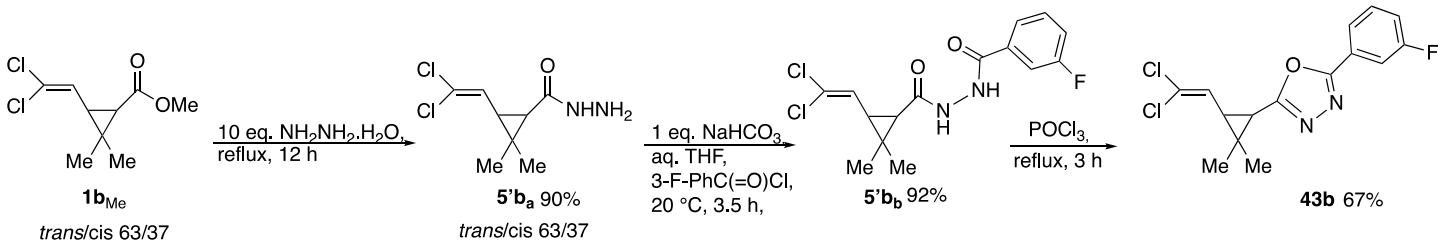
A postulated mechanism, disclosed in Scheme 67,[149] suggests the intermediate formation of the amidinium **3k** as the reactive species on which aniline reacts to produce the amide (**5a**$_a$) however direct substitution of aniline on the former intermediate **3j** cannot be precluded (See for example Scheme 69). The intermediate postulated in the reactions involving instead sulfonyl chloride is disclosed in Scheme 46, entries e,f.[126] The amide **5a**$_a$ has been subjected to iridium catalyzed lactamisation to **42** (Scheme 67).[149]



Scheme 67. Synthesis of chrysanthemic amides from chrysanthemic acid involving a carbodiimide.[149]

2.6. Synthesis of vinylcyclopropane carboxylic hydrazides (Scheme 11, Route 17)

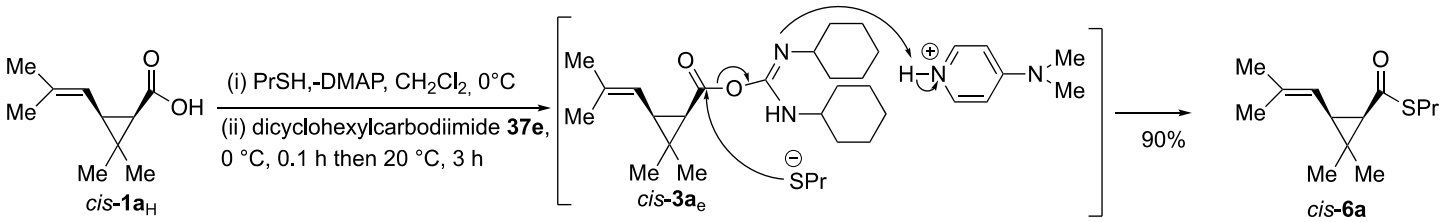
Hydrazides such as **5'b**$_a$ usually have been synthesized from the methyl and ethyl vinylcyclopropane carboxylates such as **1b** and excess of hydrazine to avoid their diacylation by the same acyl group (Scheme 68).[149-151] Subsequent reaction of hydrazides with acyl chlorides allow the synthesis of acyl hydrazides such as **5'b**$_b$ (Scheme 68). The latter on further reaction with phosphorus oxychloride lead to 1,3,4-oxadiazoles such as **43b** (Scheme 68).[149] All these compounds proved to be by far poorer insecticides than the usual pyrethroids.[149-151]



Scheme 68. Synthesis of chrysanthemic hydrazide from methyl chrysanthemate.[149]

2.7. Synthesis of vinylcyclopropyl thiolesters (Scheme 10, Route 6)

The synthesis *cis*-chrysanthemoyl propylthiolate *cis*-(**6a**) has been performed from the corresponding *cis*-chrysanthemic acid (**1a**$_H$) and *n*-propanethiol, by activation of the carboxyl group by dicyclohexylcarbodiimide in the presence of DMAP (0 °C, 0.5 h then 20 °C, 3 h, 90%, Scheme 69).[152] One of the possible mechanisms leading to *cis*-(**6a**) disclosed in Scheme 69 involves the intermediate formation of *cis*-**3a**$_e$ (Compare Scheme 69 to Scheme 67, describing an alternative mechanism on a related reaction). Thiol ester *cis*-(**6a**) on acid treatment, leads to products resulting from a cyclopropane ring opening different from that resulting from the ring opening of the related ethyl esters as it will be discussed later in this chapter (Section 5.3.2.).[152]



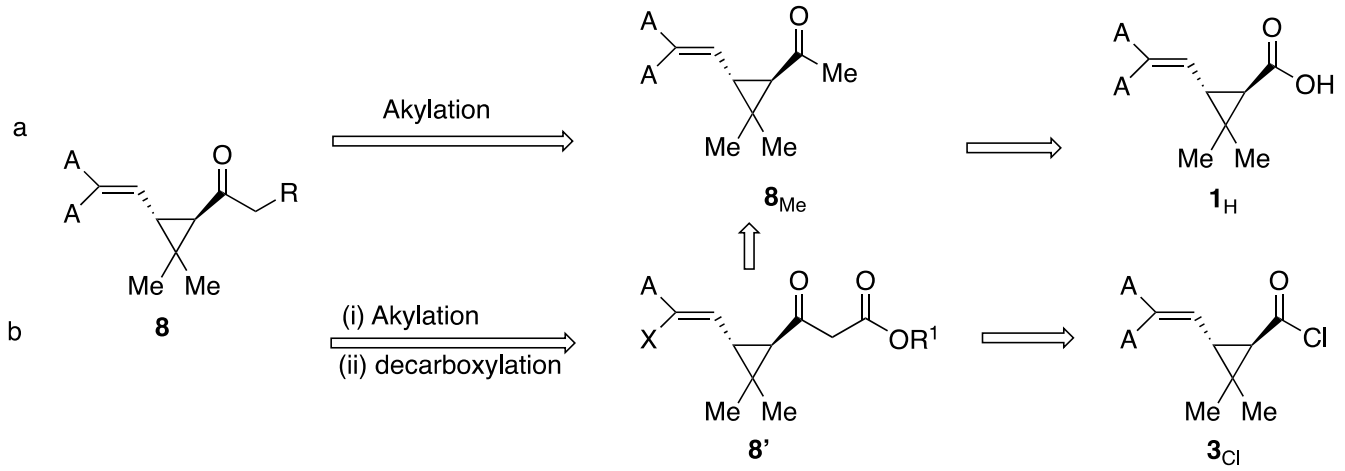
Scheme 69. Synthesis *cis*-chrysanthemoyl thiolate from chrysanthemic acid and dicyclohexyl carbodiimide.[152]

2.8. Synthesis of vinylcyclopropyl ketones (Scheme 10, Route 7)

Structural variations have been also carried out by exchanging the ester group by a keto group, especially by replacing the sp^3 oxygen by a methylene group (**8**, Scheme 10) or by inserting a methylene group between the cyclopropane ring and carbonyl group of the pyrethroids (**10**, Scheme 10). It allows access to a series of ketones isologuous to bioactive pyrethroids.[148] These have been found to possess unusual activity especially towards the larvae of the related adults.[153,154]

We will exclusively discuss in this section the reactions that generate compound **8**. The strategies used for the synthesis of these ketones are disclosed below (Scheme 70). They either involve the intermediate formation of:

(i) the related methyl ketones **8**$_{Me}$ (Scheme 70, entry a; Scheme 71,[148,154] Scheme 72,[155,156] Scheme 73[148]). The methyl ketones **8**$_{Me}$ have been in turn directly synthesized from the carboxylic acids (**1a**$_H$) (Scheme 71)[154] or (**1b**$_H$) (Scheme 71,[148] Scheme 72[155,156]) and methyllithium or on reaction of the related acid chloride **3**$_{Cl}$ with dimethyl cadmium generated from the corresponding methyl magnesium iodide and cadmium dichloride (Scheme 73),[148]

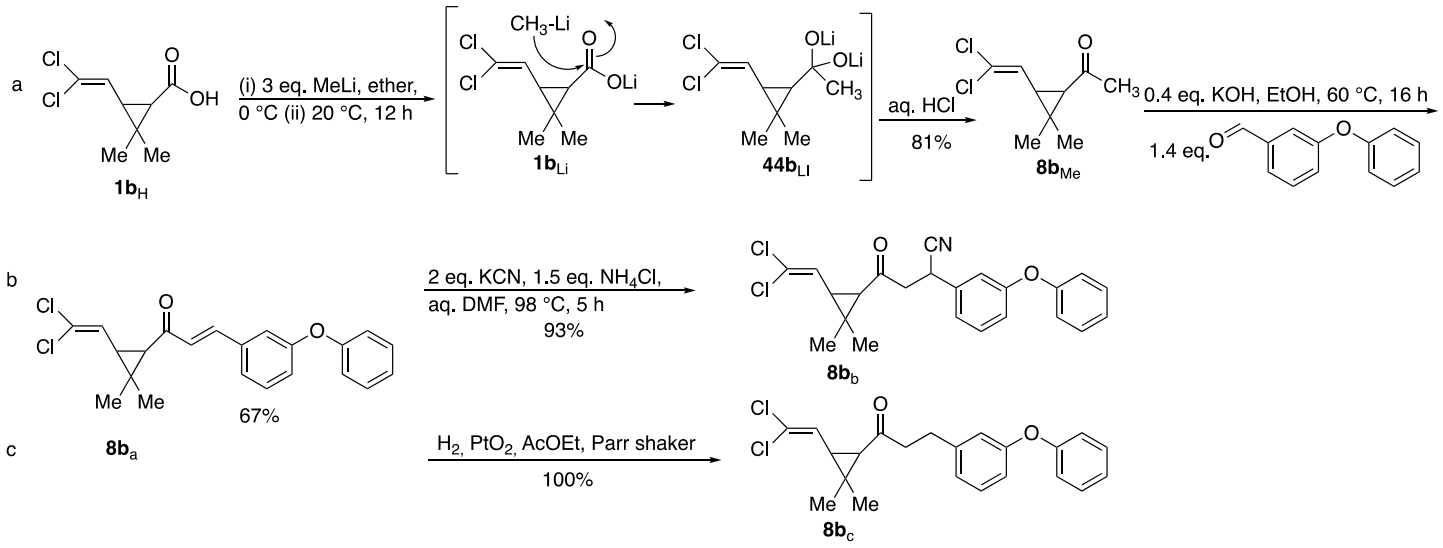


Scheme 70. Retrosynthetic analysis of chrysanthemo ketones.

(ii) the beta keto esters **8'** produced on reaction of a malonate on the carboxylic acid chlorides **27** (Scheme 70, entry c; Scheme 77) or from the carboxylic acids **1** after activation of their carboxyl (Scheme 76).[157] Note that beta keto esters have been intermediates in transformation implying methyl ketones **8'** as precursors (Scheme 70, entry b; see below Scheme 73).[148]

The different strategies used to prepare the desired isologuous ketones are disclosed in the following Schemes (see below: Scheme 71,[154] Scheme 72,[155,156] Scheme 73,[148] Scheme 74[148]) and will be discussed below.

2.8.1. Synthesis of vinylcyclopropyl ketones involving methyl ketones. The former approach is described in Scheme 71.[154] The methyl ketone **8b**$_{Me}$ has been synthesized in very high yield from the corresponding cypermethrinic acid (**1b**$_{H}$) and excess of methyllithium according to a well-known reaction, the mechanism of which is disclosed in the same scheme. It involves the intermediate formation of compound **44b**$_{Li}$ bearing two vicinal lithiumalkoxide groups at the place of the carbonyl group (Scheme 71, entry a).[158] Interestingly, base promoted HCl elimination reaction or halogen-metal exchange that could have taken place on the vinylic side chain does not compete.

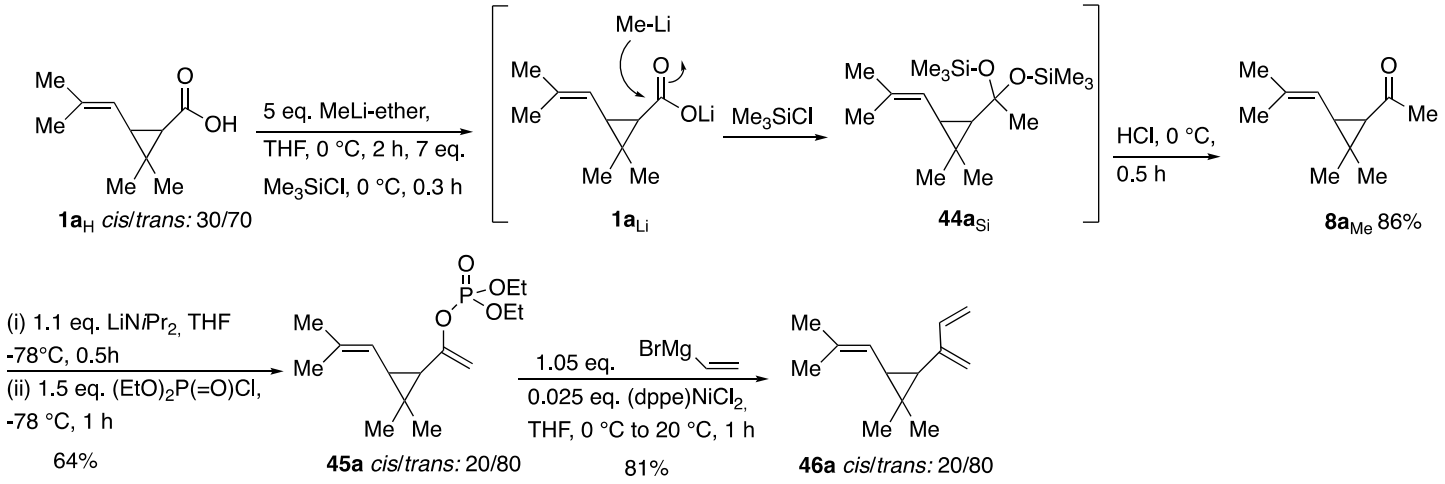


Scheme 71. Synthesis of methyl cyclopropyl ketones from cyclopropane carboxylic acids and methyllithium.[154]

Methyl ketone **8b**$_{Me}$ has been purposefully used to produce the ketones **8b**$_b$ and **8b**$_c$ analogous respectively to cypermethrin (**1b**$_d$) and permethrin (**1b**$_c$) in which the sp^3 oxygen atoms of the esters have been replaced by methylene groups (Scheme 71, entry a). **8b**$_b$ and **8b**$_c$ have been found to be potent pesticides when used to control or combat important agricultural pests.[154]

The latter transformations have been effectively achieved by potassium hydroxide promoted condensation between the methyl ketone **8b**$_{Me}$ and 3-phenoxybenzaldehyde leading to the enone **8b**$_a$ (Scheme 71, entry b),[154] followed by addition of (i) potassium cyanide leading to **8b**$_b$ (Scheme 71, entry b) or (ii) dihydrogen catalyzed by platinum leading to **8b**$_c$ (Scheme 71, entry c).[154]

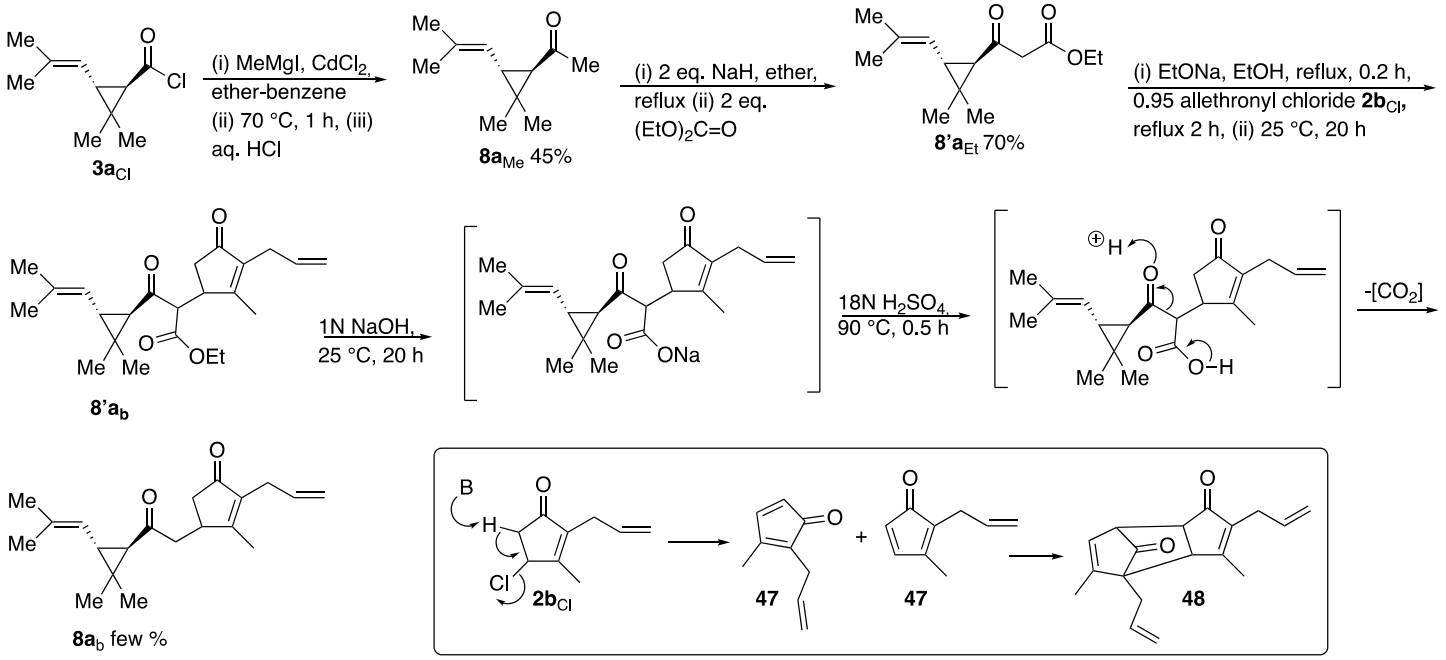
A related reaction using methyllithium has been performed on chrysanthemic acid (**1a**$_H$) and leads to the methyl ketone **8a**$_{Me}$ (Scheme 72).[155] It involves the use, besides methyllithium, of trimethylsilyl chloride that is expected to trap the intermediate to provide the more stable bis-silyloxy acetal intermediate **44a**$_{Si}$, the precursor of methyl ketone **8a**$_{Me}$ on acid hydrolysis (Scheme 72).[155,156] This method has been proposed to avoid the undesired concomitant formation of a tertiary alkyl carbinol. The latter would have resulted from the action of methyllithium on **8a**$_{Me}$, that is formed by the *in situ* decomposition of **44a**$_{Li}$ when the addition of methyllithium to the carboxylic acid (**1a**$_H$) is too rapid (Scheme 71).[155]



Scheme 72. Synthesis of methyl cyclopropyl ketones from cyclopropane carboxylic acids, methyllithium and trimethylsilyl chloride.[155]

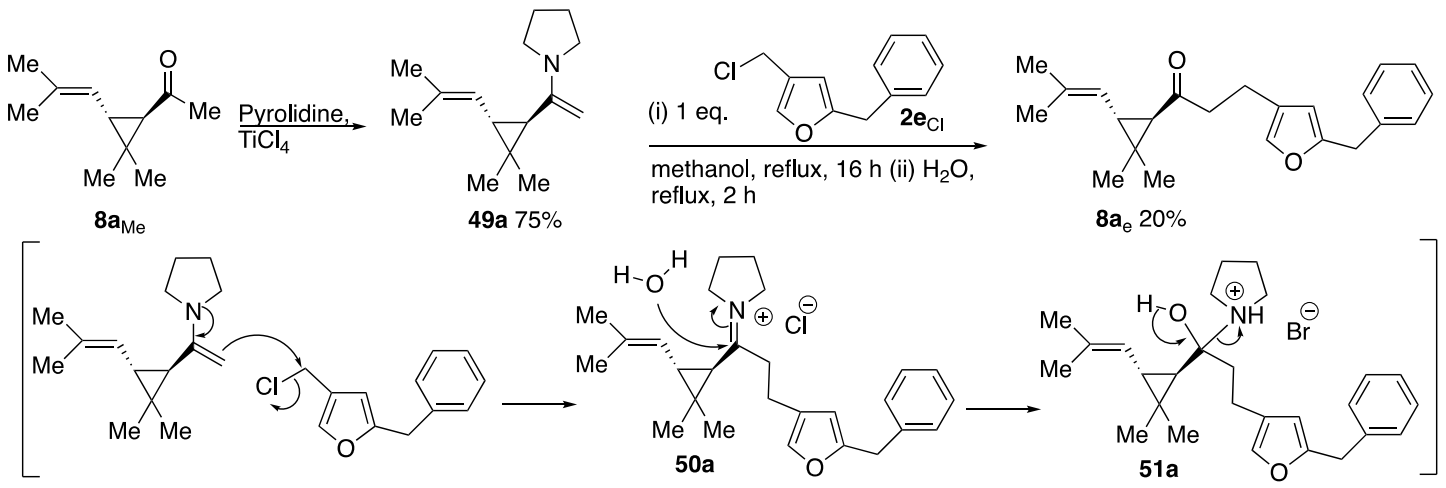
Another synthetic method involves the reaction of "dimethyl cadmium" (from methylmagnesium iodide and cadmium dichloride in diethyl ether)[159] with chrysanthemoyl chloride (**3a**$_{Cl}$) (Scheme 73).[148] The resulting methyl ketone **8a**$_{Me}$ has been then transformed to the corresponding β-keto ester **8'a**$_{Et}$ that is then alkylated to produce for example **8'a**$_b$ when alkylated with 4-chloroallethrone (**2b**$_{Cl}$) (from allethrolone and phosphorus trichloride in 60% yield).[148] The alkylation reaction competes with the elimination producing a stereoisomeric mixture of the cyclopentadienone dimer **48** that are conveniently removed at the next saponification stage from the resulting sodium carboxylate (Scheme 73).[148] Acidification followed by decarboxylation leads, in very poor overall yield, to the ketone **8a**$_b$, the structure of which is related to allethrin (**1a**$_b$) (Scheme 73).[148]

An alternative and straightforward approach to vinylcyclopropyl ketones uses the alkylation of enamine derived from the methyl ketones **8a**$_{Me}$ as a key step (Scheme 73). This strategy originally disclosed by Stork [160,161] as an excellent substitute to the alkylation of enolates, has been successfully applied to the synthesis of ketone **8a**$_e$, the structure of which, disclosed in Scheme 74, is isologous to that of resmethrin insecticide (**1a**$_e$).



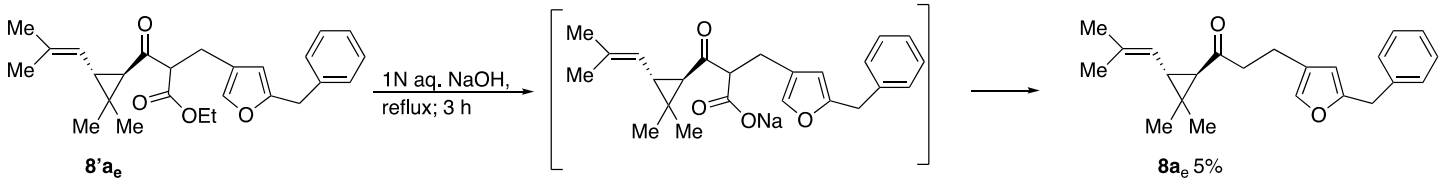
Scheme 73. Synthesis of methyl cyclopropyl ketones from cyclopropane carboxylic acid chlorides and dimethyl cadmium.[148,159]

The synthesis of the pyrrolidine enamine **49a** has been efficiently achieved (75% yield) by condensation between the methyl ketone **8a**$_{Me}$ and pyrrolidine using titanium tetrachloride in pentane to abstract water (Scheme 74).[148] Its reaction with 5-benzyl-3-furfuryl chloride (**2e**$_{Cl}$) has been carried out in methanol, a polar solvent expected to favor the required C-alkylation over the competing N-alkylation reaction.[160,161] Hydrolysis of the iminium intermediate **50a** provides the ketone **8a**$_e$ in quite poor yield (20%) probably due this competing N-alkylation reaction (Scheme 74). The different intermediates involved in this process are disclosed in Scheme 74.[148] It has been noticed[148] that the "enamine route" does not allow the synthesis allethronyl ketone **8a**$_b$, (Scheme 73) since the dimer **48** concomitantly formed as by-product in the related reaction cannot be separated as reported above (Scheme 73).



Scheme 74. Alkylation of methyl cyclopropyl ketones through an enamine.[148]

The route disclosed in Scheme 73 for the synthesis of ketone **8a**$_b$ from the methyl ketone **8a**$_{Me}$ through the keto ester **8'a**$_{Et}$ has been also applied to the synthesis of ketone **8a**$_e$ (Scheme 75).[148] However the related alkylated keto ester **8'a**$_e$ proved to be more resistant to hydrolysis than the corresponding allethronyl derivative **8'a**$_b$ and remains unaffected on reaction with 1N sodium hydroxide at 25 °C.[148] Performing the reaction at 100 °C for 3 hrs transforms directly **8'a**$_e$ to the decarboxylated ketone **8a**$_e$ but in extremely poor yield (5%, Scheme 75).[148]

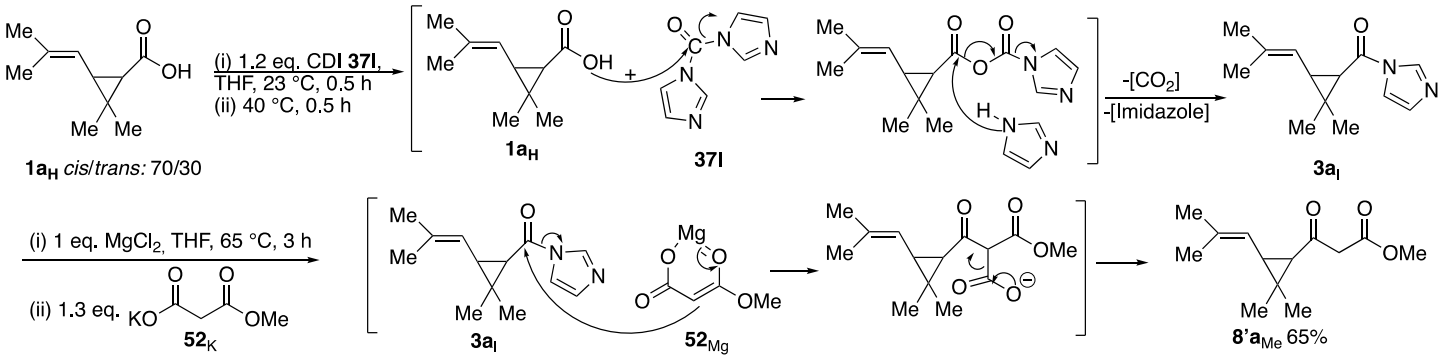


Scheme 75. Demethoxy decarboxylation of beta-ketoesters to ketones.[148]

2.8.2. Synthesis of vinylcyclopropyl ketones imbedded in a beta-keto ester. The approach (Scheme 70, entry b), that use beta-keto esters **8'** as intermediates offers the advantage of a smooth alkylation reaction but requires a decarboxydealkoxylation process to achieve the synthesis of the desired homologated ketone. The latter reaction proved quite difficult to perform in the case of allethronyl ketone **8a**$_b$ (Scheme 73)[148] and furfuryl ketone **8a**$_e$ (Scheme 75).[148]

A few other methods have been devised to synthesize beta-keto esters **8'**. These involve the condensation of a metal acetyl acetonate **52**$_M$ (Scheme 76) or the Meldrum's acid (pK_a 4.97) in the presence of pyridine (Scheme 77)[162] with an activated vinylcyclopropane carboxylic acid (**1**$_H$) such as chrysanthemoyl imidazolate **3a**$_I$ generated in situ from chrysanthemic acid and carbonyl diimidazole **37i** (CDI, Scheme 76),[157] according to a Masamune procedure[163] or acyl chlorides **3a**$_{Cl}$ and **3b**$_{Cl}$ derived from chrysanthemic and cypermethrinic acids, respectively (Scheme 77).[153]

The first approach that has been carried out on chrysanthemoyl imidazolate (**3a**$_I$) and magnesium acetylacetonate **52**$_{Mg}$ delivers in one-pot the methyl beta-ketomalonate **8'a**$_{Me}$ in fair yield from chrysanthemic acid (**1a**$_H$) (Scheme 76).[157]

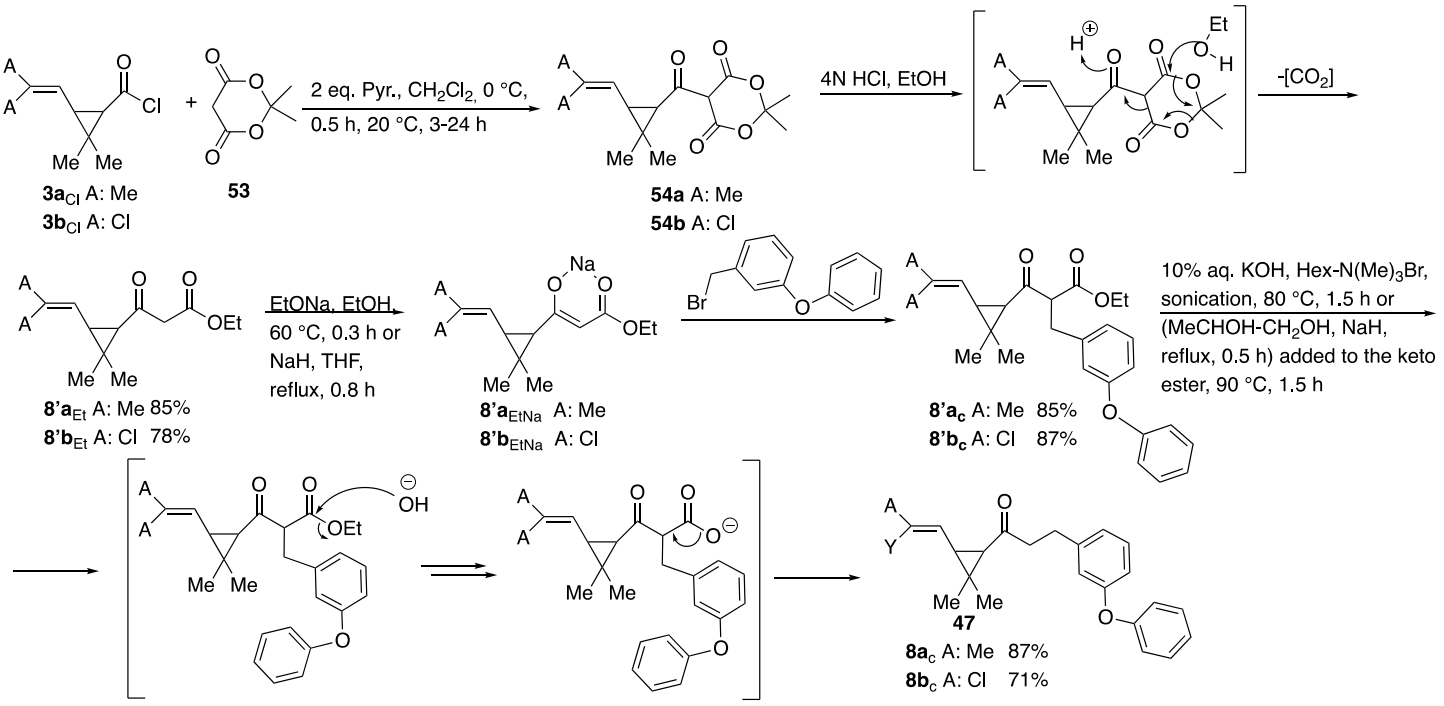


Scheme 76. From chrysanthemic acid to to the related beta-ketoester.[157]

The route involving Meldrum's acid reported in Scheme 77 allows the synthesis of ketones **8a**$_c$ and **8b**$_c$, the structures of which are isologuous to those of phenothrin (**1a**$_b$) and permethrin (**1b**$_c$) (Figure 2). [153] Reaction of the acid chlorides **3a**$_{Cl}$ and **3b**$_{Cl}$ with Meldrum's acid [162] in the presence of pyridine allows the synthesis of

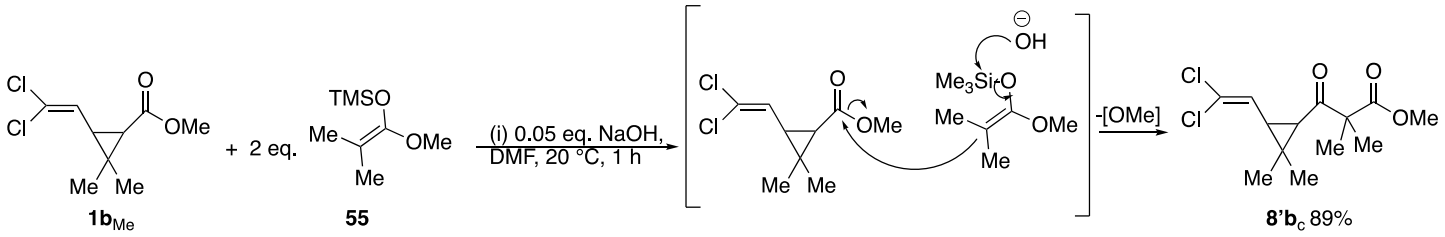
acylated Meldrum's acids **54a** and **54b**. The latter on reaction with ethanol in acidic medium delivers the beta-keto esters **8'a**$_{Et}$ and **8'b**$_{Et}$ in very decent yields (Scheme 77).[153] Alkylation of the related sodium enolate **8'**$_{EtNa}$ generated using sodium ethoxide in ethanol or sodium hydride in THF with 3-phenoxybenzyl bromide (**2c**$_{Br}$) is achieved in excellent yield although some dialkylation also takes place.

The authors[153] apparently experienced the same problems in the conversion of the alkylated beta-keto esters **8'a**$_{Et}$ and **8'b**$_{Et}$ to the related desired ketones **8a**$_c$ and **8b**$_c$ as already discussed for **8a**$_e$ from **8a**$_e$ (Scheme 75).[148] Several literature methods for decarboethoxylation proved to be unsatisfactory.[153] This is the case of the one involving pyrolysis,[164] or dealkylation using for example a nucleophile such as sodium chloride in a polar solvent.[165-16] The method of Mills[170] that employs aqueous potassium hydroxide in the presence of decyltrimethylammonium bromide as phase transfer catalyst in heptane, performed under sonication however allows the synthesis of the ketones **8a**$_c$ and **8b**$_c$ in good yields (80 °C for 1.5 h, Scheme 77).[153] Another method that instead uses 1,2-dihydroxypropane and sodium hydride under sonication proved to be equally efficient (Scheme 77).[153] The process disclosed in Scheme 77 applied to 5-benzyl-3-furfuryl chloride (**2e**$_{Cl}$) leads to the vinylcyclopropyl ketones **8a**$_e$ and **8b**$_e$ in similar good yields.[153]



Scheme 77. Reaction of vinylcyclopropane carboxylic chlorides with Meldrum acid on the way to vinylcyclopropyl ketones.[153]

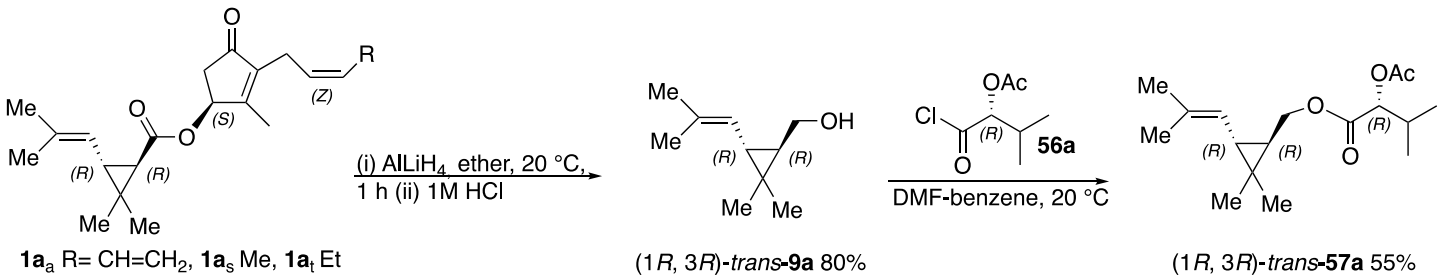
Another approach involves the sodium hydroxide catalyzed crossed-Claisen condensation of the ketene silyl acetal **55** with methyl cypermethrinate (**1b**$_{Me}$) (Scheme 78).[171] It provides access, in excellent yield, to the beta-keto ester **8'b**$_c$ possessing a dimethyl-substituted alpha-carbon, a type of substructure usually difficult to synthesize.[171]



Scheme 78. From methyl cypermethrinate to a related beta-keto ester involving ester silylenolates.[171]

2.9. Synthesis of chrysanthemol (Scheme 10, Route 8)

The synthesis of *cis*- and *trans*-chrysanthemol (**9a**) usually has been carried out by reduction of chrysanthemic acid[172] or its esters usually with lithium aluminum hydride.[74,83,173,174] This is for example the case of the (1*R*, 3*R*)-*trans*-chrysanthemol (1*R*, 3*R*)-*trans*-(**9a**) produced in 80% by reduction of a purified mixture of pyrethrins I (**1a**$_a$), cinerin (**1a**$_s$) and jasmolin (**1a**$_t$) extracted from pyrethrum (*Tanacetum cinerariifolium,* 25%), and transformed into citrophilus mealybug sex pheromone **57a** on esterification with (*R*)-2-acetoxy-3-methyl butenoyl chloride **56a** (Scheme 79).[174]

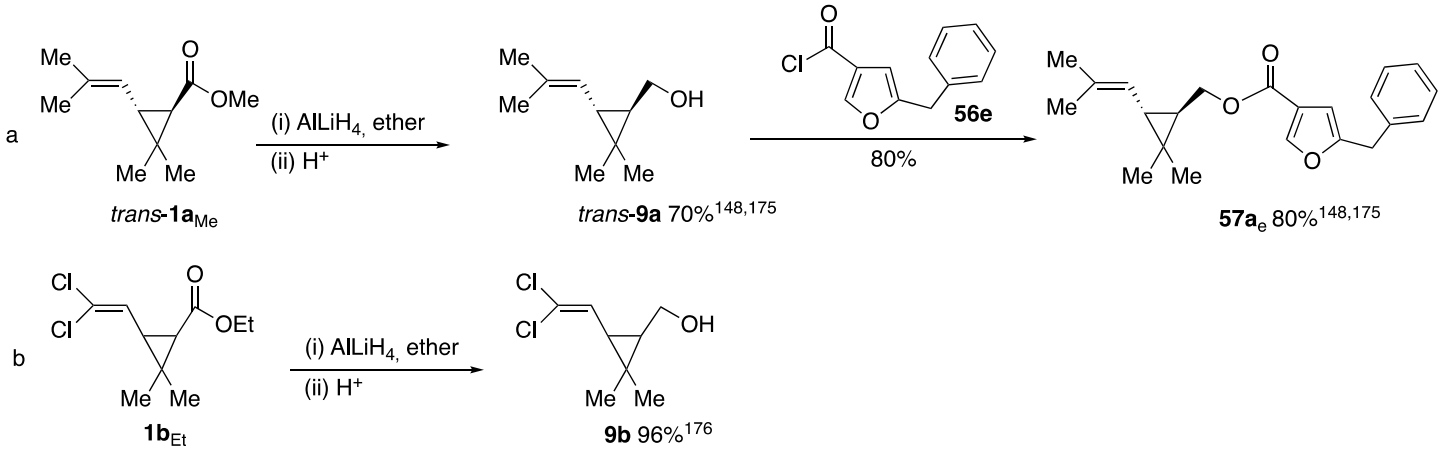


Scheme 79. Synthesis of citrophilus mealybug sex pheromone using chrysanthemol extracted from pyrethrum.[174]

Otherwise, methyl *trans*-chrysanthemate *trans*-(**1a**$_{Me}$)[74,148,175] including its (1*R*,3*R*)-stereoisomer (1*R*,3*R*)-(**1a**$_{Me}$)[175] and its ethyl analog *trans*-(**1a**$_{Et}$)[83] on reaction with lithium aluminum hydride produces, after hydrolysis, the corresponding *trans*-chrysanthemol *trans*-(**9a**). The latter has been used as precursor of the resmethrin isologue **57a**$_e$[148] that has been found to be devoid of insecticidal properties (Scheme 80, entry a).[148] This reduction has been successfully extended to ethyl cypermethrinate (**1b**$_{Et}$) that leads to cypermemethrinol (**9b**) almost quantatively (Scheme 80, entry b).[176]

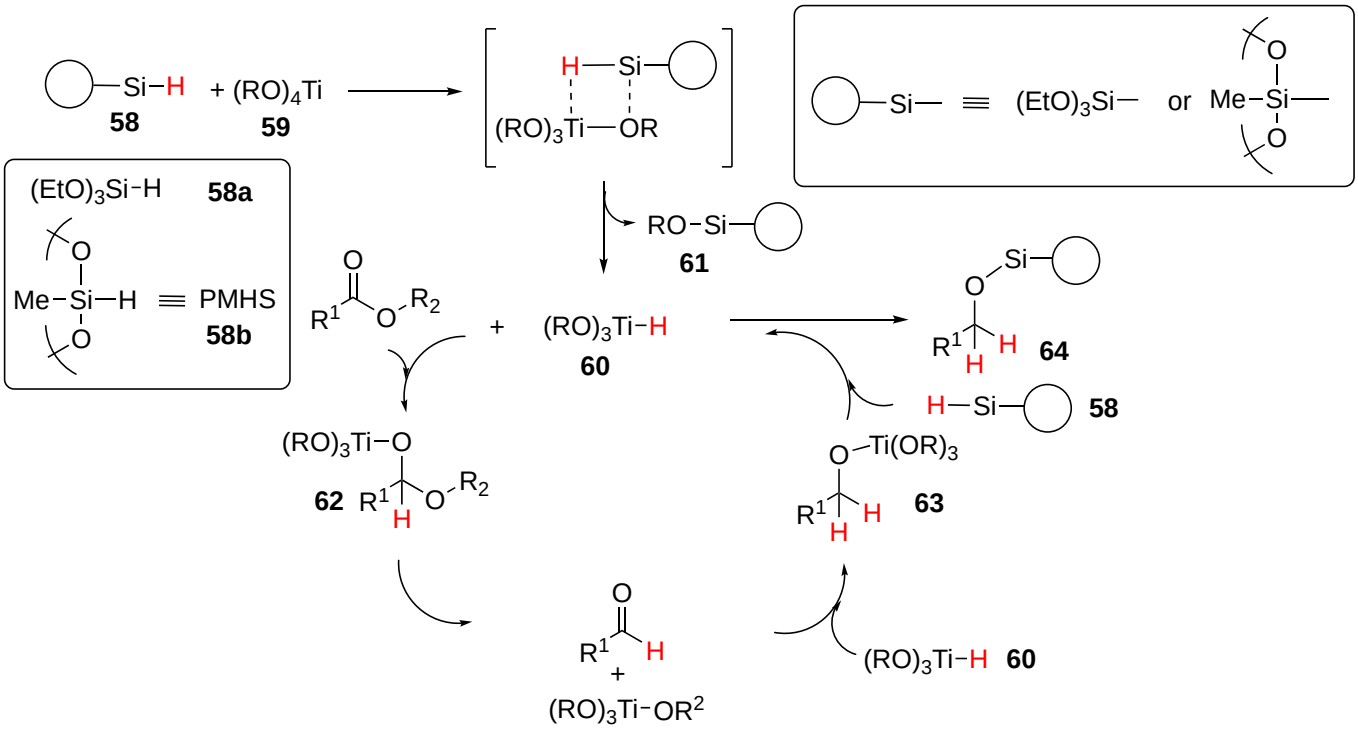
Ethyl chrysanthemate (**1a**$_{Et}$) has been also reduced to chrysanthemol (**9a**) using diisobutylaluminium hydride (DIBAL-H).[177] However both lithium aluminum hydride and DIBAl-H are unsuitable for large scale reactions required in industry due to their flammability, the danger to manipulate solid pyrophoric material in the first case and by their cost.

Hydrosilylation proved to be a good alternative, but requires the use of a transition metal catalyst. Good results have been disclosed by the teams of Buchwald [178-180] and Lawrence[181] who used triethoxysilane (**58**a) or better polymethylhydroxysiloxane (PMHS) **58b** as effective reducing agent in the presence of titanium catalysts.



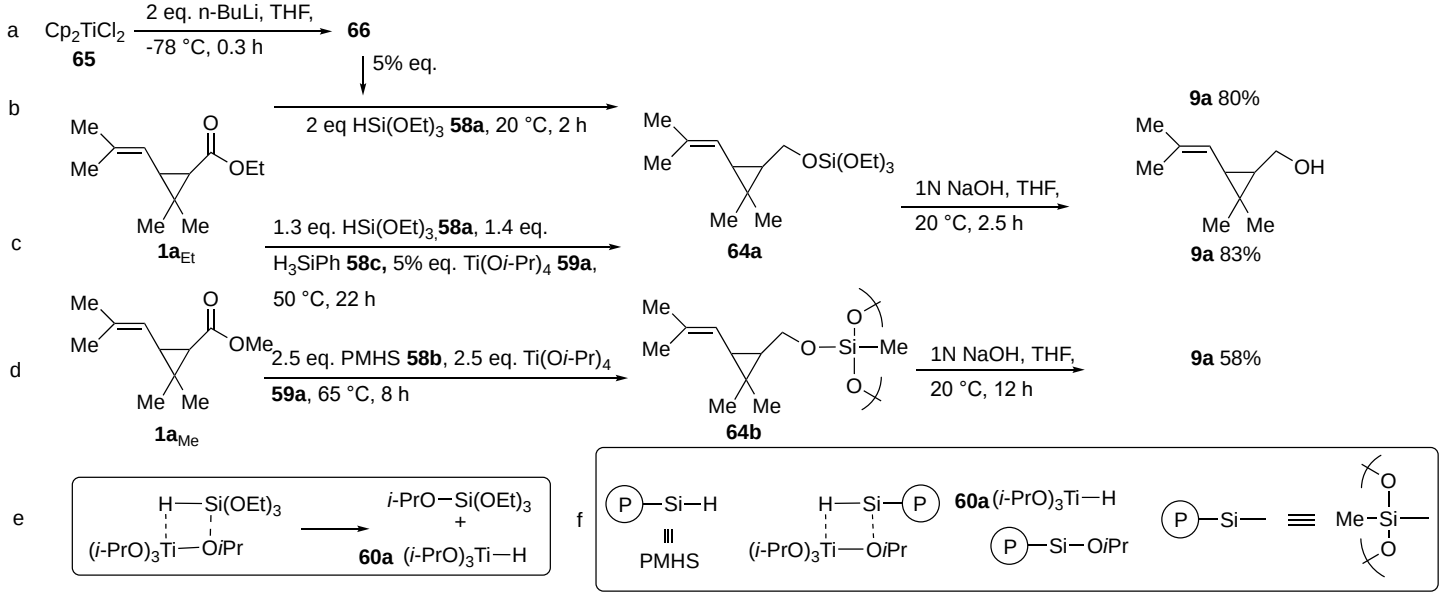
Scheme 80. Synthesis of vinylcyclopropanols from related esters and lithium aluminum hydride.[148,175,176]

The reactive species is presumably a titanium hydride such as **60** resulting from a metathesis reaction between the silanol **58** and the titanium tetraalkoxide **59** (Scheme 81). The reaction of **60** with alkyl chrysanthemates $\mathbf{1a}_R$ delivers the silylated alcohols **64** as postulated in the mechanism disclosed in Scheme 81. The latter on reaction with 1N aqueous sodium hydroxide leads to the corresponding alcohol (**9a**) (Scheme 82).



Scheme 81. Postulated mechanism of reduction of aldehydes by triethoxsilanes involving dichlorotitanocene as precatalyst.[181]

The original transformation applied to ethyl chrysanthemate ($\mathbf{1a}_{Et}$) uses two equivalents of triethoxysilane **58a** and no more that 5% of a catalyst **66** resulting from the reaction of dichlorotitanocene **65** (Cp_2TiCl_2) with two equivalents of butyllithium (Scheme 82, entries a,b).[178]

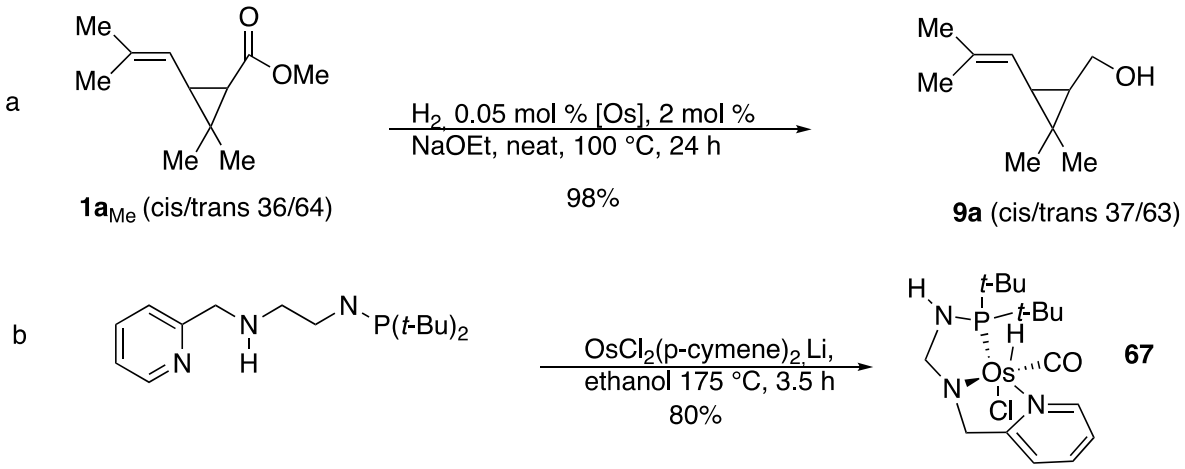


Scheme 82. Reduction of alkyl chrysanthemates by triethoxysilane in the presence of a titanium catalyst.[178-180]

Improvement of this method uses the much cheaper and commercially available titanium(IV) tetraisopropoxide (**59a**) to replace the dichlorotitanocene-butyllithium couple (Scheme 82, entry c).[179] This modification requires however to carry out the transformation at higher temperature and for longer time and since, as with aromatic esters, the reduction stops short of completion with 2 eq. of alkoxysilane **58**, it requires the concomitant use of $PhSiH_3$ (**58c**), possessing a more reactive Si-H bond, (Scheme 82, entry c).[179]

A subsequent improvement in terms of reduced toxicity and reagent cost involves the replacement of triethoxysilane (**58a**) by polymethylhydroxysiloxane (PMHS) **58b**[181,180] as the stoichiometric reductant (Scheme 82, entry d).[180] The transformation however requires compared to the one disclosed in Scheme 82, entry c, a higher amount of the titanium tetraisopropoxide **59a** pre-catalyst (1 equivalent instead of 5%), a higher temperature (65 °C instead of 20 or 50 °C), and delivers chrysanthemol (**9a**) in poorer yield (58 instead of 83%).[180] Competing cyclopropane ring opening that could have been initiated by a titanium species acting as an acid catalyst or radical promotor has never been observed.[180]

An even more straightforward route to chrysanthemol (**9a**) from methyl chrysanthemate (**1a**$_{Me}$) uses dihydrogen (50 bar, 100 °C, 24 h, Scheme 83, entry a) in presence of catalytic amounts of the readily available osmium complex **67** (0.05 mol%, prepared as disclosed in Scheme 83, entry b) and sodium ethoxide (2 mol%).[182] Chrysanthemol is produced in almost quantitative yield (98%) with complete chemo- and and stereo control (no reduction of the C=C double bond; similar *cis*/*trans* ratio 37/63 in the starting material and in the product). The osmium complex **67** is one of the rare catalysts that allow the chemoselective dihydrogenation of unsaturated esters to the corresponding unsaturated alcohols without reduction or isomerization of their C=C double bond.[182] **67** is readily available (Scheme 83, entry b), air stable and only tiny amount of catalyst is needed.[182] It should be mentioned that although the reduction of methyl chrysanthemate to chrysanthemol went smoothly, it requires a quite long time to reach complexion. This differentiates it from the other examples disclosed[182] in the same publication such as that of ethyl 10-undecanoate to 10-undecanol that requires only 4 h using 0.01 mole % catalyst (compared to 24 h and 5 time more catalyst).[182]



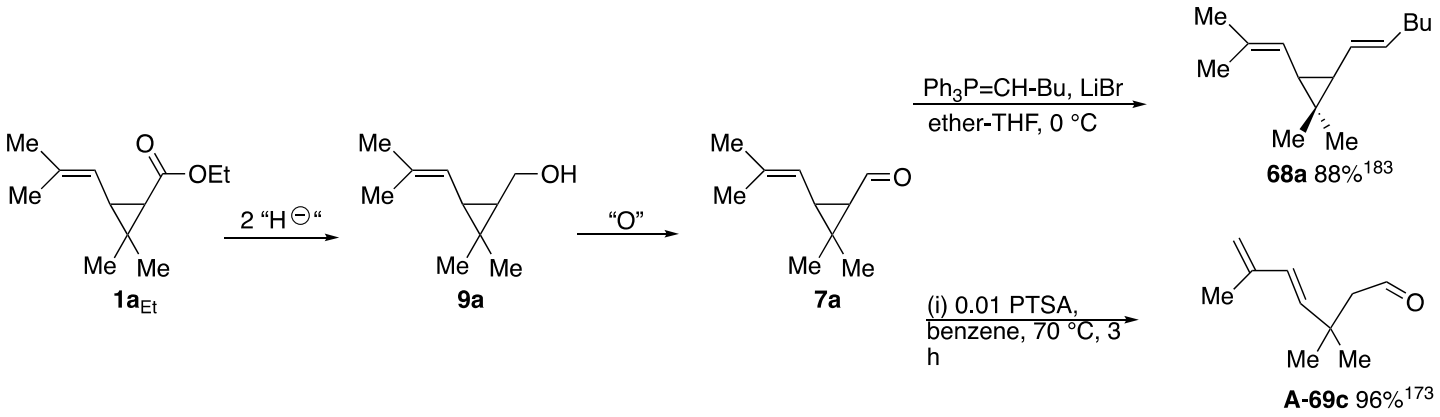
Scheme 83. Synthesis of chrysanthemol from methyl chrysanthemate dihydrogen and an osmium catalyst.[182]

2.10. Synthesis of chrysanthemal (Scheme 10, Route 14)

The synthesis of vinylcyclopropane carboxaldehydes **7** from the corresponding acid (**1a**$_H$) or esters **1a**$_R$, has not been usually carried directly but through the intermediate formation of the vinylcyclopropyl carbinols **9**. Chrysanthemal (**7a**) that has been used at several occasions as the precursor of:

(i) the diene **68a** that smells like lichen and resembles the odoriferous dictyopterene (ocean's smell) on subsequent Wittig olefination reaction,[183] or related olefination reactions such as the Horner-Wadsworth-Emmons reaction leading to an *E*-alpha,beta unsaturated esters[177] or the Ramirez reaction leading to a dibromo-vinyl derivative reminiscent to deltamethrinic acid**.**[172]

(ii) the dienal **A**-**69c** possessing the artemisil skeleton **A** on acid catalysis leading to the sex pheromone of the sandfly, *Lutzomyia longipalpis*, vectors the causative agent of visceral leishmaniasis in the new world.[173]

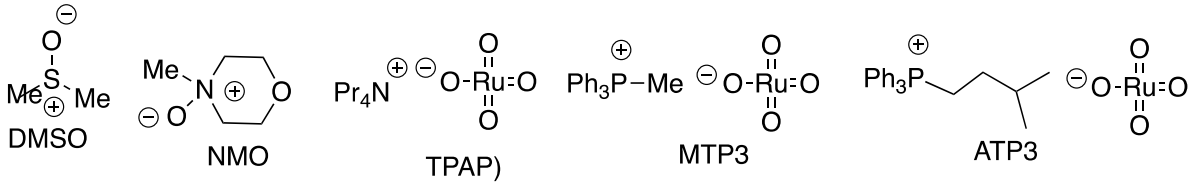


Scheme 84. Chrysanthemal uses.[183,173]

cis- and *trans*-chrysanthemal (**7a**) have been synthesized stereoselectively from the related chrysanthemol (**9a**) using several oxidants including activated manganese dioxide (Scheme 85, entries a,b), [177,183] silver carbonate, the Fetizon's regent (Scheme 85, entries c,d),[183] oxalyl chloride and dimethyl sulfoxide (DMSO, the Swern oxidation protocol; see below, Scheme 88, entry e)[172] and catalytic amounts of tetraalkylammonium perruthenates and substoichiometric amount of *N*-methyl morpholine *N*-oxide (NMO) (the Ley-Griffith protocol; Scheme 85, entries f,g,h,i).[173,184]

In some cases, the synthesis of chrysanthemal (**7a**) has been achieved from chrysanthemic acid or one of its esters avoiding isolation of the intermediate chrysanthemol (**9a**).[172] In all the cases the yields are over 70% and except the Swern reaction (Scheme 85, entry e) all methods involve metals. Among those only the Ley-Griffith protocol involving tetrapropyl ammonium perruthenate (TPAP) and related reagents involving phosphonium salts instead (MTP3 or ATP3) use catalytic amounts of metallic compounds (Scheme 85).

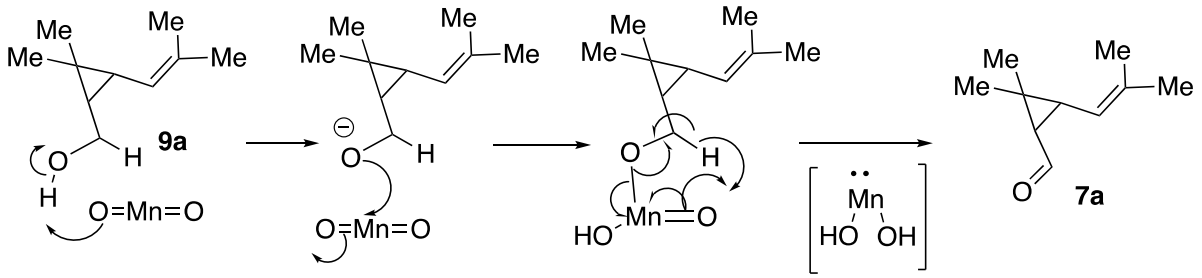
a	*cis*-**9a**	40 eq. MnO_2, hexane, 20 °C, 24 h	70 %[183]
b	*trans*-**9a**	40 eq. MnO_2, hexane, 20 °C, 24 h	75 %[183]
c	*cis*-**9a**	10 eq. Ag_2CO_3, benzene, reflux, 8 h	80 %[183]
d	*trans*-**9a**	10 eq. Ag_2CO_3, benzene, reflux, 8 h	75 %[183]
e	(1*R*,3*R*)-*trans*-**9a**	(i) 1.5 eq. $(COCl)_2$, 2.3 eq. DMSO, CH_2Cl_2, -78 °C, 1 h (ii) 5 eq. NEt_3, -78°C, 1h, -78 °C to 20 °C, 0.5 h	80 %[172]
f	*trans*+*cis*-**9a**	0.02 eq.TPAP, 2 eq. NMO, 4A M.S., CH_2Cl_2, 20 °C, 12 h	94 %[173]
g	*trans*+*cis*-**9a**	0.05 eq.TPAP, 1.5 eq. NMO, 4AMS, 20 °C, 0.5 h	76 %[184]
h	*trans*+*cis*-**9a**	0.05 eq. MTP3 1.5 eq. NMO, 4AMS, 20 °C, 0.5 h	92 %[184]
i	*trans*+*cis*-**9a**	0.05 eq.ATP3, 1.5 eq. NMO, 4AMS, 20 °C, 0.5 h	85 %[184]



Scheme 85. Oxydation of chrysanthemol to chrysanthemal using various reagents.[172,173,183,184]

2.10.1. Manganese dioxide oxidation of chrysanthemol. Manganese dioxide oxidation merits further comment (Scheme 85, entries a,b, Scheme 86).[183,185] The reagent generated from manganous sulfate, sodium hydroxide, and potassium permanganate or commercially available needs to be activated before use.[186] The reaction is best achieved in benzene by azeotropic removal of water, concomitantly produced, using in a Dean-Stark.[186,187] It has been for example described[177] that oxidation of *trans*-chrysanthemol (**9a**) to the corresponding *trans*-chrysanthemal (**7a**), carried out in dichloromethane without water removal requires 3 days and another day with fresh reagent to go to completion instead of 24 h (compare to Scheme 85, entry b).

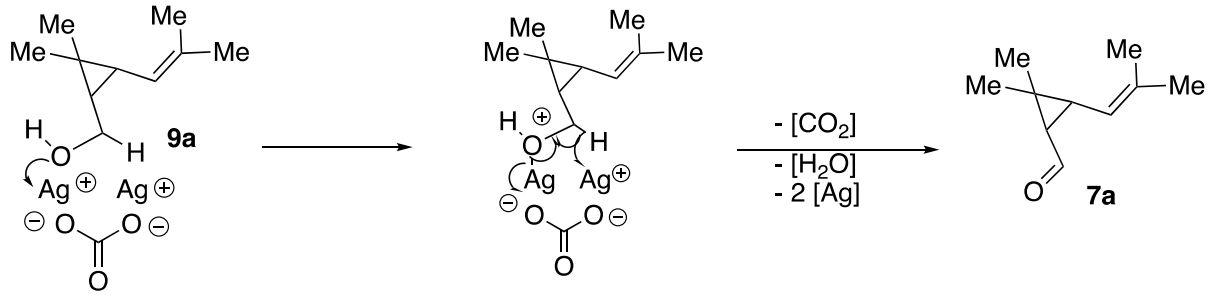
Usually the manganese oxidation is exclusively restricted to unsaturated alcohols such as benzylic-, allylic and propargylic alcohols and presumably, the successful oxidation of cyclopropyl carbinols could be due to the presence of banana bonds in the three-membered cycle (Scheme 14, section 1.2.2.2.). The suggested mechanism of action is disclosed in Scheme 86.



Scheme 86. Postulated mechanism implied in the oxidation of chrysanthemol to chrysanthemal by manganese dioxide.

2.10.2. Silver Carbonate oxidation of chrysanthemol. The reaction involving silver carbonate, discovered by Fetizon,[188,189] has been reported to be higher yielding than that of MnO_2 (Scheme 85 entry c, compare to entry a).[183] It has been reported that silver carbonate does not oxidize alcohols and that simple addition of celite to the silver carbonate does not catalyze the reaction. The silver carbonate must therefore be precipitated in the presence of celite suggesting that this method is responsible for increasing the number of active sites on the surface.[189] Surprisingly other silver salts (formate, acetate, benzoate, oxalate) similarly precipitated are ineffective although some of them possess the same (oxalate: -0.47 V) or even more negative (acetate: -0.64 V) oxidation potentials.[189] It has been postulated that chemisorption of the hydroxyl of the alcohol initially takes place and that other functional groups present on the structure of the molecule can alter the process or lower its rate.

The reagent usually precipitated on celite, gained wide acceptance due to the mildness of conditions needed to carry out the oxidation and the ease which with the aldehyde can be isolated from the by-products concomitantly produced [silver (Ag°) and the carbon dioxide] (Scheme 87).[189]

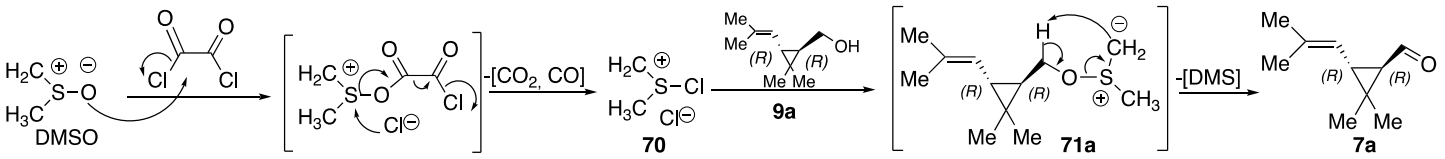


Scheme 87. Postulated mechanism implied in the oxidation of chrysanthemol to chrysanthemal by silver carbonate.

The clean oxidation of chrysanthemol (**9a**) to chrysanthemal (**7a**) and the absence of products resulting from a rearrangement or cyclopropane ring opening, preclude the intermediate formation of cyclopropylcarbinyl carbenium ion, carbanion or radical.[189,190] Furthermore, these results broaden the scope of this reaction often confined to saturated steroidal alcohols.[188,189]

2.10.3. Swern oxidation of chrysanthemol. The Swern oxidation reaction, that has been successfully applied to chrysanthemol (Scheme 88),[172] is part of the wider family of reactions that involve "activated sulfoxide reagents". It involves nucleophilic attack of the hydroxyl group of the alcohol on the sulfur atom of the sulfonium (**70**) generated on reaction with oxalyl chloride. The latter is the most useful activator for the conversion of

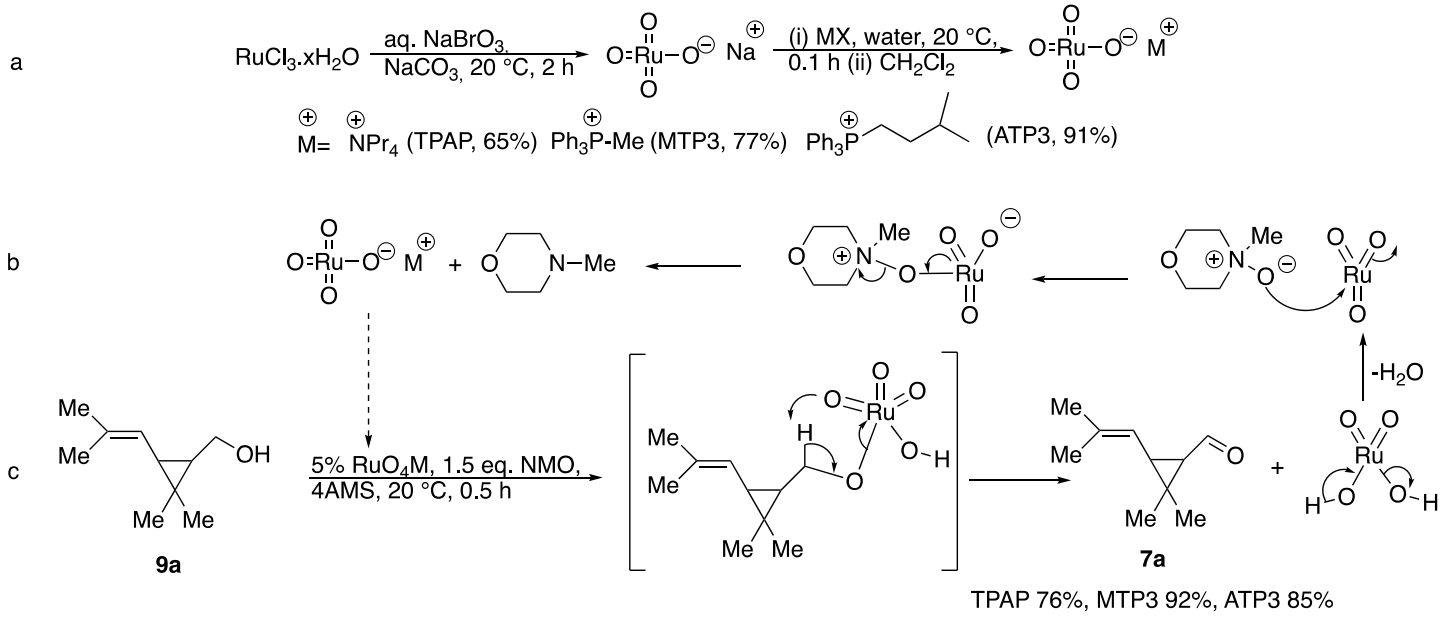
alcohols to their alkoxysulfonium salts which upon basification leads to the ylide such as **71a** that decomposes through an intramolecular process to deliver chrysanthemal (**7a**) and dimethyl sulfide as co-product (Scheme 88).[191-193]



Scheme 88. Oxidation of chrysanthemol to chrysanthemal using the Swern oxidation reaction.[172]

The reaction is usually carried out at 0 °C since the intermediate dimethylsulfide dichloride (**70**) is not stable above this temperature and has been successfully applied to various alcohols including long chain alcohols, aromatic and heteroaromatic alcohols, carbohydrates, ketols including alpha-ketols leading to the related carbonyl compounds at the exclusion of acetylenic alcohols. It offers over most of the methods of oxidation of alcohols to carbonyl compounds, the advantage of avoiding the use of metals.

2.10.4. Perruthenate (TPAP) oxidation of chrysanthemol. Tetrapropylammonium perruthenate (TPAP) easily available from ruthenium trichloride (Scheme 89, entry a) has been used as an efficient reagent for oxidation of alcohols to aldehydes and ketones especially due to its high solubility in organic solvents, air stability, limited toxicity, high chemoselectivity , mild conditions required (20 °C) and high product yields.[194,195] As ruthenium is a rather expensive transition metal, methods have appeared that allow in situ recycling of the reduced ruthenium species back to its original oxidation level. This is particularly the case for the most popular one that



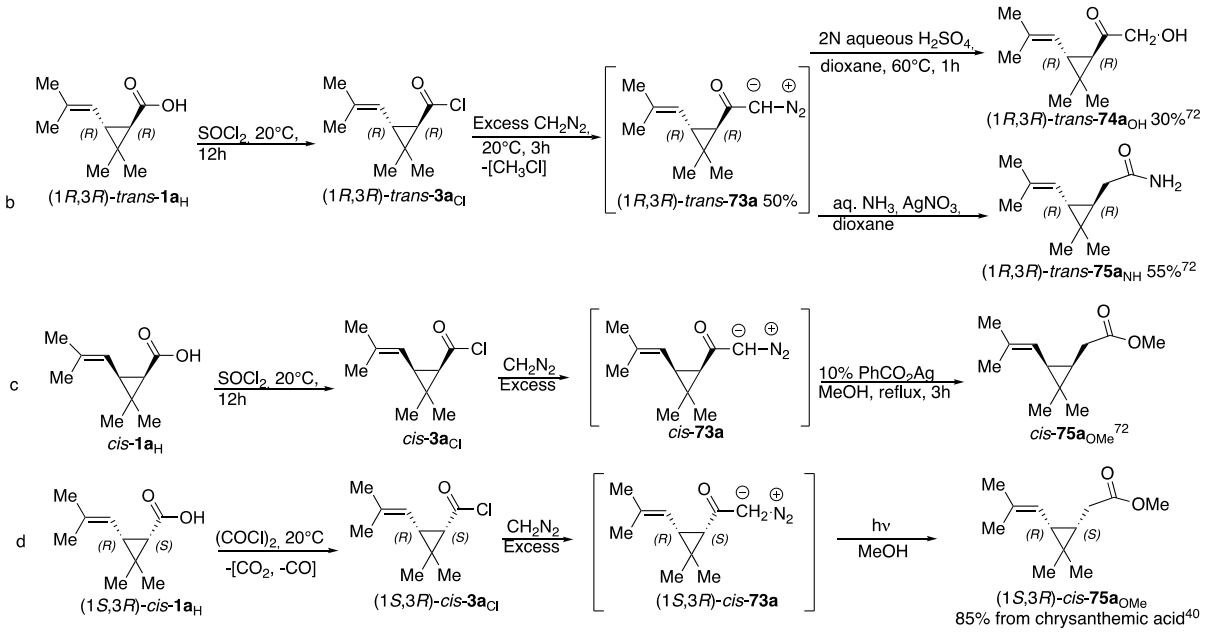
Scheme 89. Perruthenate oxidation of chrysanthemol to chrysanthemal.[184]

uses no more than 5% of TPAP in the presence of *N*-methylmorpholine *N*-oxide (NMO) as a stoichiometric oxidant,[194] dioxygen,[196,197] and even electrochemical recycling[195] have also been successfully used for the same purpose. Polymer supported perruthenate (PSP),[197] and immobilized perruthenate on mesoporous silicate [197] have been also proposed, as well as perruthenates possessing a counter ion different from the

tetrapropylammonium one such as (i) ammonium [184] (tetraethyl ammonium, triethyl benzyl ammonium, alkyl-imidazolium)[198] (ii) phosphonium[184] (tetraphenylphosphonium, methyltriphenyl phosphonium (MTP3), isopentyltriphenyl phosphonium (ATP3)) and (iii) arsonium.[184] ATP3 and especially MTP3 are easily synthesized and proved to be particularly efficient for the transformation of chrysanthemol to chrysanthemal (Scheme 89, entries c and b). Their main advantage over TPAP has been claimed to be their bench stability although their molecular weights are higher.[184]

2.11. Reaction of carboxylic acid involving the insertion of a carbon or a nitrogen atom (Scheme 10, Route 13)

2.11.1. Synthesis of homochrysanthemic acid by homologation of chrysanthemic acid. *cis*- and *trans*-Chrysanthemic acid (**1a$_H$**), including its enantiopure forms, have been transformed through the corresponding acid chloride (**3a**) and the related keto diazonium chloride **72** to the related diazoketone **73a** (Scheme 90). [40,72]



Scheme 90. Synthesis of methyl homochrysanthemate and related amide by homologation of chrysanthemic acid through its acid chloride and diazomethane.[40,72,200]

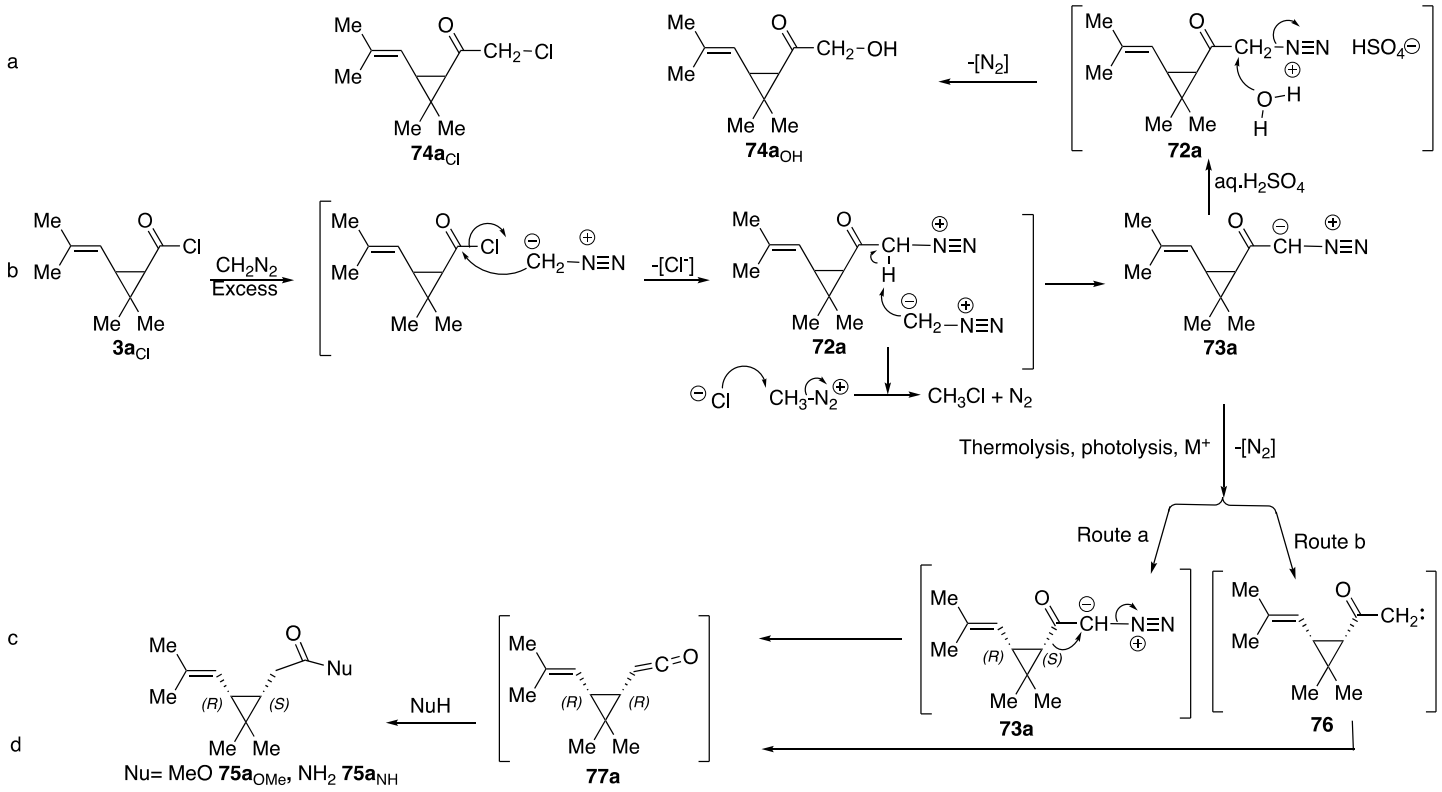
The latter, depending on the reagent and the conditions, either produces:

(i) the chloro-ketone **74a**$_{Cl}$ or the hydroxy-ketone **74a**$_{OH}$ resulting from the direct substitution of the diazo group by the chloride ion or a hydroxyl group on reaction with sulfuric acid (Scheme 90, entry a)[72] or

(ii) the homochrysanthemic amide **75a**$_{NH}$ (Scheme 90, entry b)[72] or the methyl homochrysanthemate (**75a**$_{Me}$) (Scheme 90, entry c)[40] resulting from a 1,2-migration of the methylene group on reaction with ammonia promoted by a silver nitrate or better silver benzoate (Scheme 90, entries b),[72] or with methanol in the presence of silver benzoate (Scheme 90, entries c), or under UV light irradiation (Scheme 90, entry d) respectively. In all cases the reaction proved to be highly stereospecific occurring with retention of configuration[199] at the migrating cyclopropyl carbon.

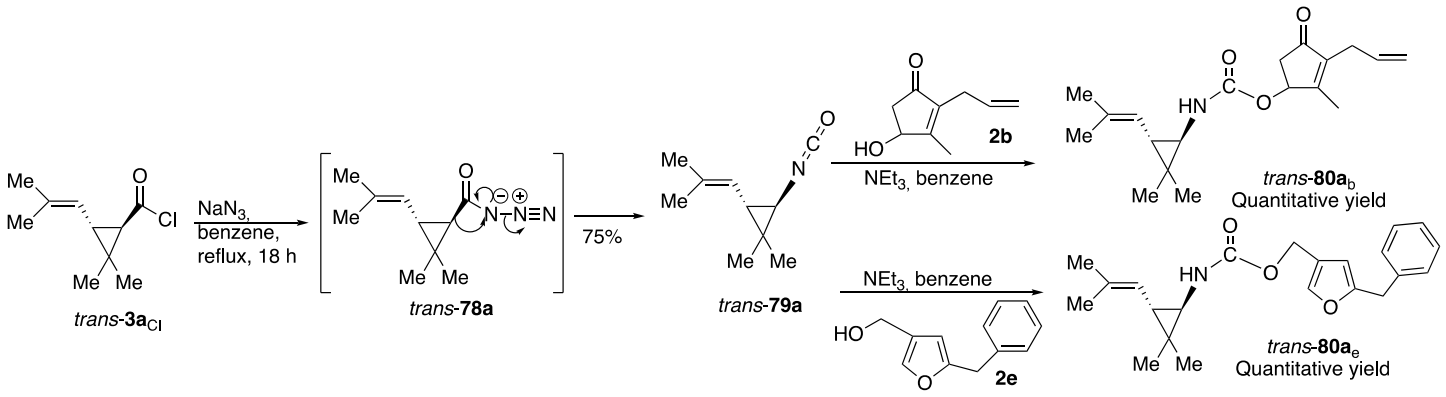
As far as the mechanism is concerned (Scheme 91), all those reactions involve the intermediate formation of **72**$_{Cl}$ that is produced on reaction of the first equivalent of diazomethane that acts as a nucleophile on the carbonyl group of the acyl chloride **3**$_{Cl}$. It leads to the substitution of the chloride ion by the diazomethyl group (Scheme 91, entry b). The second equivalent metallates the resulting intermediate **72** leading to the diazoketone

73 and methyl chloride (Scheme 91, entry b).[201] The last steps of the process involve the Wolff rearrangement[200,201] initiated by thermolysis, photolysis, or metal ion catalysis. It produces the intermediate ketene **77**, either through a concerted process (Scheme 91, entry a) or through the intermediate formation of the ketocarbene **76** (Scheme 91, entry c), which is then trapped by ammonia or methanol to produce either the amide **75**$_{NH}$ or the ester **75**$_{OMe}$ (Scheme 91, entry d).[40,72]



Scheme 91. Mechanism of reactions involving diazomethane and chrysanthemoyl chloride.[40,72]

2.11.2. Synthesis of urethanes from of chrysanthemic acid. Transformation of chrysanthemic acid (**1a**$_H$) to the chrysanthemoyl isocyanate (**79a**) has been achieved through the corresponding chysanthemoyl chloride (**3a**$_{Cl}$) and its further reaction with sodium azide at reflux of benzene for 18 h (Scheme 92).[148,202,203] The resulting chrysanthemoyl azide (**78a**) is unstable and decomposes *in situ* by losing dinitrogen that initiates the migration, with retention of configuration, of the cyclopropyl moiety from the carbonyl group carbon of the chrysanthemoyl azide (**78a**) to the remaining nitrogen as previously described in the Curtius rearrangement (Scheme 92).[148,202,203,204]



Scheme 92. Synthesis of an isocyanate from chrysanthemoyl chloride and sodium azide.[148,202]

It has been reported[202] that the Hofmann rearrangement of carboxamides that involves bromine and is another efficient method to generate isocyanates, cannot be used to synthesize chysanthemoyl isocyanate (**79a**) due to the presence of bromine-labile cyclopropane ring and ethylenic linkage.[205]

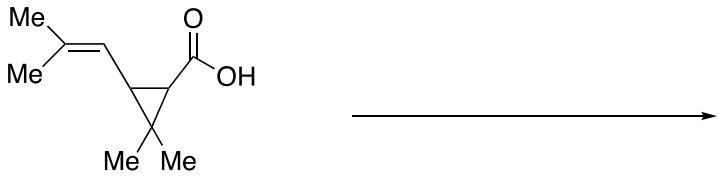
Reactions of chrysanthemyl isocyanate with alcohols including allethrolone (**2b**) (Scheme 92, entry a)[148] and 5-benzyl-3-furfurylmethyl alcohol (**2e**) (Scheme 92, entry b),[148] provide the corresponding urethanes **80a**$_b$ and **80a**$_e$ in quantitative yields. Those do not possess insecticidal activity.[148] Reaction with amines has been successfully achieved and leads to the corresponding ureas in good to excellent yield (40-93%).[202]

3. Reactions Affecting the Isobutenyl Moiety of Chrysanthemic Acid/Esters

3.1. Reactions affecting the C=C double bond of chrysanthemic acid/esters

3.1.1. Reduction of the C=C double bond of vinylcyclopropane carboxylic acids (Scheme 13, Route 19). Hydrogenation of *trans*-,[81,206,207] and *cis*-[208] chrysanthemic acid (**1a**$_H$) and some of its esters **1a**$_R$ has been achieved by hydrogen in the presence of metal catalysts such platinum oxide,[208,207] the Adams catalyst, or palladium oxide in acetic acid[208] or in ethanol.[81,207] These reactions lead stereoselectively to dihydrochrysanthemic acid (**13**$_H$) without cleavage of the cyclopropane ring or reduction of the carboxyl group (Scheme 93).

The same occurs when Raney nickel is instead used but at the condition that a single equivalent of dihydrogen is used (Scheme 93, entry c) otherwise two equivalents of hydrogen are absorbed suggesting that the cyclopropane ring is cleaved.[208]



1a$_H$ **13**$_H$

a	*cis*-**1a**$_H$	H_2, 0.85 % weight eq. PtO_2, AcOH, 20°C, atm pressure	*cis*-**13**$_H$	70%
b	*cis*-**1a**$_H$	H_2, PdO, AcOH, 20°C, atm pressure	*cis*-**13**$_H$	not reported
c	*cis*-**1a**$_H$	H_2, 1% aq. NaOH, 0,3 weight eq. Raney Ni, 10 atm	*cis*-**13**$_H$	not reported
d°	*trans*-**1a**$_H$	H_2, 0.42 weight eq. PtO_2, AcOH, 20°C, atm pressure	*trans*-**13**$_H$	not reported

° contains some iso-*trans*-chrysanthemic acid

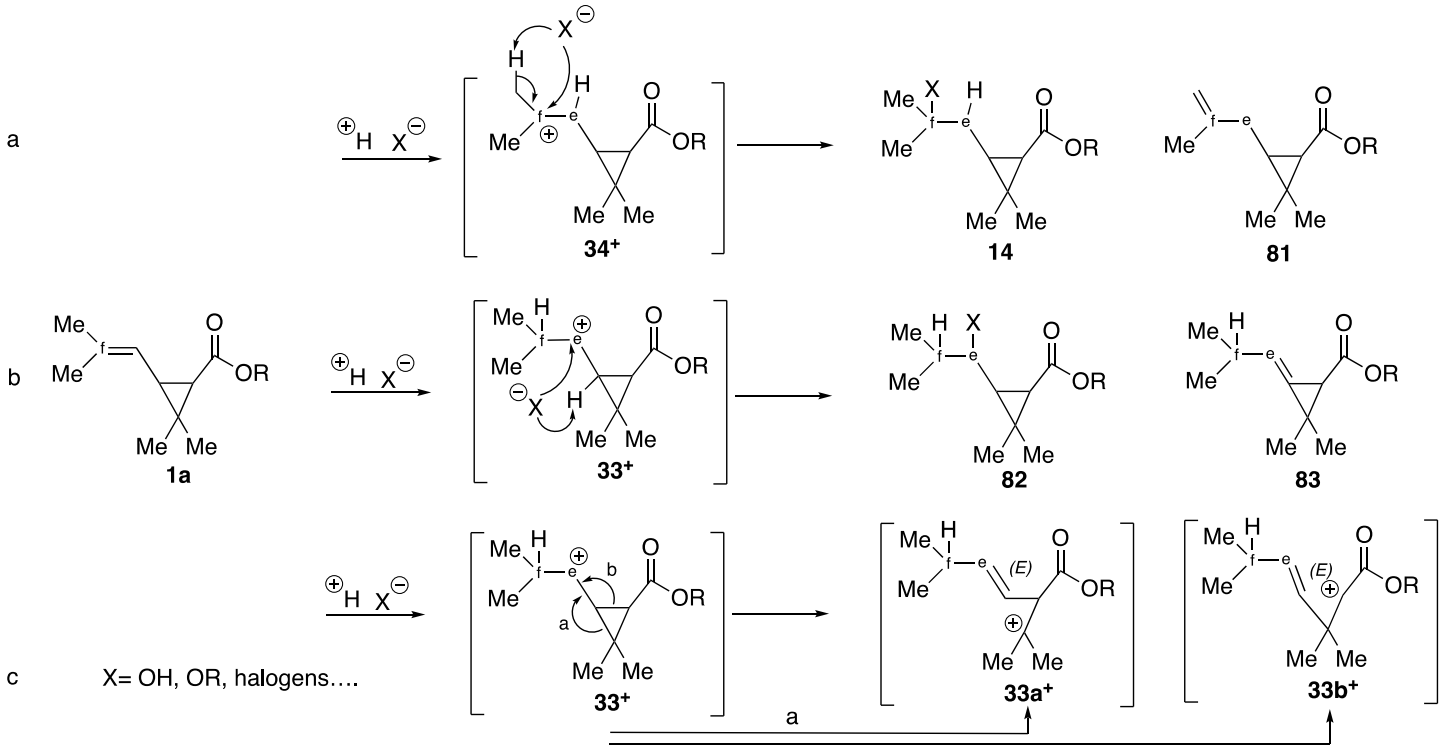
Scheme 93. Catalytic dihydrogenation of the isobutenyl moiety of chrysanthemic acid.[207,208]

Dihydrogenation of chrysanthemonitrile using platinum oxide[207] has been also successfully achieved. Transformation of methyl *trans*-dihydrochrysanthemate (**13**$_{Me}$) to allethrin or resmethrin analogues bearing an isobutyl instead of the isobutenyl moiety that possess reduced insecticidal properties has been also reported.[209]

3.1.2. Isohypsic additions on the C=C double bond of vinylcyclopropane carboxylic acids/esters (Scheme 13, Route 20). The C=C double bonds of chrysanthemic acid (**1a**$_H$) and its esters **1a**$_R$ have a high propensity to react with electrophiles especially in the presence of acids. Under the latter conditions, the proton, as already disclosed in Scheme 17 (Section 1.2.2.2.) can either reacts:

(i) at [Ce] of **1a**, following the "Markovnikow rule"[210,211] to produce **34**$^+$ possessing a well stabilized tertiary carbenium ion at [Cf] (Scheme 94, entry a). The latter can evolve by (a) addition of a nucleophilic entity at [Cf] leading to **14a** or (b) by elimination of a proton from one of the methyl groups to produce the isomeric isochrysanthemic acid or its esters **81**,

(ii) at [Cf] of (**1a**) producing **33**$^+$ possessing a carbenium ion at [Ce] at a cyclopropyl carbinyl position (Scheme 94, entry b). The latter can evolve by (a) addition of a nucleophilic entity at [Ce] leading to **82** regioisomeric to **14a** (X= OH) or (b) by elimination of a proton leading to the alkylidene cyclopropane **83** regioisomeric to **81** but this process is highly improbable due to the steric strain involved, or (c) by cyclopropane ring opening as it is the most probable (Scheme 94, entry c).[211]



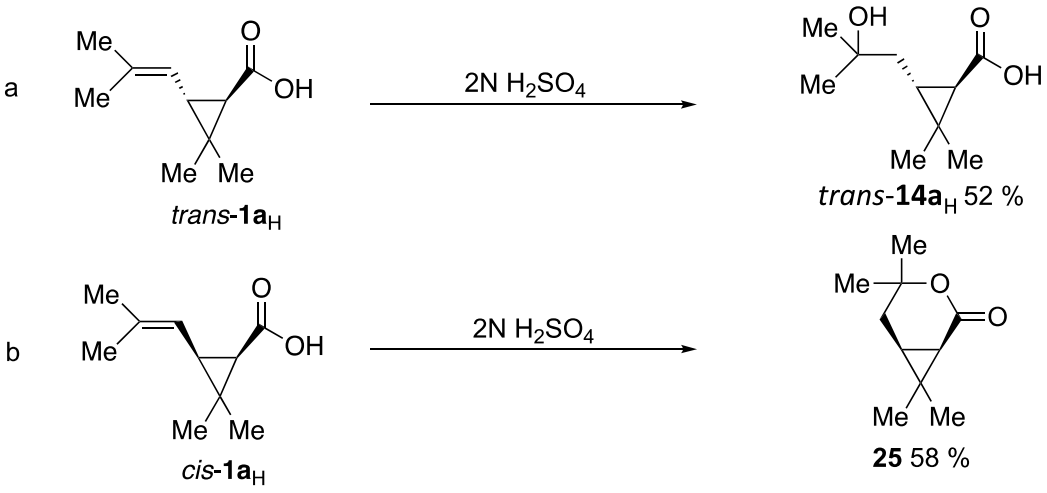
Scheme 94. Potential reactions of protic acids with chrysanthemic derivatives.

The intermediates **34**$^+$ and **33**$^+$ have been formally produced from compounds **14a** and **82** bearing a leaving group at [Cf] or [Ce] and found to possess these behaviors. In particular elimination reactions on **14a** provides, under kinetically controlled conditions a mixture of **1a**, expected from the "Hofmann rule"[212] and **81** expected from "Zaitsev's rule". [211] It has been found that the **1a** is produced quantitatively from the **14a** (X= OH) in the presence of an acid catalyst under thermodynamically controlled conditions.[213]

The transformation of **82** to **1a** is far from easy and leads often to products arising from cyclopropane ring opening initiated by the intermediate formation of **33a**$^+$ or **33b**$^+$ resulting from the strain released by the destruction of the cyclopropane ring (Scheme 94).[211]

3.1.2.1. Hydration of chrysanthemic acid. Hydration of *trans*-chrysanthemic acid *trans*-(**1a**$_H$), carried out with 2N sulfuric acid at reflux for 3 h, leads to *trans*-hydroxy-dihydrochrysanthemic acid *trans*-(**14a**$_H$) in 52% yield and recovery of the starting material (48% yield, Scheme 95, entry a).[35,39,88,214,215] The reaction takes another course when carried out on the *cis*-chrysanthemic acid *cis*-(**1a**$_H$) and delivers instead the bicyclic lactone (**25**), in similar yield (2N or dilute sulfuric acid reflux, 3 h, 58% yield) through an intramolecular cyclization reaction and leads also to recovered starting material (38%, Scheme 95, entry b).[88,214,215]

The same lactone (**25**) has been formed, under milder condition and better yield, on reaction of *cis*-(**1a$_H$**) with boron trifluoride etherate (20 °C, 12 h)[88] or on reaction of sulfuric acid on *iso*-*cis*-chrysanthemic acid *cis*-**81**$_H$.[216]



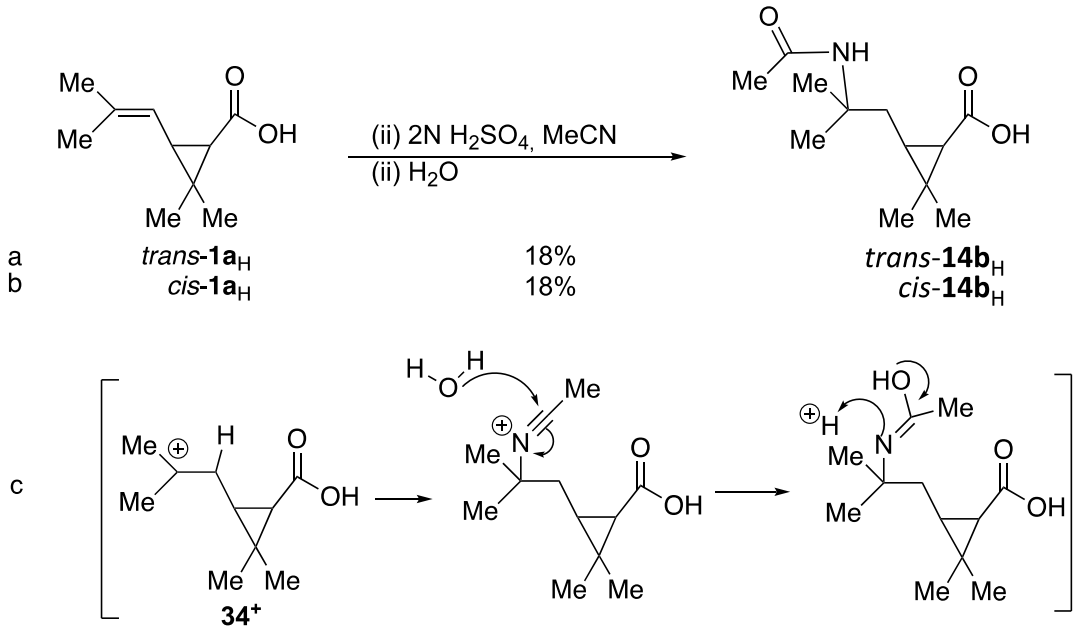
trans-**1a**$_H$ *trans*-**14a**$_H$ 52 %

cis-**1a**$_H$ **25** 58 %

Scheme 95. Reaction of *cis*- and *trans*-chrysanthemic acid with sulfuric acid.[88,116,214]

The reaction of *trans*-chrysanthemic acid *trans*-(**1a**$_H$) and sulfuric acid carried out in acetonitrile (20 °C, 20 h) takes another course and delivers after hydrolysis the related *trans*-acetamido-dihydrochrysanthemic acid *trans*-14**b**$_H$ in poor yields (18%, Scheme 96, entry a).[217] The reaction is expected to proceed through the carbenium **34**$^+$ (Scheme 96, entry c) that is trapped by acetonitrile in a process originally described by Ritter[218] (The Ritter reaction).

The same process takes also place with *cis*-chrysanthemic acid *cis*-(**1a**$_H$) and leads to *cis*-acetamido-dihydrochrysanthemic acid *cis*-**14b**$_H$ in similar yield as from the *trans*-stereoisomer (18%, Scheme 96, entry b).[217] Note that no bicyclic lactone (**25**) is produced in this process (Compare Scheme 96, entry b to Scheme 95, entry b).



Scheme 96. Reaction of sulfuric acid with chrysanthemic acid in the presence of acetonitrile.[217]

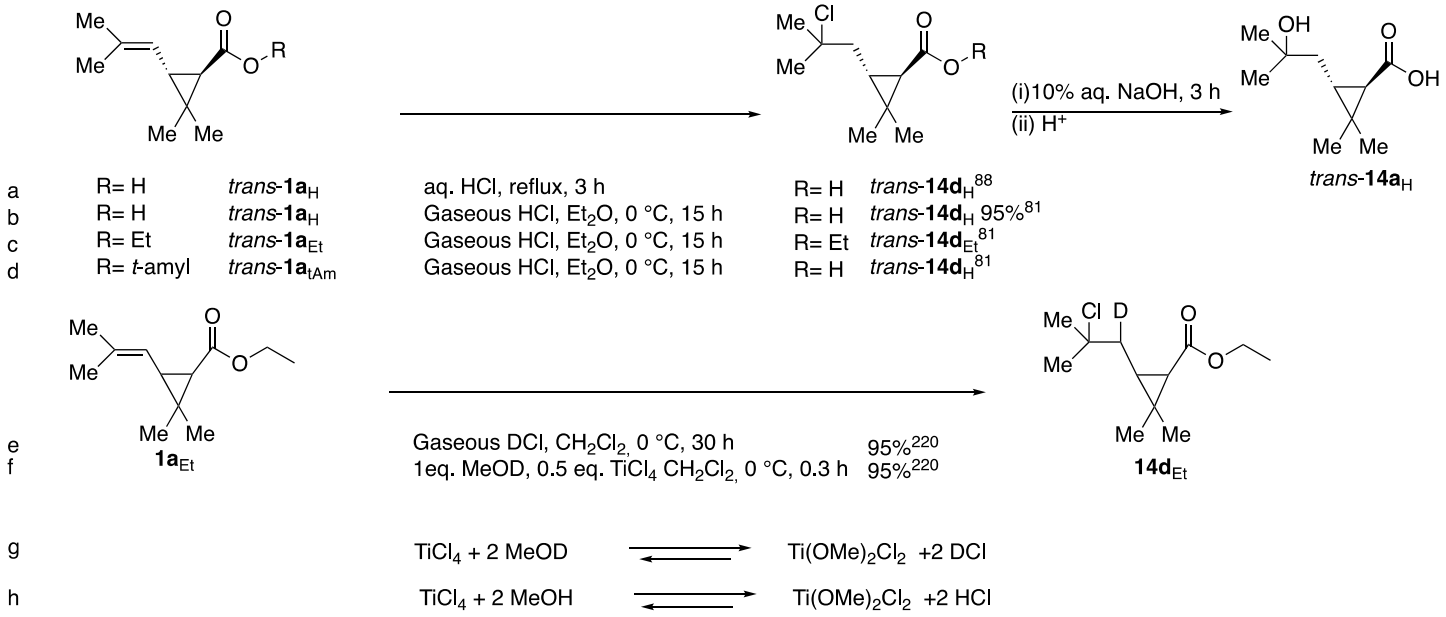
3.1.2.2. Addition of methanol to chrysanthemic acid. *trans*-Chrysanthemic acid *trans*-(**1a**$_H$) with methanol in acidic media and leads to methyl *trans*-methoxy-dihydrochrysanthemate (**14c**$_{Me}$) in poor yield (20%) implying a concomitant esterification reaction[51] (Scheme 40, entries b,c, see also Section 5.3.1.).[90]

3.1.2.3. Addition of hydracids to the [C=C] double bond of chrysanthemic acid and related esters. *trans*-Chrysanthemic acid *trans*-(**1a**$_H$) has been reacted with aqueous hydrochloric acid at reflux for 3h[88] or in flux of gaseous hydrogen chloride in ether at 0 °C for 15 h to deliver *trans*-chloro-dihydrochrysanthemic acid *trans*-(**14d**$_H$) in up to 95% yield[81] (Scheme 97, entries a,b). Some contradictory results have however been reported later.[219] These conditions have been successfully extended to ethyl *trans*-chrysanthemate *trans*-(**1a**$_{Et}$) (Scheme 97, entry c).

The same conditions applied to *tert*-amyl *trans*-chrysanthemate *trans*-(**1a**$_{tAm}$) produce instead *trans*-chloro-dihydrochrysanthemic acid *trans*-**14d**$_H$ in quantitative yield by addition of HCl across its C=C double bond and concomitant acid catalyzed dealkylation of its carboxylate (Scheme 97, entry d).[81]

As already pointed out, addition of HCl requires a very long time to proceed to completion (30 h) at room temperature and the same has been observed when DCl is instead used (Scheme 97, entry e).[220] Hassner has found that the presence of dimethoxytitanium dichloride favors the addition of HCl that takes place in only 0.3 h.[220] The synthesis of dimethoxytitanium dichloride is achieved along with that of HCl, by mixing, at 0 °C a slight excess of methanol (2.2 eq.) to titanium tetrachloride and the same can be achieved to produce DCl and dimethoxytitanium dichloride by replacing methanol by deuteromethanol. The resulting mixture has allowed the almost quantitative access to **14d**$_{Et}$ (Scheme 97, entry f) the deuterated analog of **14d**$_{Et}$ (Scheme 97, entry c) from ethyl chrysanthemate (**1a**$_{Et}$) (Scheme 97, compare entry f to entries d,e).[220]

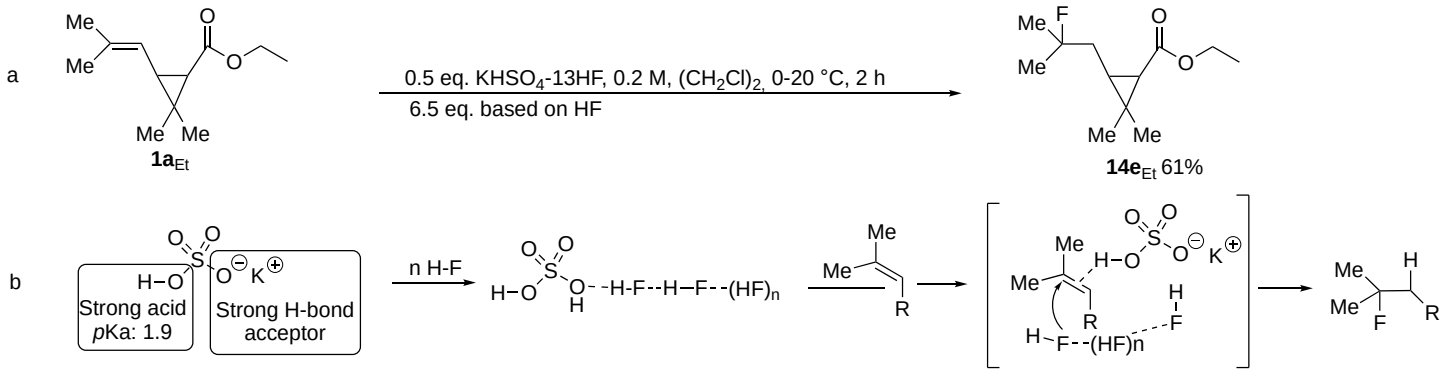
Hydrofluorination of ethyl chrysanthemate (**1a**$_{Et}$) has been efficiently achieved using $KHSO_4 \cdot 13HF$ (Scheme 98, entry a)[221,222], an easily handled bifunctional reagent (Scheme 98, entry b).[221] Hydrofluoration of olefins is a challenging process that only recently found theoretical and practical solutions.



Scheme 97. Hydrochlorination of chrysanthemic acid and alkyl chrysanthemates.[81,88,220]

The high efficiency observed in this reaction hinges on the activation of HF using a highly "acidic" hydrogen bond acceptor. Stable liquid "$KHSO_4$·13HF" readily synthesized by dissolving as much gaseous HF in solid $KHSO_4$ (Scheme 98, entry b),[221] has a higher content of HF than other reagents[221] such as pyridine·9HF, Olah's reagent or DMPU·12HF.[221] It was suggested that shorthcomings observed in hydrofluorination were caused by the acidity of HF (pKa = 3.2), less than that of HCl (pK_a = -8.0) or HBr (pK_a = -9.0), which is not strong enough to activate functionalized alkenes". The hydrogen bond acceptors that include organic bases like triethylamine, pyridine and DMPU used to complex the toxic and corrosive HF gas, allowing thus an easy handling, usually reduce its acidity and its propensity to activate the alkenes.[221]

As the mechanism disclosed in Scheme 98, entry b suggests, "$KHSO_4$·13HF" has been used as a bifunctional reagent able to activate the olefinic compound through its strong acidic moiety and delivery of the complexed fluoride ion to achieve the addition regioselectively from (**1a**$_{Et}$), avoiding the cleavage of its cyclopropane ring and delivering ethyl fluoro-dihydrochrysanthemate *trans*-**14e**$_{Et}$ in reasonably good yields.

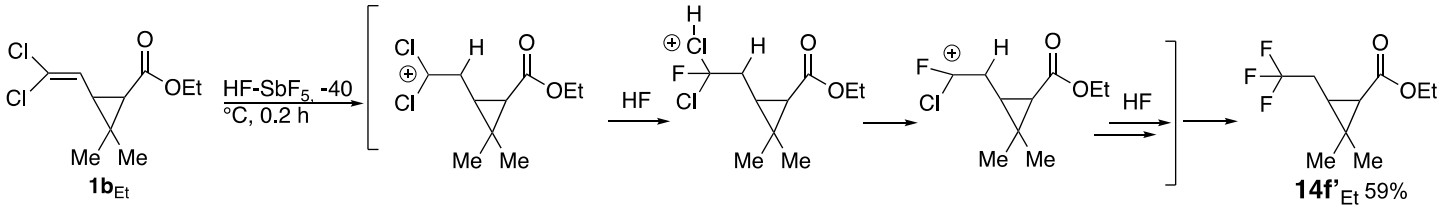


Scheme 98. Hydrofluorination of chrysanthemic acid and alkyl chrysanthemates.[221,222]

An inexpensive ion exchange resin-supported hydrogen fluoride has also been used for the hydrofluorination of compounds possessing terminal or trisubstituted [C=C] double bonds including ethyl chrysanthemate (**1a**$_{Et}$) in a flask as well as in some cases in a flow process.[223] The resin-supported hydrogen

fluoride has been prepared in two steps from commercially available Amberlite A26 ion exchange resin bearing ammonium hydroxide moiety by sequential treatment by sulfuric acid leading to the ammonium hydrosulfate that has been then treated with HF and left at room temperature in open air.[223]

Hydrofluoric acid does not react with ethyl cypermethrinate (**1b**$_{Et}$) unless antimony pentafluoride is present.[224] In the latter case and although the reaction with HF-SbF_5 is carried out at low temperature for a short time (-40 °C, 0.2 h), the trifluoromethyl derivative **14f'**$_{Et}$ is produced that results from an initial addition across the [C=C] double bond of ethyl cypermethrinate (**1b**$_{Et}$) followed by substitution of each of the remaining chlorine by fluorine atoms subsequent to their protonation (Scheme 99).[224]



Scheme 99. Hydrofluorination of ethyl cypermethrinate: addition and substitution processes.[224]

3.1.2.4. Addition of carbonyl compounds to the [C=C] double bond of chrysanthemic acid and related esters. The cyclopropane ring of chrysanthemic acid (**1a**$_H$) and its alkyl esters **1a**$_R$ is cleaved on irradiation leading for example to their *trans*/*cis*-isomerization by cleavage of their [Cb-Cd] bonds as it has been disclosed in Scheme 4,[12] and to senecioates **84**$_R$ (Scheme 100, entry a) that involves the cleavage of both their [Cb-Cd] and [Cc-Cd] bonds.

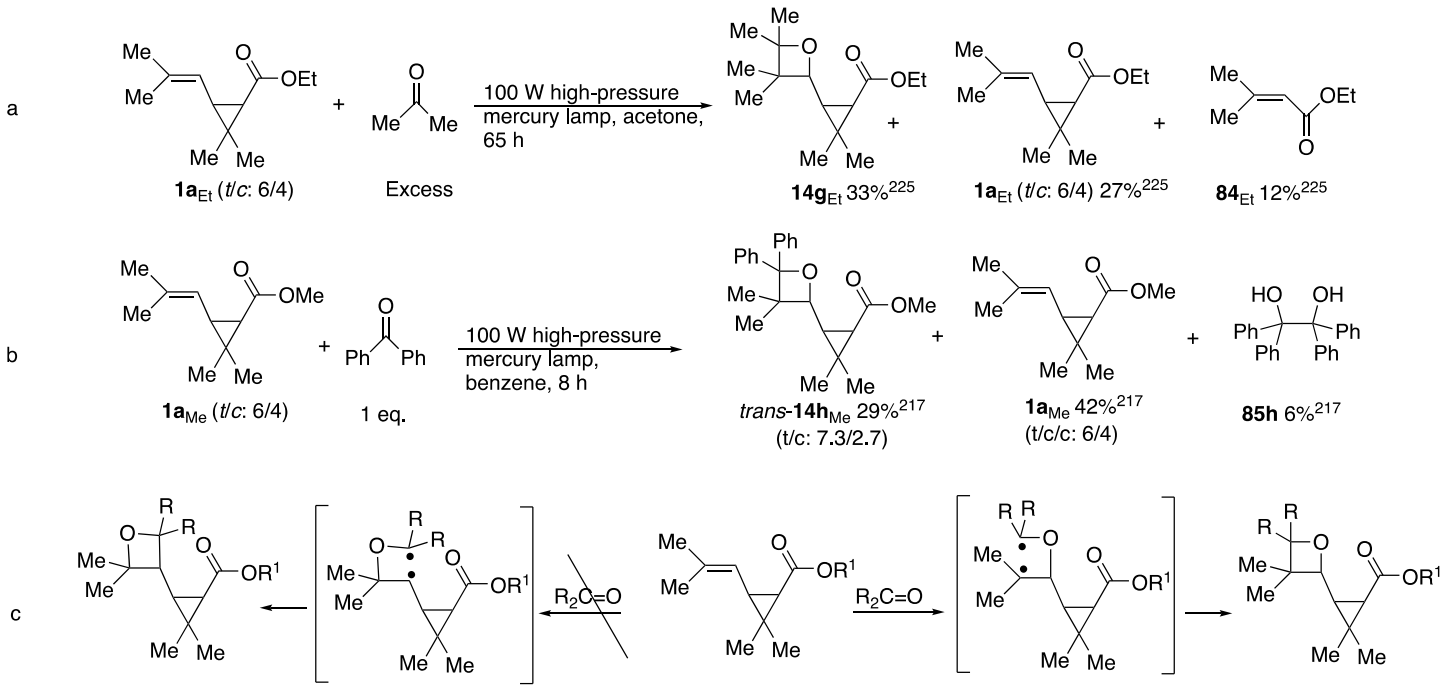
In the presence of carbonyl compounds such acetone or benzophenone the reaction, however takes another course and oxetanes are formed in modest yield through a 2+2 photochemically induced cycloaddition across the C=C double bond (Scheme 100, Scheme 101)[217,225] known as the Paterno-Büchi reaction.[226,227]

Thus, ethyl chrysanthemate reacts with acetone in a solvolytic process to produce, after 65 h of irradiation, regioselectively the oxetane **14g**$_{Et}$ in 33% yield.[225] An important amount of ethyl chrysanthemate (**1a**$_{Et}$) (27%) whose *cis*/*trans*-ratio resemble that of the starting material and ethyl senecioate (**84**$_{Et}$) that results from a competing retro 2+1 cycloaddition are also isolated.

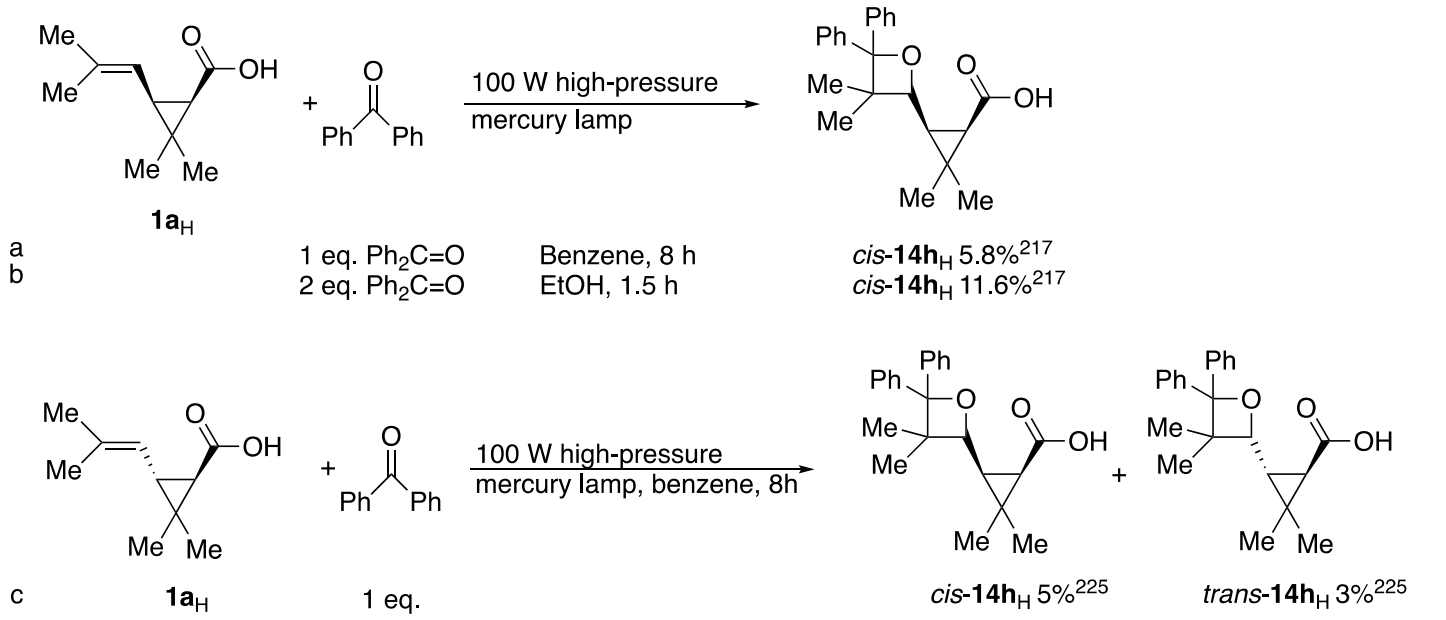
The reaction has been extended to benzophenone. In such case the reaction is performed in benzene with stoichiometric amount of benzophenone and leads to the oxetane **14h**$_{Me}$ in almost similar yield (29%) besides recovered methyl chrysanthemate (**1a**$_{Me}$) (42%) and benzpinacol (**85h**) (6%) resulting from coupling of two benzophenone units (Scheme 100).[217]

The cycloaddition, performed with stoichiometric amount of benzophenone and each of the two diastereoisomers of chrysanthemic acid *cis*-(**1a**$_H$) and *trans*-(**1a**$_H$) in benzene, delivers the oxetane **14h**$_H$ in very modest yield (Scheme 101).[217] Performing the reaction with two instead of one equivalent of benzophenone in ethanol instead of benzene leads to oxetane *cis*-**14h**$_H$ in twice amount and in shorter time (1.5 h instead of 8 h, Scheme 101, compare entry b to entry a).[217]

The reaction takes place with complete stereocontrol when carried out on *cis*-chrysanthemic acid *cis*-(**1a**$_H$) and leads to the *cis*-oxetane *cis*-**14h**$_H$ (Scheme 101, entry a,b)[217] whereas it delivers a *cis*-/*trans*-mixture when performed on *trans*-chrysanthemic acid *trans*-(**1a**$_H$) instead (Scheme 101, entry c).[217] This therefore suggests a benzophenone initiated photoisomerization of *trans*-(**1a**$_H$) to *cis*-chrysanthemic acid *cis*-(**1a**$_H$) prior the photocycloaddition and this proved to be effectively the case.[217] It is rather surprising that a similar observation has not been reported on the mixture of alkyl chrysanthemates disclosed in Scheme 100.[217,225]



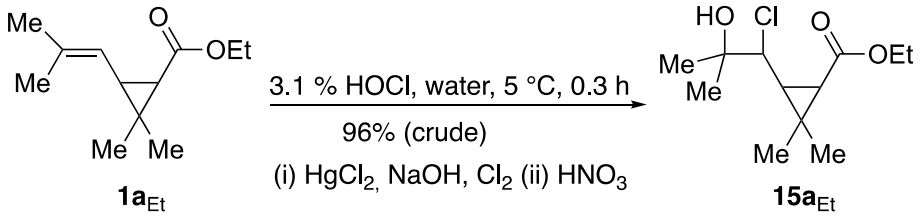
Scheme 100. 2+2 Photocycloaddition of alkyl chrysanthemates with ketones.[217,225]



Scheme 101. 2+2 Photocycloaddition of chrysanthemic acid with ketones.[217,225]

The reaction is expected to proceed through a diradical process favoring the formation of regioisomers **14g** and **14h** in which each radical is better stabilized (two methyl- and two phenyl- groups, Scheme 100, entry c). The absence of the regioisomers that involves instead the intermediate formation of cyclopropylcarbinyl radicals does not mean that these radicals are not formed but that they do not cyclize to produce the regioisomeric oxetanes, probably due to competing cyclopropane ring opening (section). This could account for the extremely poor yields in **14g** and **14h**.

3.1.3. Oxidation of the C=C double bond of vinylcyclopropane carboxylic acids/esters. 3.1.3.1. Chlorohydrin synthesis (Scheme 13, Route 21). Hypochlorous acid solution prepared [228,229] by passing chlorine into aqueous sodium hydroxide solution containing mercuric chloride and further acidification, reacts with ethyl chrysanthemate (**1a$_{Et}$**) at 5 °C to deliver the crude adduct **15a$_{Et}$** in 96% yield as well as mercuric oxide as co-product (Scheme 102).[230]



1a$_{Et}$ **15a$_{Et}$**

Scheme 102. Regioselective chlorohydrin synthesis from ethyl chrysanthemate.[230]

3.1.3.2. Epoxidation reaction (Scheme 13, Route 22). Oxido-phenothrin (1*R*,3*R*)-*trans*-(**16a$_c$**) has been found[12] amongst the products resulting from the photodegradation of phenothrin (1*R*,3*R*)-*trans*-(**1a$_c$**) (Scheme 5) and similarly (*S*)-oxido-bioallethrin (*S*,1*R*,3*R*)-*trans*-(**16a$_b$**) has been formed by the action of sunlight in oxygenated benzene of (*S*)-bioallethrin (*S*,1*R*,3*R*)-*trans*-(**1a$_b$**) (Scheme 6).[13] They are expected to be formed[12] from the reaction of triplet oxygen[231] on the isobutenyl moiety of these pyrethroids.

Otherwise oxido-chrysanthemic acid (**16a$_H$**) derived from chrysanthemic acid (**1a$_H$**)[217] (Scheme 103, entries a,b) and oxido-chrysanthemates (**16a$_R$**) derived from its alkyl esters such as methyl (**1a$_{Me}$**) , ethyl (**1a$_{Et}$**) (Scheme 103, entries c,d,e) [83,232-236] 3-phenoxy benzyl- (**1a$_c$**)[12] and allethronyl- (**1a$_b$**) chrysanthemates have been synthesized on reaction with peracids (Scheme 103, entries a-e),[12,83,217,232,235] or with hydrogen peroxide in the presence of (i) formamide (Scheme 103, entry f), [233] in a reaction derived from the Payne reaction,[237] or (ii) sodium hydrogenocarbonate catalyzed by manganese sulfate (Scheme 103, entry g).[234,236]

1a **16**

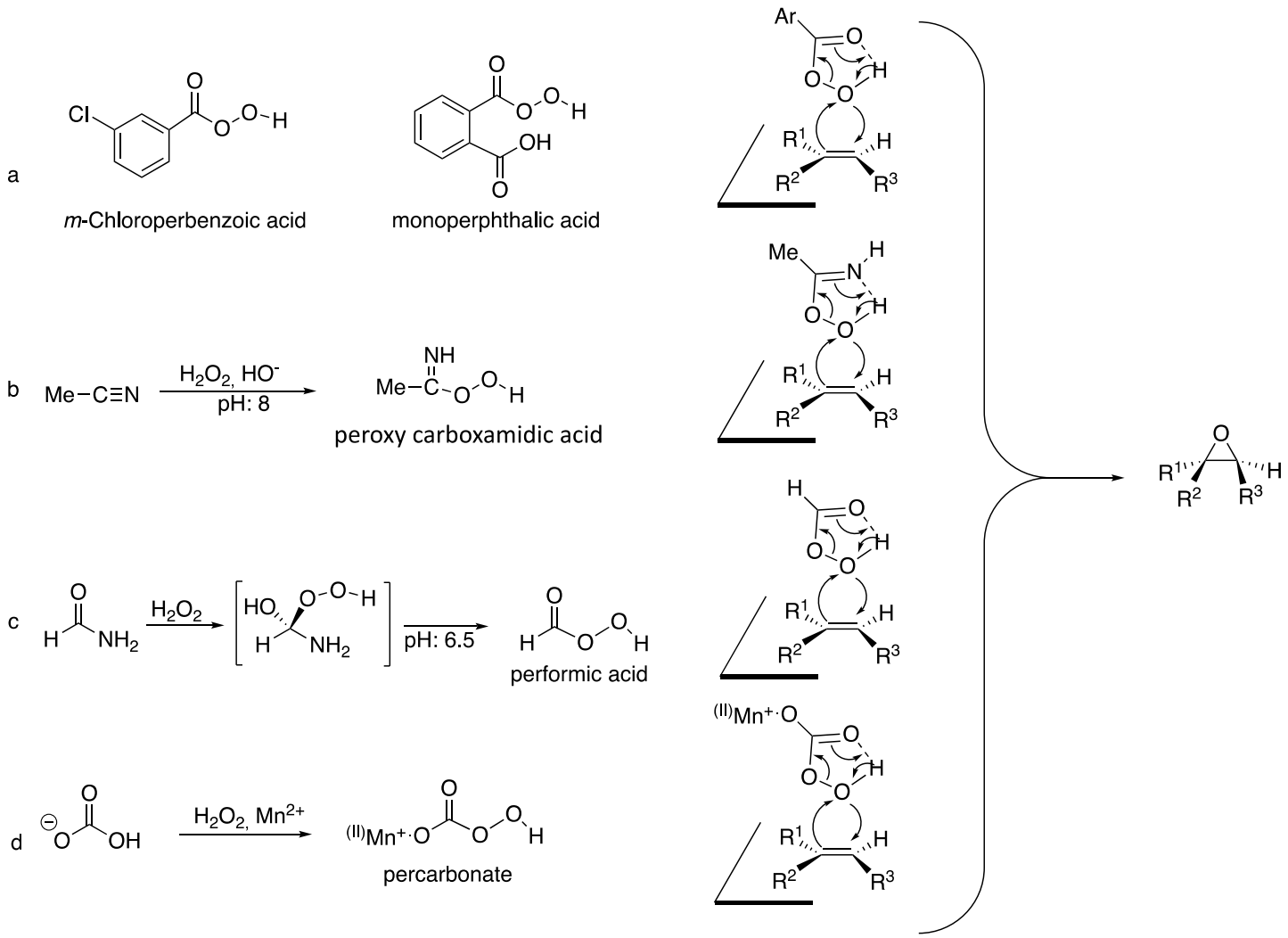
a	*trans*-**1a$_H$**	1eq. Monoperphalic acid, ether, reflux, 5 h	*trans*-**16$_H$**	21%[217]
b	*cis*-**1a$_H$**	1eq. Monoperphalic acid, ether, reflux, 5 h	*cis*-**16$_H$**	0%[217]
c	*trans*-**1a$_{Me}$**	1.5 eq. *m*-CPBA, CH_2Cl_2, 20 °C, 1 h	*trans*-**16$_{Me}$**	87%[83,232]
d	**1a$_{Et}$**	1.3 eq. m-CPBA, CH_2Cl_2, 0-20 °C, 1 h	**16$_{Et}$**	95%[235]
e	(1*R*,3*R*)-*trans*-**1a$_c$**	Excess *m*-CPBA, CH_2Cl_2, 20 °C	(1*R*,3*S*)-*trans*-**16$_c$**	95%[12]
f	**1a$_{Et}$**	15 eq. H_2O_2, 10 eq. $HCONH_2$,NaH_2PO_4, MeOH, 50 °C, 3 h	**16$_{Et}$**	69%[233]
g	**1a$_{Et}$**	10 eq. H_2O_2, 0.2 M $NaHCO_3$, 0.01 eq. $MnSO_4$, pH 8	**16$_{Et}$**	92%[234,236]

Scheme 103. Synthesis of oxido-chrysanthemic acid and related esters.[12, 83,217,232-236]

The reaction proceeds in all the cases with controlled stereochemistry on the cyclopropane ring but delivers in all the cases checked[12, 83,232,235] a mixture of epimeric epoxides at C-4 [for example a 54/46 mixture of(1*R*,3*R*,4*S*)-(**16$_{Me}$**) / (1*R*,3*R*,4*R*)-(**16$_{Me}$**) (de 8%) on reaction of (**1a$_{Me}$**) with meta-chloroperbenzoic acid (*m*-CPBA,

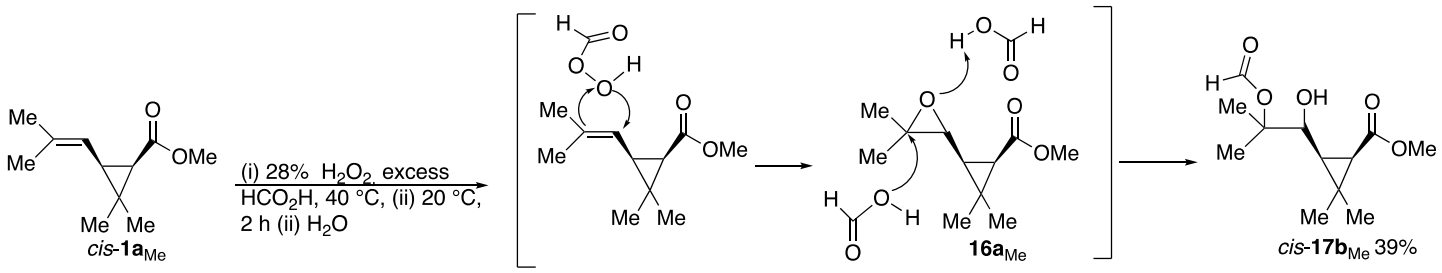
Scheme103, entry c)].[232] Although most of the reactions have been carried out on alkyl *cis*/*trans*-mixtures or *trans*-chrysanthemates **1a**$_R$, it seems that both stereoisomers react equally well at least with *m*-CPBA and with all the reagents tested except with monoperphthalic acid that has been reported to react poorly on *trans*-chrysanthemic acid *trans*-(**1a**$_H$)[217] and not at all with its *cis*-stereoisomer *cis*-(**1a**$_H$) probably due to unfavorable steric interactions (Scheme 103, compare entries a,b).[217]

The epoxidation of olefins with peracids, the Prilezhaev reaction,[238] is one of the easiest and most efficient method to produce epoxides from trisubstituted olefins, that are amongst the most reactive olefins; It usually produces stereoselectively epoxides possessing the same stereochemistry as the starting olefins (Scheme 103, entries a-e, Scheme 104, entry a).[12,83, 217,232,235] Although several peracids are used for such purpose, *m*-chloroperbenzoic acid, proved to be one of the most efficient: it is stable enough to be commercially available and enough reactive due to the presence of the electron-withdrawing chloro substituent on the aromatic ring. It can be easily prepared by reaction of hydrogen peroxide with *m*-chlorobenzoic acid in the presence of an acid or by reaction of an acid chloride with hydrogen peroxide.[238] This reagent however suffers from the concomitant formation of *m*-chloroperbenzoic acid besides the epoxide and therefore reactions that use hydrogen peroxide offers the advantage to use lower molecular weight reagent and delivers water as the co-product.



Scheme 104. Reagents able to perform the epoxidation of chrysanthemic acid and its esters and postulated mechanisms involved in the processes.

Oxidation of olefins by hydrogen peroxide can be carried out stepwise by oxidation of a carboxylic acid as discussed above (Scheme 104, entry a). Alternatively, the peracid can be produced in situ in the presence of the olefins from the carboxylic acid and hydrogen peroxide but the process is not always successful. For example, reaction of methyl *cis*-chrysanthemate *cis*-(**1a**$_{Me}$) with hydrogen peroxide in formic acid delivers regioselectively the formiate *cis*-**17b**$_{Me}$ rather than the expected epoxide **16**$_{Me}$ (Scheme 105). The formate *cis*-**17b**$_{Me}$ could be formed by regioselective acid catalyzed epoxide ring opening and trapping the intermediate at the more alkyl substituted carbon that can accommodate the most efficiently a carbenium ion (Scheme 105).[239]



Scheme 105. Oxydation of methyl chrysanthemate through intermediate formation of the related methyl oxido-chrysanthemate.[239]

One of successful methods to produce epoxides from hydrogen peroxide, the Payne reaction,[237] uses acetonitrile as the solvent and pre-reagent. It produces in the presence of bicarbonate (pH 8) peroxy carboxamidic acid, the structure of which is close to that of peracids, able to deliver *in situ* oxygen to the olefins in a way similar to that already disclosed for peracids (Scheme 104, compare entries a,b). The Reymond reaction[233] uses instead formamide and hydrogen peroxide in the presence of a phosphate buffer (pH 6.5) that, in the presence of olefins, is expected to deliver epoxides through the intermediate formation of performic acid (Scheme 103, entry f; Scheme 104, entry c compare to entries a,b).[233]

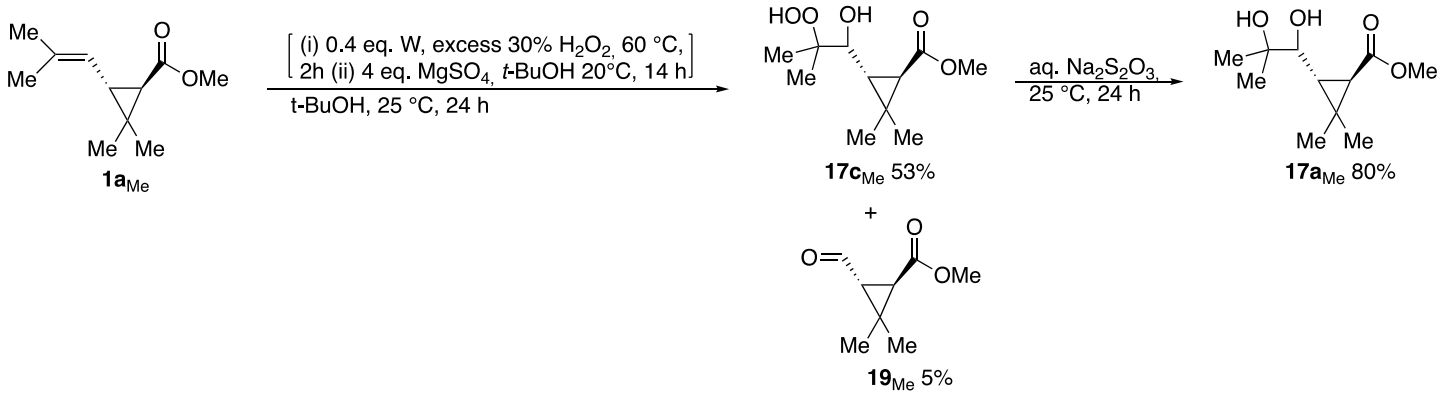
An even more expeditious route to epoxides involves the use of of 30% hydrogen peroxide (10 eq.) as terminal oxidant, catalytic amounts of manganese sulfate (0.001 eq.) and sodium bicarbonate in DMF (Scheme 103, entry g, Scheme 104, entry d).[234,236] Manganese sulfate has been selected among 68 diverse compounds expected to enhance the rate of the epoxidation reaction. This reaction proceeds efficiently with several types of olefins with the exclusion of monoalkyl-substituted ones.[236] Bicarbonate buffer seems to be essential for the epoxidation process, and peroxymonocarbonate complexed by Mn^{2+} that is expected to act as a Lewis acid, seems to play a key role in the process (supported by NMR experiments with $NaH^{13}CO_3$ and by the pH dependence of the reaction).[236] This suggests that the mechanism depicted in Scheme 104, entry d is operative among the various potential mechanism postulated.[236]

3.1.3.3 Dihydroxylation of and related reaction. (Scheme 13, Route 23). **3.1.3.3.1 Reactions involving hydrogen peroxide and preformed tungsten or molybdenum peroxides.** Although hydrogen peroxide itself does not react with olefins, additives allow oxidation reactions. We have for example disclosed above that the reaction carried out in the presence of acetonitrile, formamide, and sodium carbonate smoothly transforms the [C=C] double bond of alkyl chrysanthemates **1a**$_R$ to the corresponding epoxides **16**$_R$.

The reaction takes another course when carried with hydrogen peroxide in the presence of a preformed catalyst generated by heating hydrogen peroxide at 60 °C for a few hours (1-2h) (i) in *t*-butanol with tungsten metal (W) or related compounds such as tungsten boride, tungsten silicide, tungsten carbide in the presence or

absence of boric anhydride and magnesium sulfate in *t*-butanol or (ii) in *t*-butyl methyl ether with molybdenum (Mo) (Scheme 106).[239]

The reaction with **1a**$_{Me}$ proceeds at room temperature in about 24h and often delivers the beta peroxy-alcohol adduct **17c**$_{Me}$ in which the hydroperoxy group is attached to the tertiary carbon [Cf], in medium yields (50-60%) besides a few percent of methyl hemicaronate (**19**$_{Me}$) resulting from the cleavage of the [C=C] double bond of the isobutenyl moiety of **1a**$_{Me}$ (Scheme 106).[239] The hydroperoxy group has been efficiently reduced to the corresponding alcohol for example on reaction with sodium thiosulfate and that allowed the synthesis of the diol **17a**$_{Me}$ (80% overall yield) from **17c**$_{Me}$ (Scheme 106).[239]



Scheme 106. Stepwise dihydroxylation of methyl chrysanthemate.[239]

The amount of methyl hemicaronate (**19**$_{Me}$) can at best reach 30% using tungsten sulfide or tungsten silicide and increases by increasing the temperature. This suggests that it occurs from a subsequent rather than from a competing reaction.

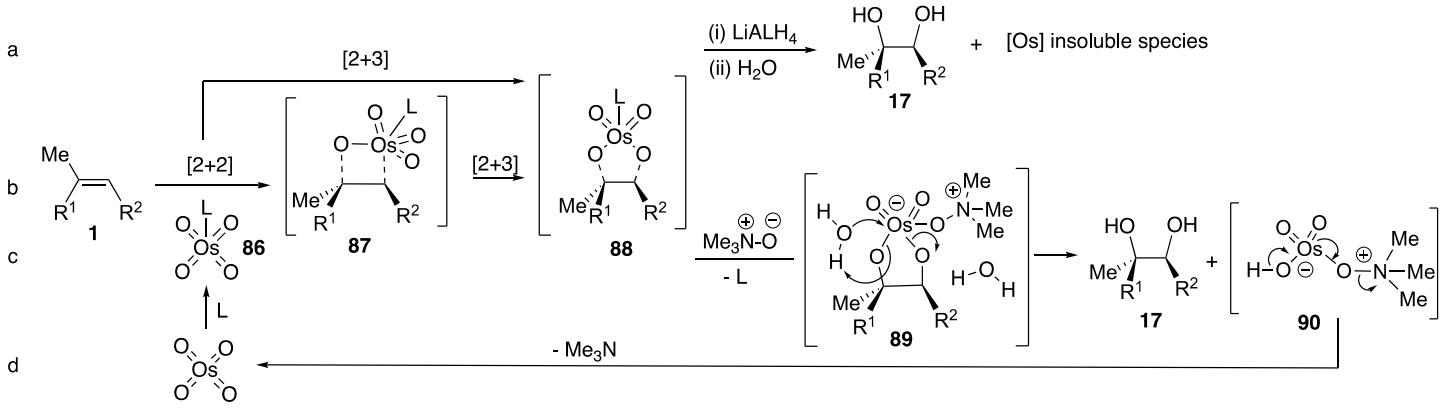
Anyhow, although the diol is produced from the chrysanthemates in less that 50 % yield, this method offers the advantage of a very benign reagent that compares well with other methods that proceed with (i) toxic compounds but in almost quantative yield (OsO_4) or (ii) low-price reagent ($KMnO_4$) but with poor chemoselectivity as will be reported below.

3.1.3.3.2 Reactions involving osmium tetroxide. The dihydroxylation of alkenes has been the subject of long-standing interest both theoretically and practically.[240,241] The reaction originally proceeds using equimolar amount of the alkene and osmium tetroxide (OsO_4) in the presence of an amine ligand (L) that greatly enhances the reaction rate[242] and delivers an osmiate ester **88** through a *syn*-addition of the two incoming groups (Scheme 107, entry b). The formation of the diol **17** is not obvious and required a further step:

(i) a reduction step (Scheme 107, entry a) using for example potassium or sodium bisulfites or lithium aluminium hydride[240] or

(ii) an oxidation step (Scheme 107, entry c) involving amine oxides,[123,243] (such as morpholine *N*-oxide the Upjohn protocol),[243] potassium ferricyanide: $K_3Fe(CN)_6$,[244, 245,246] hydrogen peroxide,[247] selenoxides,[241,248] and even dioxygen in the presence of selenides and light,[241,248]

All those reactions usually proceed in almost quantitative yield but the transformations, exhibited important drawbacks: (i) the prohibitive cost of the reagent (ii) its volatility and (iii) its toxicity.



Scheme 107. Postulated mechanism of osmium tetroxide dihydroxylation of trisubstituted alkenes.

The mechanism was quite unclear for sometimes and is now expected to proceed via a concerted [2+3] cycloaddition reaction[240] (Scheme 107) as proposed by Criegee,[242] Corey,[249] Sharpless,[245] and Hoffmann,[250] leading to **88**. It could also involve at first a reversible [2+2] cycloaddition leading to an osmaoxetane **87** (Scheme 107).[49,245] This mechanism has been supported by ^{18}O-labelling experiment that confirms that each of the two oxygens in the glycol come exclusively from the osmium reagent. Variation of that mechanism have since been published.[240,248-250]

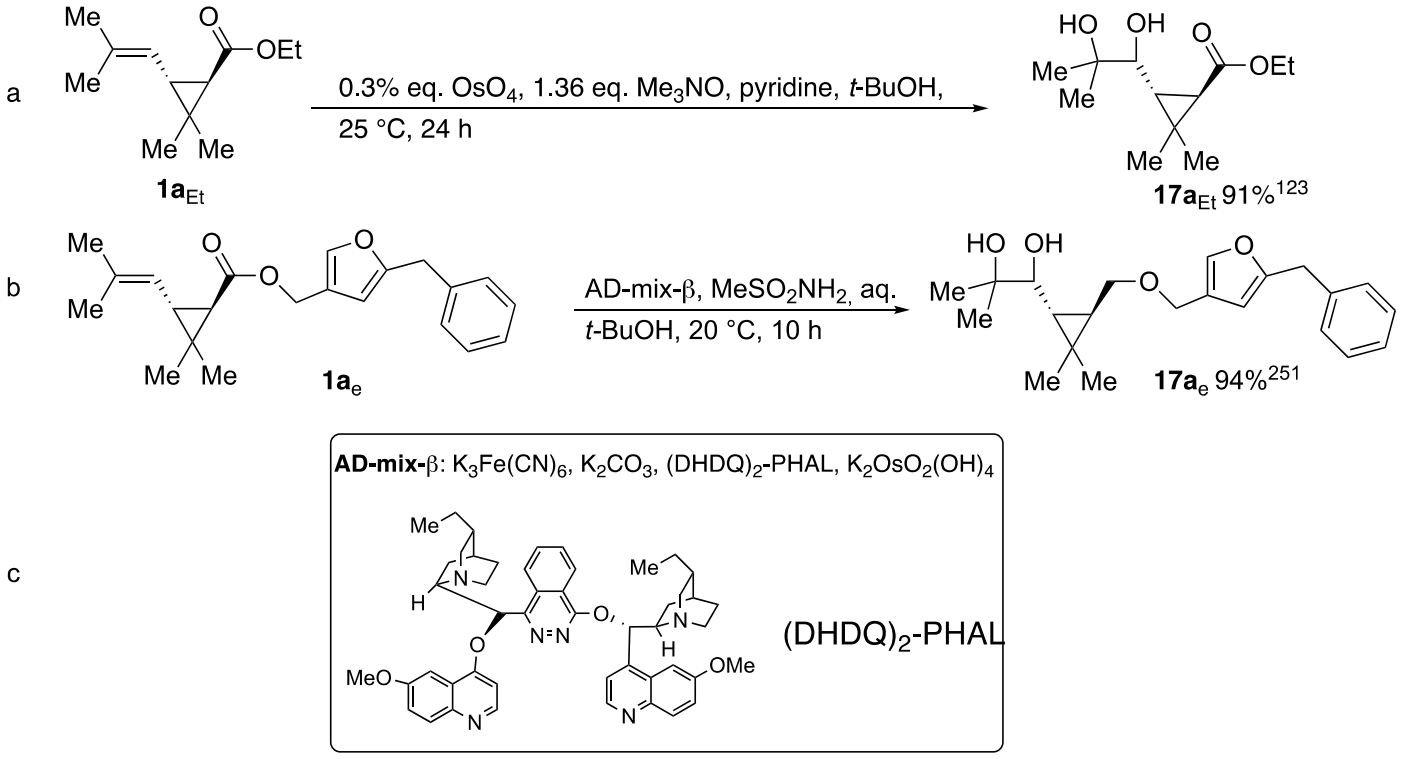
The formation of the diol using the oxidation protocol offers the advantage not only to generate the diol **17** but also:

(i) to oxidize the reduced osmium species produced, as the result of the oxido-reduction process initiated by osmium tetroxide. It allows recycling under mild conditions the [Os(VI)] of the osmate esters as well as from the non-volatile potassium osmate $K_2OsO_2(OH)_4$)] to Os(VII) allowing to establish in the presence of a sacrificial oxidant, a catalytic version of the original dihydroxylation reaction.

(ii) to produce an amine, if an amine oxide is used as the oxidant (morpholine *N*-oxide in the Upjohn process),[243] that greatly enhances the reaction rate by complexing the [Os(VII)] reagent (Scheme 107, leading to **86**).[242] The original catalytic dihydroxylation reaction has been originally published by the researchers from the Upjohn company.[243]

The Sharpless AD reaction[244,245,246] uses adequately the two aspects disclosed above to propose a combination of reagents commercially available (ADmix-beta and ADmix-alpha) able to carry out the dihydroxylation of alkenes enantioselectively on each of the two faces of compounds containing C=C double bonds by selecting the proper reagent.[244,245,246] ADmix-reagent contain potassium ferricyanide: $K_3Fe(CN)_6$ as sacrificial oxidant and a chiral amine such as dihydroquinidine $(DHDQ)_2$-PHAL (Scheme 108, entry c) in which the pyridine moiety is imbedded into a asymmetric environment, that enhances the reaction rate and induces the chiral induction of the ligand.

Dihydroxylation of the isobutylene moiety present in ethyl chrysanthemate (**1a**$_{Et}$) (Scheme 108, entry a)[123] and in resmethrin (**1a**$_e$) (Scheme 108, entry b)[251] has been successfully achieved in very high yields using catalytic amounts of osmium tetroxide.



Scheme 108. Dihydroxylation of methyl *trans*-chrysanthemate and resmethrin using catalytic amounts of osmium tetroxide.[123,251]

In the former case, trimethyl amine oxide[123] proved to be superior compared to morpholine *N*-oxide,[243] used in the original Upjohn protocol[243] and in the latter case, the Sharpless reagent is so mild that it dihydroxylates the [C=C] double bond of the isobutenyl moiety keeping unaffected the furan ring usually highly sensitive to oxidation. Double asymmetric induction[252] was expected to take place but the stereochemical outcome of the reaction has not been disclosed, since the diol produced **17a**$_e$ has been immediately engaged in a subsequent reaction that produced the related aldehyde **19**$_e$ in which the asymmetric center produced in the dihydroxylation reaction at [Ce], has been subsequently destroyed (Scheme 108, entry b).[251]

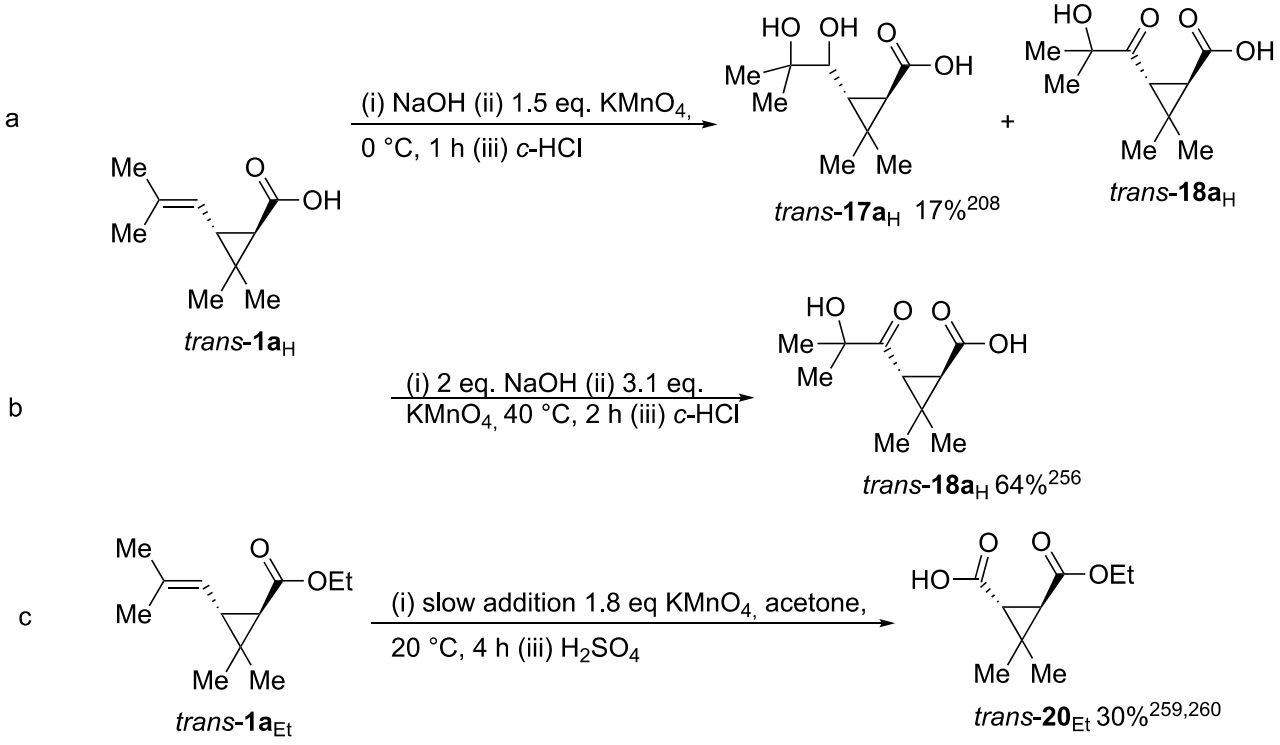
3.1.3.3.3 Reactions involving potassium permanganate. (Scheme 13, Route 23, Route 24). Reaction of potassium permanganate ($KMnO_4$) with chrysanthemic acid and its esters has been used quite early.[208,253,254] It can be observed in the selection of reactions disclosed in Scheme 109, Scheme 110, Scheme 111, that several types of compounds have been produced such as the diols **17a**, the alpha-ketoalcohol **18a**, and the carboxylic acid **20** that proceeds through the oxidative cleavage of the [C=C] double bond originally present.

The results depend upon the amount of reagent used and the pH of the medium that changes along the process and the stereochemistry of the starting material since in the case of the cis-stereoisomer epimerization takes often place on **18a** (see below).

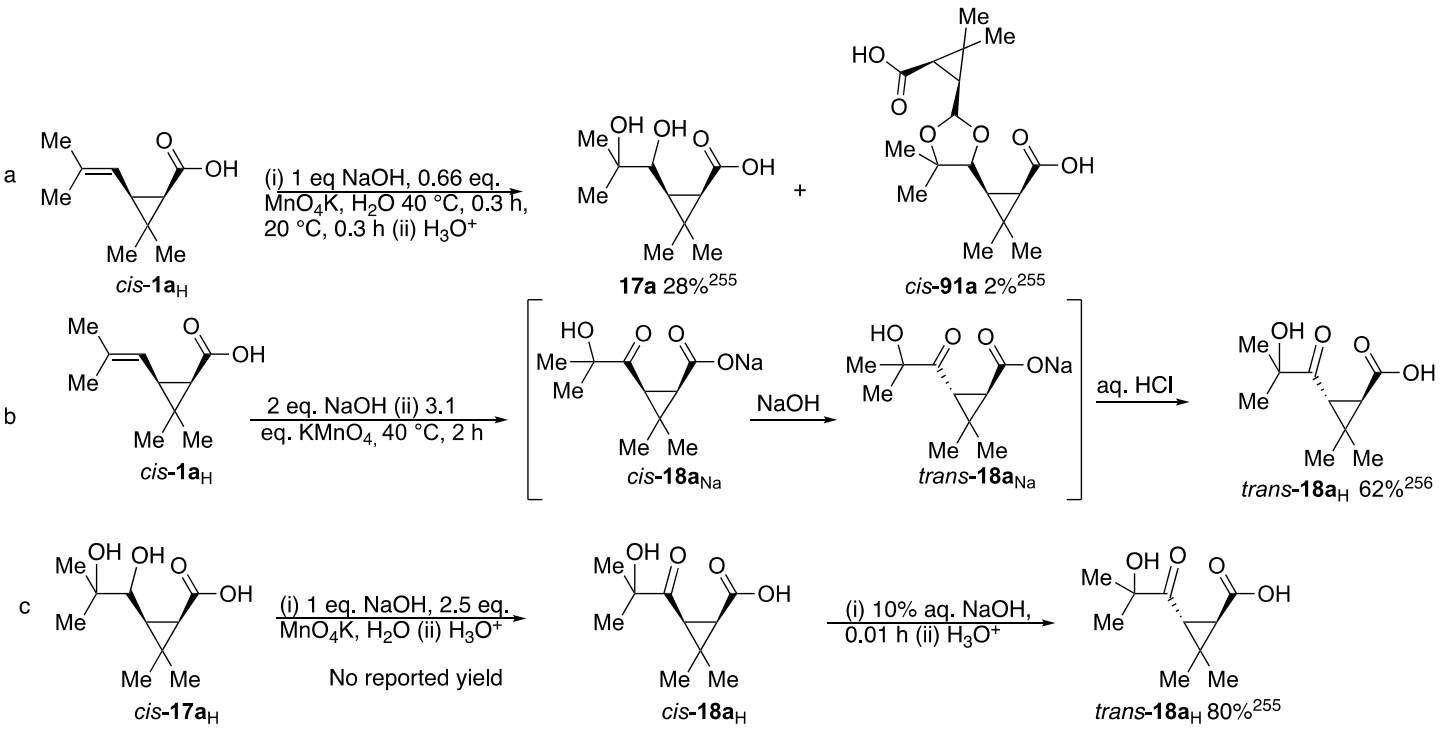
The former reactions carried out in basic media on *trans*- and *cis*-chrysanthemic acid (**1a**$_H$) with 0.66 equivalents of potassium permanganate delivered, after acid treatment, the diols **17a**$_H$ in modest to poor yields (Scheme 109, entry a,[208] Scheme 110, entry a[255]). It was later found that another compound was isolated in minute amounts, besides the diol on reaction of the *cis*-stereiosomer *cis*-(**1a**$_H$). Originally believed to be a stereoisomer of the *cis*-diol *cis*-**17a**$_H$,[208] it proved to be the acetal *cis*-**91** (Scheme 110, entry a).[255]

Since then, a different protocol has been used that involved a larger amount of reagents (NaOH: 2eq.; $KMnO_4$: 3.1 eq.). It delivers after acid treatment the keto alcohol *trans*-**18a**$_H$ starting either from the *trans*-(**1a**$_H$)

or the *cis*-(**1a**$_H$) chrysanthemic acid (Scheme 109 entry b; Scheme 110, entry b).[256] These results suggest that epimerization takes place alpha to the carbonyl group of the *cis*-ketol *cis*-**18a**$_{Na}$ prior to acidification.[256]



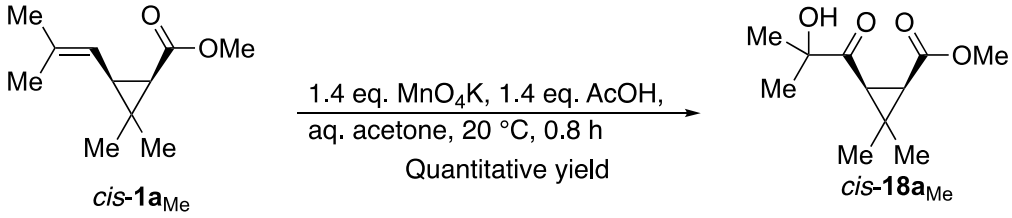
Scheme 109. Oxidation of chrysanthemic acid and its ethyl ester by potassium permanganate.[208,256]



Scheme 110. Synthesis of beta-hydroxy-ketones in basic media.[255,256]

In a separate experiment the *cis*-diol *cis*-**17a**$_H$ has been reacted[255] with 2.5 equivalents of potassium permanganate in the presence of a single equivalent of sodium hydroxide and delivered after acid hydrolysis stereoselectively the *cis*-ketol *cis*-(**18a**$_H$) (Scheme 110, entry c).[255] The latter on treatment with 10% aqueous sodium hydroxide and subsequent acid hydrolysis was instantaneously epimerized to its *trans*-stereoisomer *trans*-(**18**$_H$) (Scheme 110, entry c).[255]

Treatment of methyl *trans*-chrysanthemate *cis*-(**1a**$_{Me}$) with 1.4 equivalent of potassium permanganate in the presence of acetic acid according to the protocol disclosed by Srinivasan[257] avoids the epimerization reported above and delivers the ketols *cis*-(**18**$_{Me}$) stereoselectively and in almost quantitative yield (Scheme 111).[258]



Scheme 111. Synthesis of beta-hydroxy-ketones in acidic media.[258]

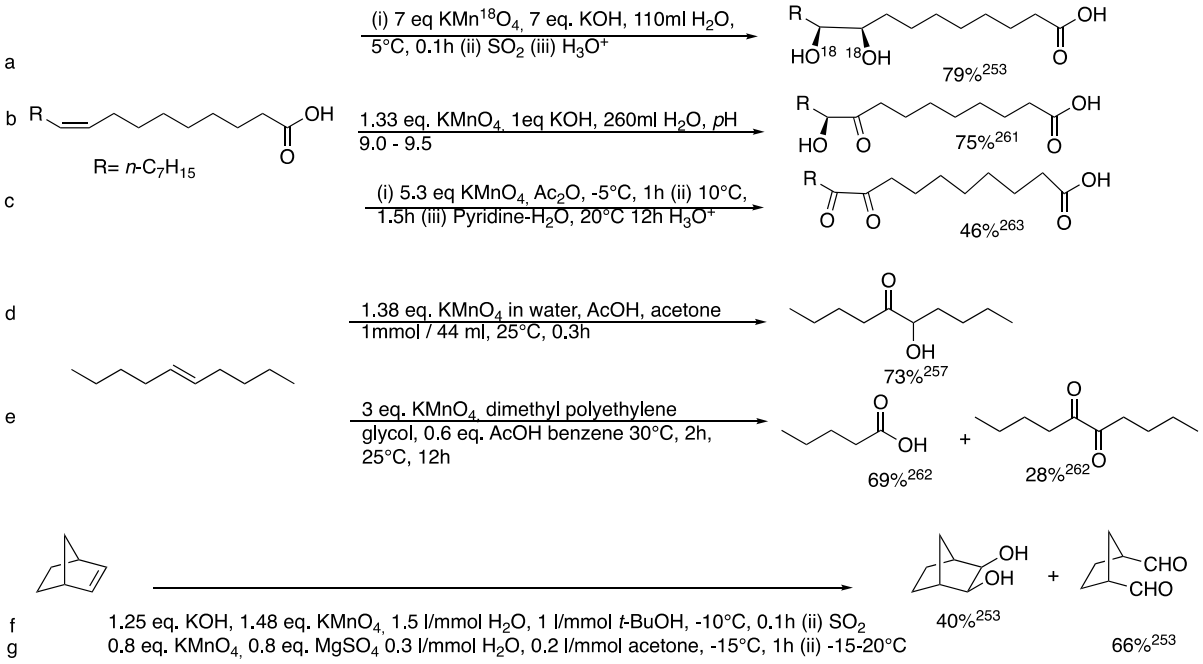
This result differs from the one carried out in acidic media on ethyl *trans*-chrysanthemate *trans*-(**1a**$_{Et}$) with 1.8 equivalent of potassium permanganate, sulfuric acid and sodium sulfite that instead delivers in poor yield mono-ethyl *trans*-caronate *trans*-(**20**$_{Et}$) (Scheme 109, entry c).[259,260]

Potassium permanganate has been for long used for dihydroxylation of compounds possessing [C=C] double bonds in their structure. It offers the advantage over osmium tetroxide to be non-toxic, less hazardous, much less expansive especially for industrial applications and to produce in fine manganese dioxide a brown solid co-product easy to separate by simple filtration. Potassium permanganate however suffers from a poor solubility in organic solvents (the reaction being usually carried out in water or aqueous *t*-butanol), a much low chemoselectivity since for example, at the contrary of osmium tetroxide, potassium permanganate oxidizes alcohols, but also delivers depending upon the conditions, and the substitution around the C=C double bond, a large variety of compounds in medium yields, often resulting from overoxidation of the diol primarily produced.[253,261-263]

We have gathered in Scheme 112 interesting results that include those reported on chrysanthemic acid in a wider context.

Conditions disclosed in Scheme 112, might favor the selective formation of (i) diols (1.5 eq. aq. $KMnO_4$, very dilute, highly basic solution; Scheme 112, entry a),[261,253] (ii) alpha-keto alcohols (1.33 eq. aq. $KMnO_4$: slightly basic solution,[261] Scheme 112, entry b or better under acidic conditions, Scheme 112, entry d[257]), alpha-diketones (1.33 eq. $KMnO_4$ anhydrous conditions,[263,264]) or products resulting from the oxidative cleavage of the original C=C double bond leading to dialdehydes (0.8 eq. $KMnO_4$-$MgSO_4$, anhydrous conditions, Scheme 112, entry g)[253] or carboxylic acids besides apha-diketones (3 eq. $KMnO_4$-phase transfer catalysis by ammonium salt or polyethers, anhydrous conditions, Scheme 112, entry e).[262,265]

As general trends (Scheme 112, entry a),[253,261,266] the synthesis of glycols is best achieved using low permanganate and high base concentration (pH> 12 for acyclic, pH> 9 cyclic compounds), at temperatures not higher and eventually lower than room temperature. The synthesis of ketols is best achieved at relatively high permanganate and low base concentrations (pH 4-8).[257-261]

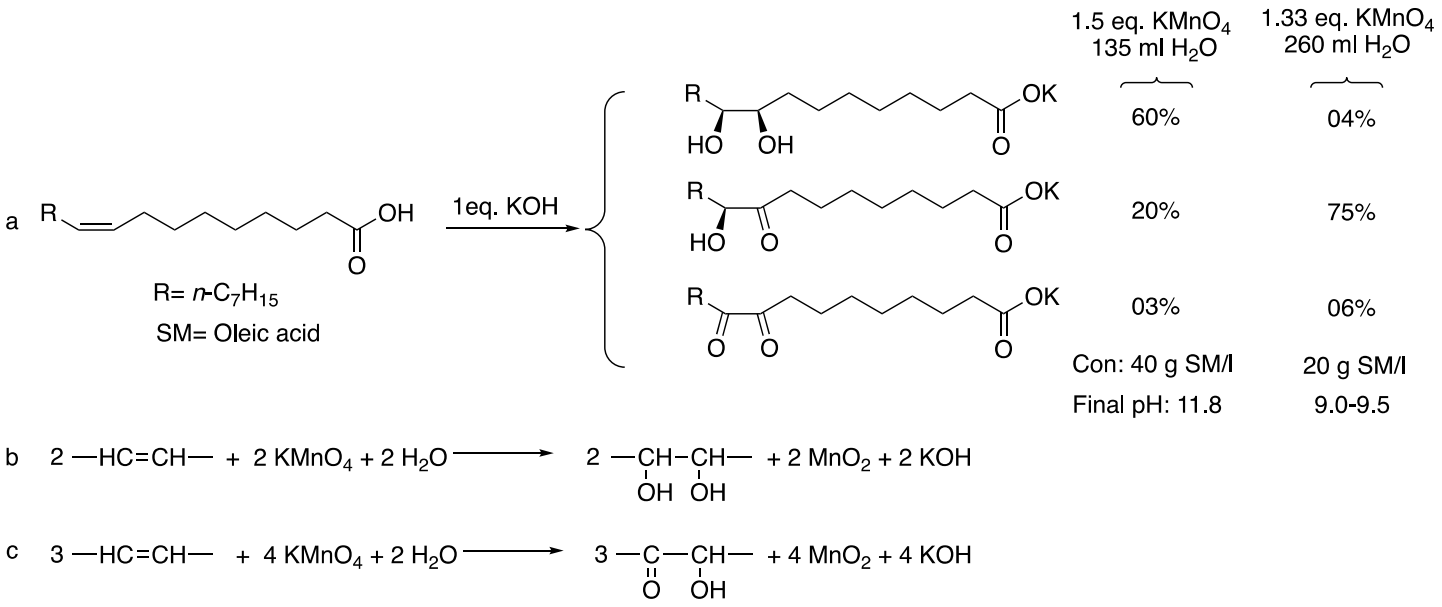


Scheme 112. Model reactions of potassium permanganate under various conditions on disubstituted alkenes.[253,261-263]

Solubilization of permanganate has been achieved by performing the reaction between potassium permanganate and the olefin in the presence of a phase transfer catalyst such as an ammonium salt, a crown ether or glyme polyethers able to exchange[265] or to complex[266] the potassium cation. For example, the reaction between 1-octene and aqueous neutral $KMnO_4$ that is not observed even after several hours at room temperature becomes exceedingly exothermic by addition of a 5% solution of a quaternary ammonium salt, in benzene and delivers in 0.5 h nonanoic acid in 90 % yield that result from the oxidative cleavage of the C=C double bond of 1-octene.[265] Similar results have been obtained[262] using Adogen 464, dimethyl polyethylene glycol or dicyclohexano-18-crown-6 in the presence of acetic acid (8-10%).

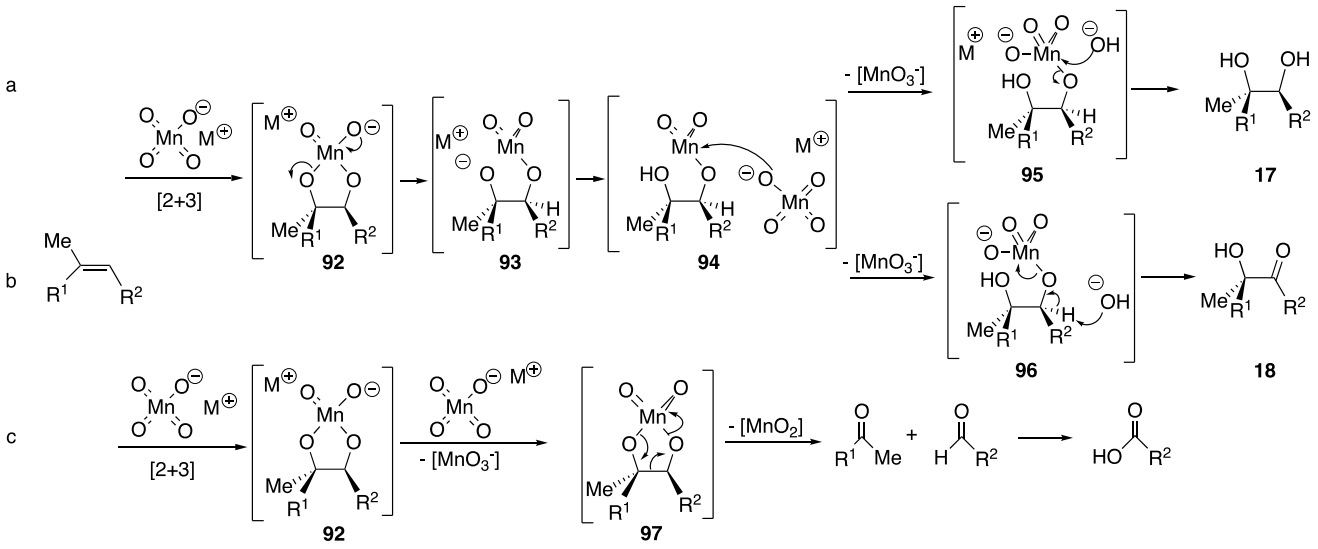
As already mentioned, the *p*H of the medium has an important impact on the outcome of the process. In such context we have to recall that the balanced equations that account for diol (Scheme 113, entry a) and ketol (Scheme 113, entry b)[261] formation from olefins suggest that the medium should become rapidly strongly alkaline because of the concomitant formation of sodium hydroxide, which proved to be the case (Scheme 113, entries b,c).[261]

Rational for the formation of different types of compounds resulting from the reactions of potassium permanganate with compounds possessing a C=C double bond is reported in Scheme 114.[253] It involves the intermediate formation of the cyclic manganese(V) ester **92** as the result of a 3+2 syn-cyloaddition reaction related to the one disclosed for osmium tetroxide (Section 3.1.3.3.2., Scheme 107) in which the Mn(VII) in $KMnO_4$ is transformed to Mn(V). Accordingly, the two oxygen atoms present in the beta-diols **17** (Scheme 114, entry a) originate from the permanganate as supported by the ^{18}O-labelling experiment disclosed in Scheme 112, entry a). The formation of each of the functional groups involves the cyclic intermediate **92**. Its ring opening leads through **95** to diol **17 (**Scheme 112, entry a), whereas beta-elimination reaction through **96** produces the ketols **18** (Scheme 114, entry b)[253,266]



Scheme 113. Effect of the amount of potassium permanganate on the pH of the medium and the nature of the product formed.[261]

The postulated mechanism leading to carbonyl or carboxyl compounds is disclosed in Scheme 114, entry c.[253]

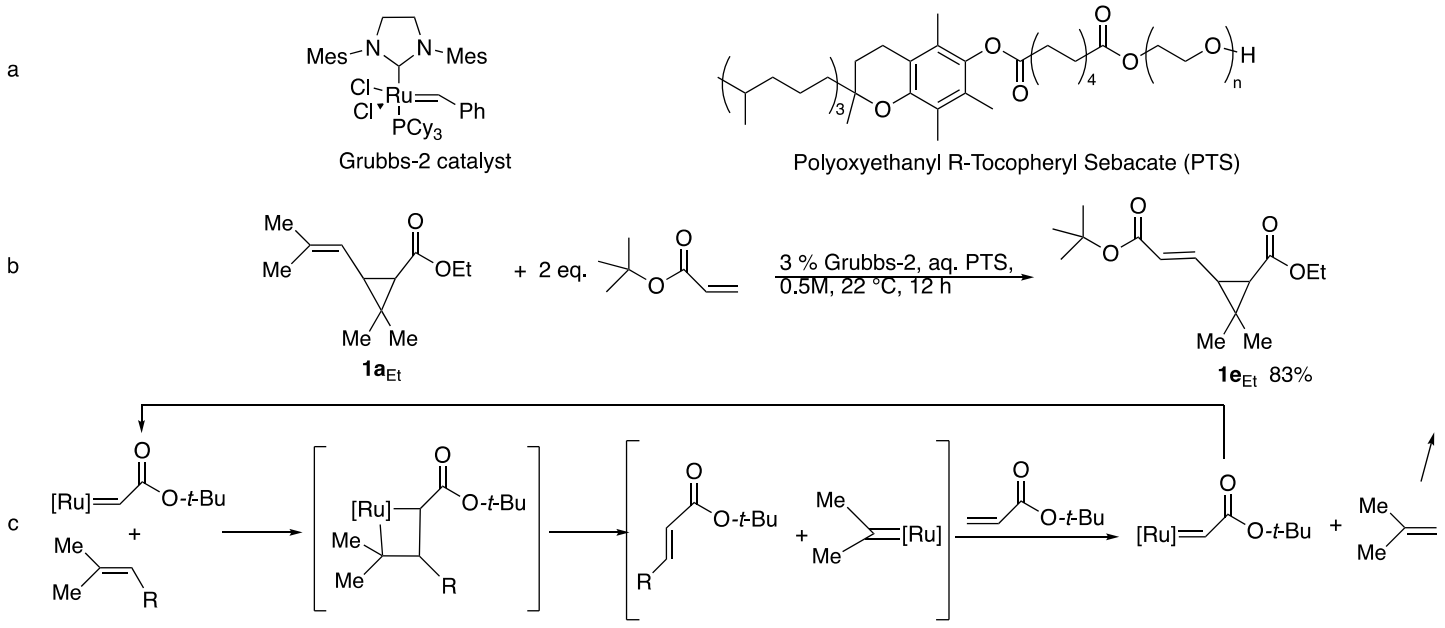


Scheme 114. Postulated mechanisms involved in the potassium permanganate transformations of alkenes to diols, ketoalcohols and cleavage of their C=C bond.

3.2. Reactions that involve the cleavage of the C=C double bond of chrysanthemic acid/esters (Scheme 13, Route 25)

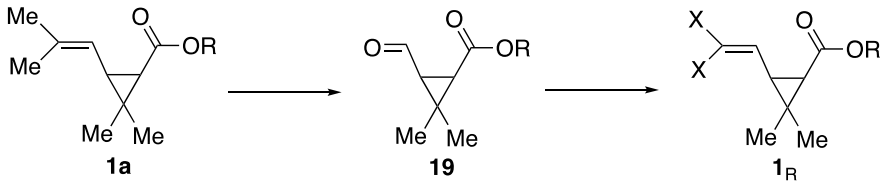
Reactions that offer the cleavage of the C=C double bond of chrysanthemic acid and its esters have played a key role for the synthesis of pyrethric acid and the exploration and discovery of novel pyrethroids such as cypermethrin (**1b**$_d$) and deltamethrin (**1c**$_d$)**.**

3.2.1. Cross-coupling metathesis. The transition metal catalyzed cross-coupling olefin metathesis reaction, the mechanism of which is disclosed in Scheme 115 entry c),[267] belongs to this category but has rarely be used on chrysanthemates. It has however been reported [268] that ethyl chrysanthemate (**1a**$_{Et}$) as a mixture of stereoisomers reacts with only two equivalents of *tert*-butyl acrylate in the presence of Grubbs-2nd generation catalyst produces at room temperature the unsaturated ester **1e**$_{Et}$ in 83% yield based on recovered starting material (50% isolated, Scheme 115, entry b).[268] The reaction proceeds in water in a micellar environment generated by polyoxyethanyl (*R*)-tocopheryl sebacate (PTS) (Scheme 115, entry a).



Scheme 115. Transition metal catalyzed cross-coupling olefin metathesis applied to ethyl chrysanthemate.[268]

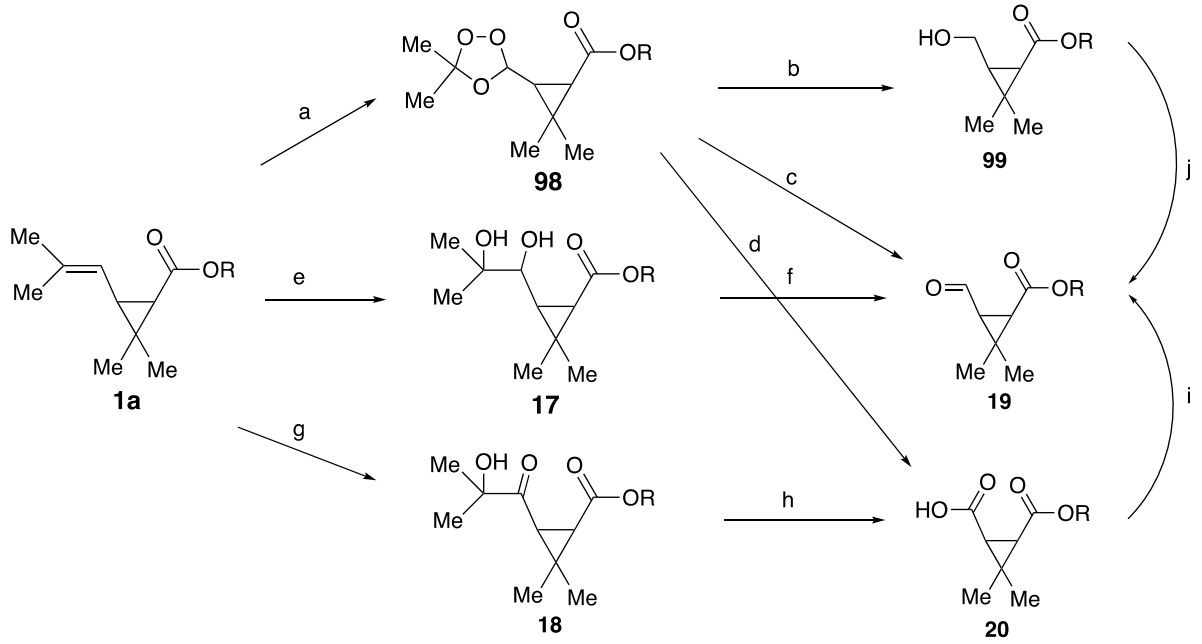
A more conventional approach involves the intermediate synthesis by oxidative cleavage of the C=C bond of chrysanthemic acid (**1a**$_H$) and its esters **1a**$_R$ leading to the formylcyclopropane carboxylic acid (hemicaronaldehyde, (**19**$_H$)) and its esters **19**$_R$ that are still used in some industrial syntheses of pyrethroids (Scheme 116). The synthetic strategies involved in the synthesis of several pyrethroid **1**$_R$ using **19** as an intermediate will be discussed in the forthcoming chapter (Chapter IVb).



Scheme 116 Multistep strategy used for the synthesis of chrysanthemate analogues bearing different substituents on their C=C double bond.

The cleavage of the C=C double bond of chrysanthemic acid (**1a**$_H$) and its esters **1a**$_R$ has been either performed through ozonides **98** (Scheme 117, entry a), diols **17** (Scheme 117, entry e), or keto alcohols **18**

(Scheme 117, entry g), and delivers depending upon the reagent used for the subsequent step, alcohols **99** (Scheme 117, entry b), aldehydes **19** (Scheme 117, entries c,f,i,j), or carboxylic acids **20** (Scheme 117, entry h).



Scheme 117. Strategies used to cleave the C=C double bond of chrysanthemic acid and its esters.

3.2.2. Ozonolysis. (Scheme 13, Route 25). Due to its capacity to cleave chemoselectively [C=C] double bonds, ozonolysis has played a crucial role in the pyrethrin field not only for their structure determination but also as a key step for the synthesis of valuable pyrethroids such as cypermethrin (**1b**$_d$) and deltamethrin (**1c**$_d$).

Ozonolysis [269-271,272,273] has been the subject of constant interest since the seminal work of Schönbein,[274] who discovered ozone,[275-278] a blue gas (O_3), as an allotrope of dioxygen (O_2). Harries,[279] described its reaction with ethylene first then on most complex organic compounds possessing an unsaturation. Harries built, as the head of the laboratory of the Siemens company, the first ozonizer able to produce as much as 15% of ozone in dioxygen, coined the terms ozonolysis and ozonide to name the process and the product of the reaction and also suggested its use for the structure determination of complex natural products,[4,276-278,279]

Criegee[269] proposed a unified mechanism for the above reaction, supported later by ^{17}O labelling experiments.[270] It features a 1,3-dipolar cycloaddition ([3+2]-cycloaddition) between the [C=C] double bond and ozone leading to a primary ozonide (molozonide) **100** (Scheme 118) that decomposes, through a cycloreversion reaction, leading to a carbonyl compound **19** and a carbonyl oxide **101**, an extremely reactive 1,3-dipole. The latter reacts with the carbonyl compound through another 1,3-dipolar cycloaddition to produce the secondary ozonide **102** possessing the trioxolane structure if the reaction is carried out in an inert solvent such as cyclohexane, benzene, chloroform or dichloromethane. In alcohols, usually methanol, the reaction takes another course since the carbonyl oxide **101** is trapped by the solvent and leads instead to the alkoxy hydroperoxide **103** (Scheme 118, route c).[66,280-283]

Ozonides **100** and **102** and hydroperoxides such as **103** are usually unstable and explosive compounds that have been further decomposed by heating (caution!) or using reductive or oxidative work-ups.

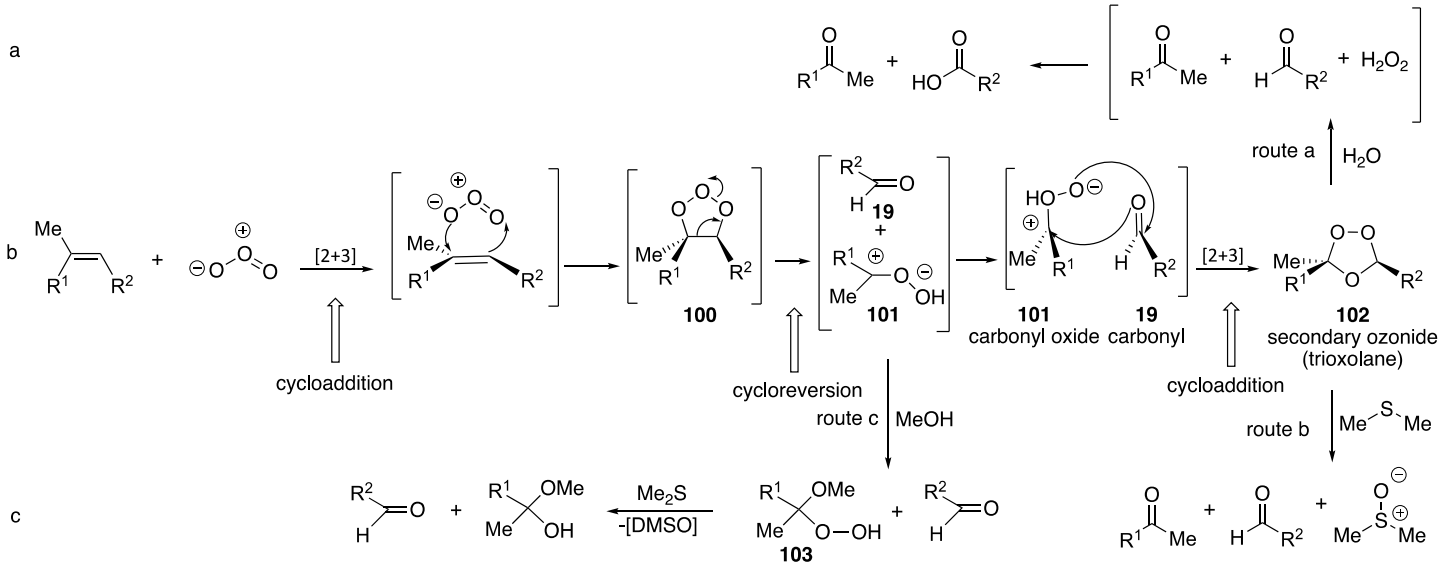
Upon reductive work-up, aldehydes and/or ketones (Scheme 118, route b) result from the cleavage of the [C=C] double bond of the alkene. Reductive work-up has been achieved using a series of reagents and conditions such as those involving sufites,[284] zinc in acetic acid (Scheme 124, entry f),[60,65] sodium iodide,

triphenylphosphine,[12,283] trimethylphosphite,[281] dimethylsulfide (Scheme 124, entry c),[282,285] thiourea,[282] or catalytic hydrogenation.[116,286] Concomitant formation of acetals has been reported and will be discussed in due course.[282]

Performing the work-up using sodium borohydride[287] or lithium aluminum hydride[287] able to reduce carbonyl compounds to alcohols, leads directly to the alcohols instead.

The reaction takes another course if the work-up is performed with water (Scheme 118, route a), hydrogen peroxide,[43,288] performic acid,[280] the Jones reagent (CrO_3/H_2SO_4)[289] or potassium permanganate since carboxylic acids are formed except from tetraalkyl substituted alkenes (Scheme 118, compare route a).

Decomposition of the ozonide with water often leads to a carboxylic acid and has been rationalized by the *in situ* formation of hydrogen peroxide from water and the peroxide (Scheme 118, route a).

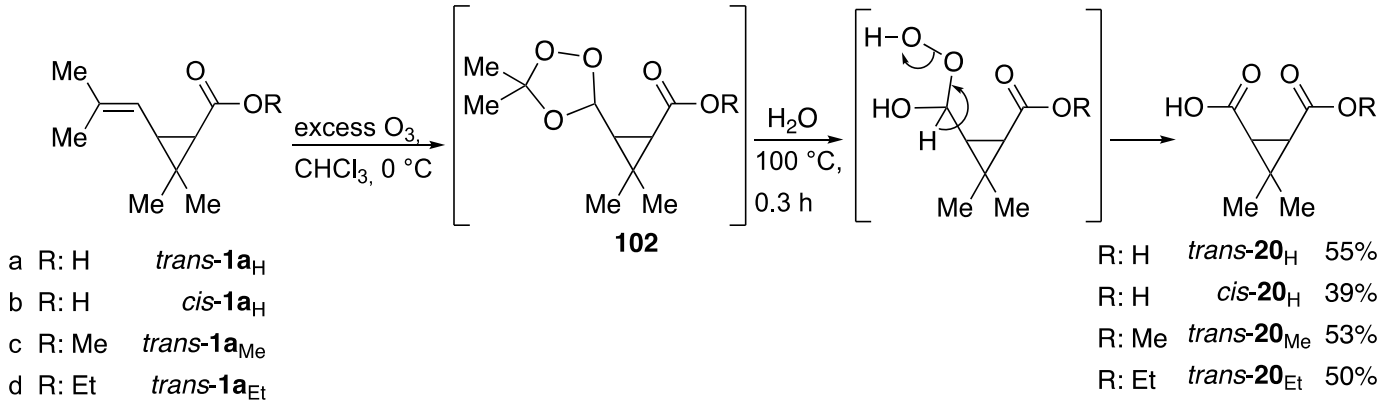


Scheme 118. Postulated mechanism to rationalize the effect of ozone of trisubstituted alkenes and products resulting from the subsequent treatment of the secondary ozonide first formed.

Ozonolysis of chrysanthemic acid (**1a**$_H$) (Scheme 119, entries a,b) and alkyl chrysanthemates **1a**$_R$ (Scheme 119, entries c,d) dates back before the work of Criegee and allowed their structure elucidation. Work-up with hot water was used to produce caronoic acid (**20**$_H$) or its monoalkyl esters (**20**$_R$).[31]

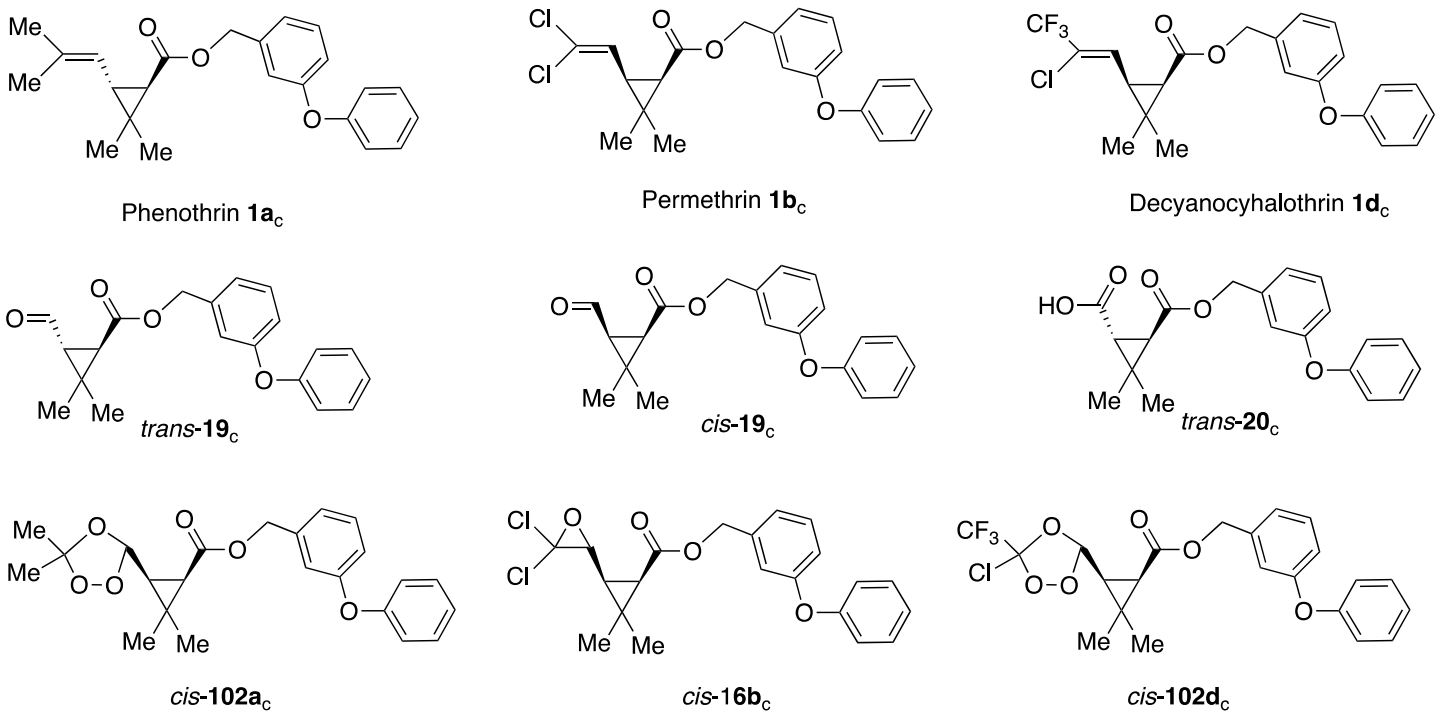
Since then, most of the conditions used to "ozonolyze" alkyl chrysanthemates **1a**$_R$ produce alkyl hemicaronates **19**$_R$ in routes to the synthesis of modified pyrethroids possessing a differently substituted [C=C] double bond.

Originally, the reactions have been carried out at room temperature by addition of methyl chrysanthemate (**1a**$_{Me}$) to a saturated solution of ethyl acetate containing up to 50% of ozone[116] and the methyl hemicaronate (**19**$_{Me}$) was obtained in extremely poor yield (7%) after subsequent reduction of the ozonide with hydrogen over palladium on calcium carbonate.[116] A better yield (30%) has been observed if the ozonolysis is instead carried out at -78 °C.[116]



Scheme 119. Oxidative cleavage of chrysanthemic acid and esters leading to caronic derivatives.[31]

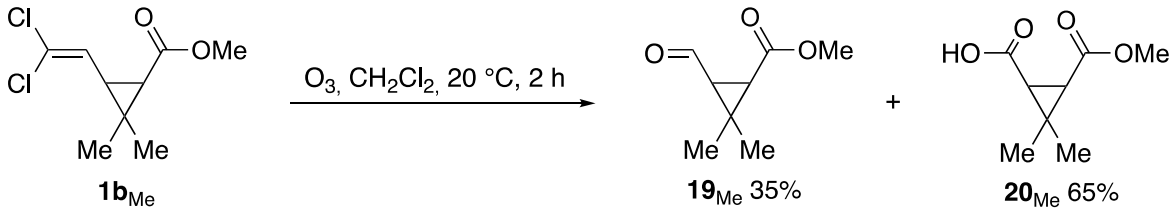
Ozonolysis on the other hand has been carried out on thin films on pyrethroids to check the mutagenicity of their degradation products. Thus, *trans*-phenothrin (**1a**$_c$) dissolved in dioxane-d_8 or cyclohexane-d_{12} has been subjected to a flow of ozone. The content of the resulting products directly analyzed without further treatment delivers[290] the related *trans*-hemicaronate **19**$_c$,[68,290] the related mono-ester of *trans*-caronic acid **20**$_c$ and presumably some related secondary ozonide **102a**$_c$. The presence of the latter in the mixture is suspected [290] from its signature in the NMR spectra and an increase of the signals of the aldehyde on further reaction [290] with triphenylphosphine that has been found to reduce ozonides to carbonyl compounds.[12,283]



Scheme 120. Products resulting from the ozonolysis of phenothrin, permethrin and decyanocyhalothrin.[290]

The same process applied [290] to permethrin (**1b**$_c$), deltamethrin (**1c**$_d$) and the decyanohalothrin (**1d**$_c$) delivers interesting results. Thus, the behavior of deltamethrin (**1c**$_d$) and permethrin (**1b**$_c$) are similar but differs from that of phenothrin (**1a**$_c$). They deliver, at different advancement of the reactions, the hemicaronates **19** and the

epoxides **16** as the major compounds. This is the case for the *cis*-**19**$_c$ and *cis*-**16**$_c$ from permethrin (**1b**$_c$), (Scheme 120). These results are different from those reported previously by the same group on methyl cypermethrinate (**1b**$_{Me}$) (Scheme 121).[291]



Scheme 121. Ozonolysis of methyl cypermethrinate.[291]

The reaction of ozone on decyanohalothrin (**1d**$_c$) proceeds 30 folds slower than that of *trans*-phenothrin (**1a**$_c$) and at 70% conversion delivers the *cis*-hemicaronate *cis*-(**19**$_c$) and presumably the secondary ozonide (**102d**$_c$) (as a mixture of stereoisomers?) as suggested[290] by ^{19}F and ^{1}H NMR. Trifluoroacetic acid is also formed it presumably results from the hydrolysis of trifluoro acetyl chloride formed beside *cis*-hemicaronate *cis*-(**19**$_c$) by decomposition of the secondary ozonide **102d**$_c$ (Scheme 120).[290] The methyl ester related to dicyanohalothrin (**1d**$_{Me}$) has been found to behave similarly although to ratio of ozonides differs.[290]

It has been however described that ozonolysis of 5-benzyl-3-furylmethyl (1*R*)-*trans*-chrysanthemate failed to give the corresponding hemicaronate and therefore the synthesis of this compound has been achieved using a different strategy (see Scheme 108).[251]

Otherwise, most of the work has been performed to produce alkyl hemicaronates **19**$_R$ the more conveniently, safely, (two explosions have been reported during the thin film reaction disclosed above) and in the larger amount possible. Ozonolysis usually has been performed at low temperature in round bottom flask, the chrysanthemate being dissolved in one of the solvents reported below with a calibrated flux of ozone and until a bluish color, characteristic for ozone, still remains for some time to ensure that all the starting material has reacted. Flushing the medium with an inert gas to remove the excess of ozone before work up is a precaution that should be followed (an explosion occurred when this precaution was omitted once in the author's lab).

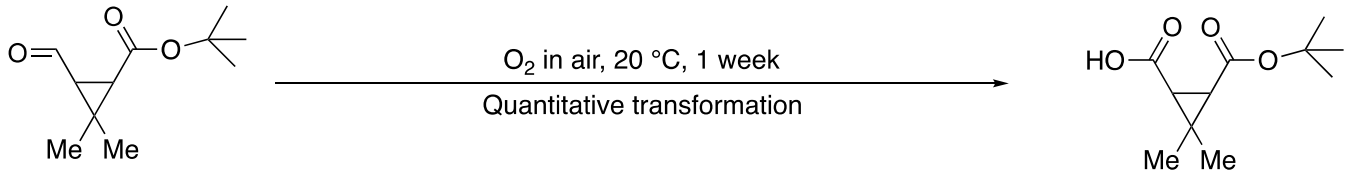
It has been for example reported[12] that successful ozonolysis of chrysanthemic esters has been performed under flow chemistry. This process allows the scale up from grams to tons using a 450 L loop reactor, to produce effectively 0.5 t of alkyl hemicaronates **19**$_R$ per day.[292] The Lonza bench-scale unit that is an exact scale down of the plant system is disclosed in a publication.[292]

The ozonolysis of enantiomerically pure-, racemic mixtures of *trans*- or *cis*-chrysanthemic acid (**1a**$_H$) and related esters **1a**$_R$,[31,35,43,71,**116**,283,284,293] has been carried out by bubbling a mixture of ozone in oxygen into different solvents such as dichloromethane,[283,293] dichloromethane-acetone (8/2),[251] chloroform,[31,43] hexane,[12] cyclohexane,[290] dioxane, [290] ethyl acetate,[116] acetic acidic. [65,209,284] and the resulting ozonides have been then reduced to the corresponding hemicaronates using dihydrogen in the presence of pre-reduced palladium on calcium carbonate (Scheme 122, entries a,b)[116] or zinc in acetic acid, (Scheme 122, entries c-e).[60,65,209,284]

a	R: Me	*trans*-**1a**$_{Me}$	(i) Excess O_3 solution, AcOEt, -78 °C (ii) 5% Pd/$CaCO_3$, 20 °C, 12 h	*trans*-**19**$_{Et}$ 30%[116]
b	R: Me	*cis*-**1a**$_{Me}$	(i) Excess O_3 solution, AcOEt, 0 °C (ii) 5% Pd/$CaCO_3$, 20 °C, 12 h	*cis*-**19**$_{Et}$ 7%[116]
c	R: Et	*trans*-**1a**$_{Et}$	(i) O_3, AcOH, 12 °C, 5 h (ii) 4 eq. Zn, Et_2O, 17 °C, 0.5 h	*trans*-**19**$_{Et}$ 76%[284]
d	R: *t*-Bu	*trans*-**1a**$_{tBu}$	(i) O_3, AcOH, 12 °C, 5 h (ii) 4 eq. Zn, Et_2O, 17 °C, 0.5 h	*trans*-**19**$_{tBu}$ 90%[65]
e	R: *t*-Bu	*cis*-**1a**$_{tBu}$	(i) O_3, AcOH, 12 °C, 5 h (ii) 4 eq. Zn, Et_2O, 17 °C, 0.5 h	*cis*-**19**$_{tBu}$ 82%[65]

Scheme 122. Ozonlysis of alkyl chrysanthemates and subsequent reductive treatment of the ozonide intermediate.[65,116,284]

It is interesting to note that the *t*-butyl esters resist these acidic conditions,[65] and that alkyl hemicaronates **19**$_R$ exhibit a high propensity to be autoxidized to the mono ester of caronic acid **20**$_R$ if this is not carefully prevented (Scheme 123).[51,65]



a *trans*-**19a**$_{tBu}$
b *cis*-**19a**$_{tBu}$

trans-**20**$_{tBu}$
cis-**20**$_{tBu}$

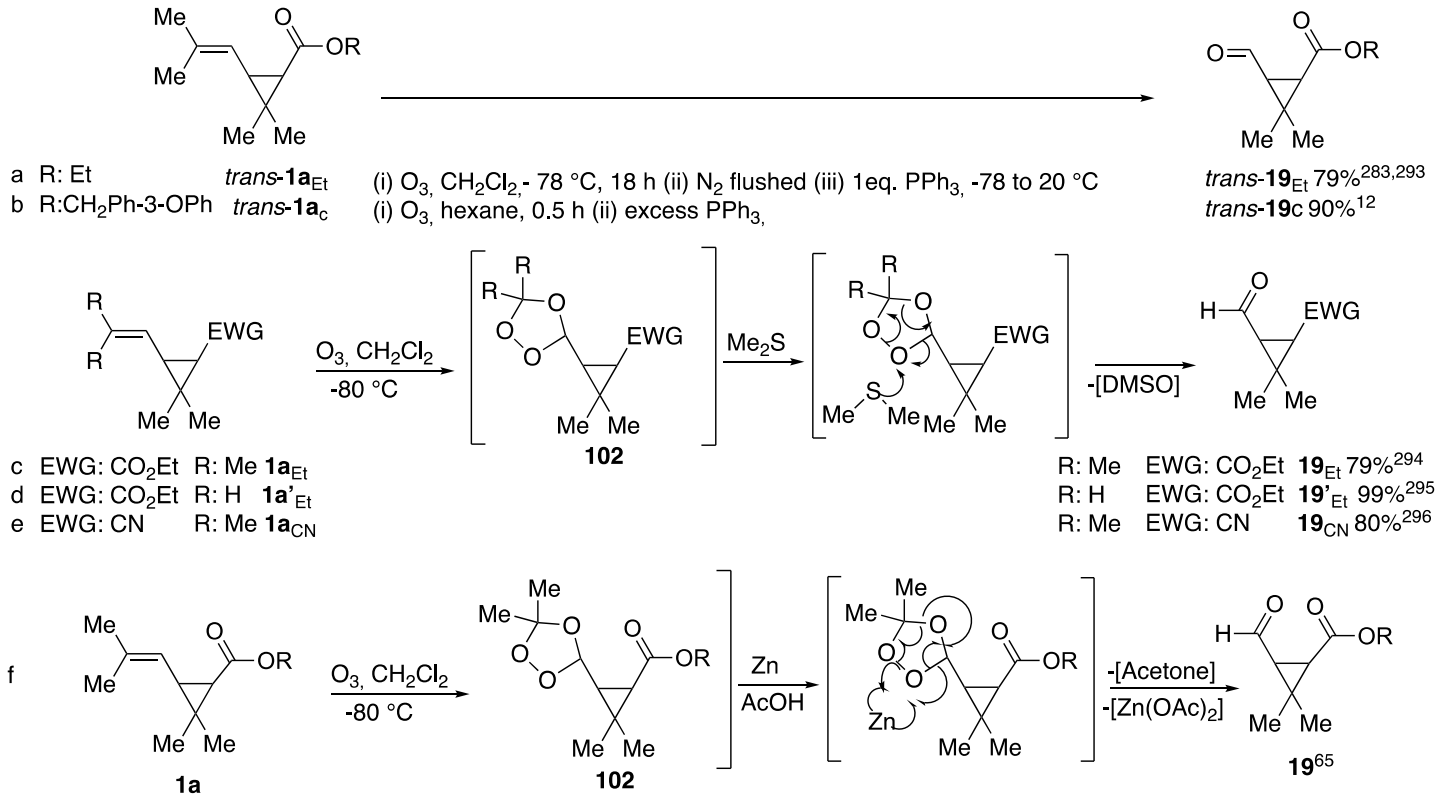
Scheme 123. Easy autoxidation of *t*-butyl hemicaronate in air.[65]

Reduction of ozonides, generated from chrysanthemic esters in inert solvents has been more recently successfully achieved using triphenylphosphine (Scheme 124, entries a,b)[12,283,290,293] or dimethyl sulfide (Scheme 124, entry c).[294] It has been extended to analogues possessing a terminal [C=C] double bond (Scheme 124, entry d),[295] and to the related chrysanthemonitrile (Scheme 124, entry e).[296]

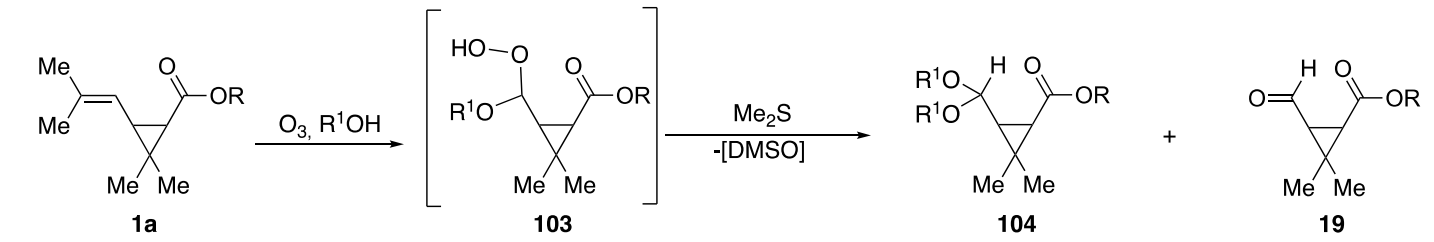
Although it possesses a faintly odor, dimethyl sulfide offers the advantage to possess a low molecular weight and to deliver on oxidation the water-soluble dimethyl sulfoxide.

Dimethyl sulfide has been also used[55, 57,60,66, 68,297-299] in the work-up of ozonized alkyl chrysanthemates **1a**$_R$ and chrysanthemic acid (**1a**$_H$) carried out in alcohols, especially in methanol,[43,55,57,60,66,68,299] as well as for the synthesis of alkyl oxobutenoates precursors of chrysanthemic acid.[58] Under these conditions, alpha-alkoxyperoxides **103** are expected to be formed rather than ozonides **102** (Scheme 125). The reaction usually leads to the acetals **104** unless an acidic work-up is included that delivers hemicaronic acid (**19**$_H$) or its esters (**19**$_R$) instead (Scheme 125, compare entry a to entries b,c). The formation of the acetals is unexpected and is unlikely to proceed from the corresponding aldehydes **19** and the alcohol used as the solvent since the conditions are not suitable and therefore their synthesis should have a different origin as will be discussed later.

The results disclosed[66] Scheme 125, entry c, are quite difficult to interpret due to the many ingredients (including (hydrazinocarbonylmethyl)trimethylammonium chloride, Girard reagent T) used in the work-up that involve acids, expected to allow the separation of any products lacking an aldehyde function.[66]



Scheme 124. Postulated mechanism of ozonolysis of ethyl chrysanthemate and chrysanthemonotrile through further treatment with dimethyl sulfide in dichloromethane or zinc in acetic acid. [12,65,283,293-296]

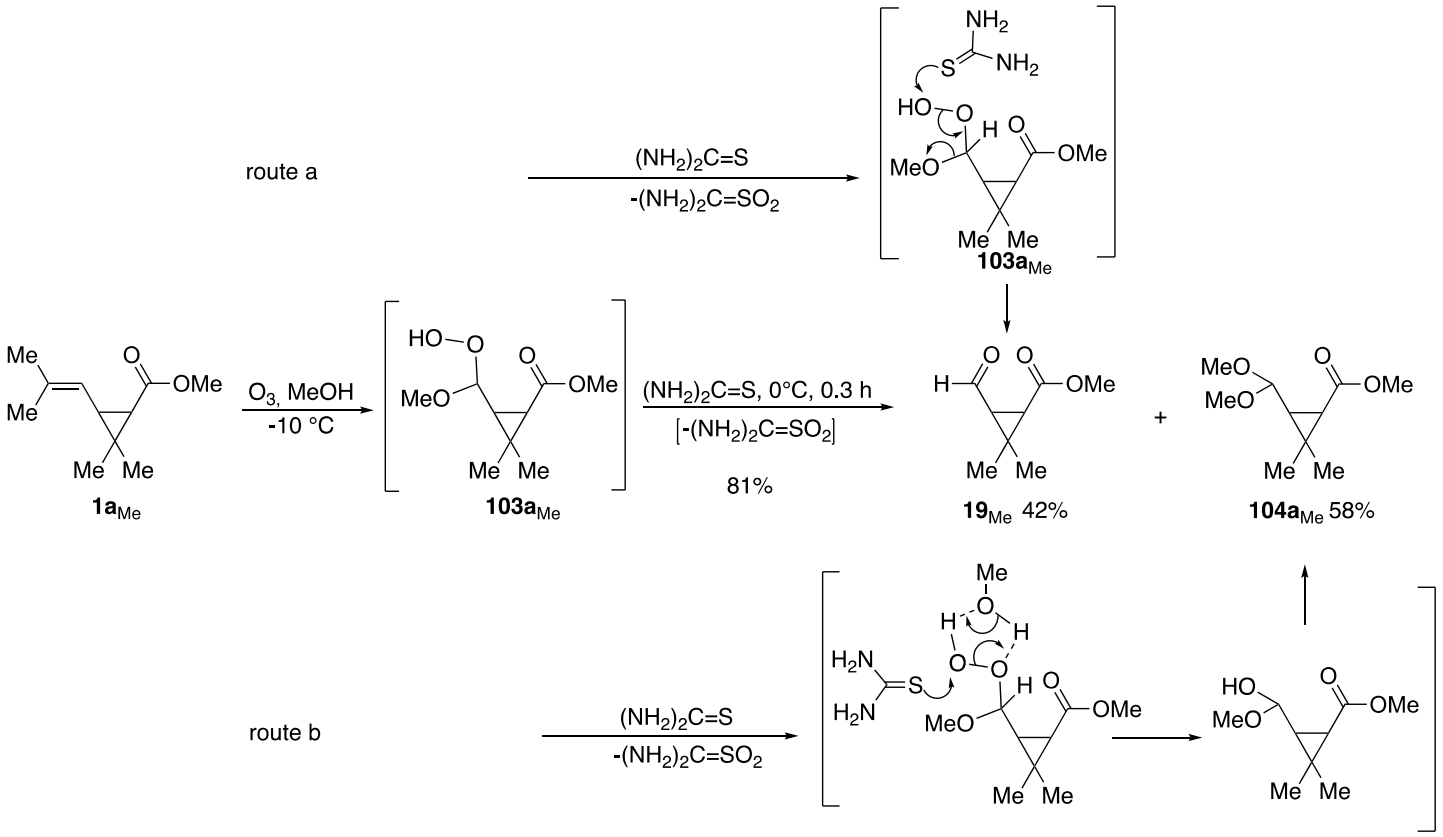


Scheme 125. Products resulting from the ozonolysis of chrysanthemic acids and its esters in methanol followed by reduction of the ozonide with dimethyl sulfide.[66,297,298]

A related process performed in methanol on methyl chrysanthemate (**1a**$_{Me}$) uses thiourea in place of dimethyl sulfide (Scheme 126)[282] and offers the advantage to use, contrary to the previous case, an odorless reductant that moreover performs the reduction rapidly (0.2 h), already at -10 °C, with only 0.5 molar equivalent of reductant. It however produces, in up to 80% yield a 40/60 mixture of the methyl hemicaronate (**19**$_{Me}$) and the related dimethoxy acetal **104a**$_{Me}$ (Scheme 126).[282]

The acetal **104a**$_{Me}$ cannot arise from methyl hemicaronate (**19**$_{Me}$) since under the reaction conditions, this aldehyde does not undergo acetalization.[282] The formation of each of these compounds has been rationalized by decomposition of the common methoxy hydroperoxide intermediate **103a**$_{Me}$ either (i) by destruction of the hydroperoxide group and the concomitant elimination of the methoxy group leading to the aldehyde (**19**$_{Me}$) (Scheme 126, route a) or (ii) solvent-assisted proton transfer that involves the destruction of the peroxo group [282] leading to the hemiacetal intermediate precursor of the acetal **104a**$_{Me}$ (Scheme 126, route b).[282]

The latter process allows one to bypass the usual formation of a hemiacetal in route to an acetal from an aldehyde and an alcohol that has been found[300] to be the limiting step of the acetalisation reaction. It also gives some support to the formation of the acetal **104a**$_{Me}$ under such unusual conditions and the related observation when dimethyl sulfide is instead used (Scheme 125).[60,66,297,298]



Scheme 126. Products resulting from the ozonolysis of chrysanthemic acids and its esters in methanol followed by reduction of the ozonide with thiourea.[282]

3.2.3. Oxidative cleavage of the C=C double bond of chrysanthemic acid and chrysanthemate involving high valent iodine reagents. The synthesis of hemicaronic acid (**19**$_H$) and *cis*- and trans-alkyl hemicaronates **19**$_R$ has been also achieved from chrysanthemic acid (**1a**$_H$) or its esters **1a**$_R$ through a multistep sequence that involves their dihydroxylation, using usually osmium tetroxide (Scheme 127,[251] Scheme 128;[255] see also section 3.1.3.3.2.) and more rarely their epoxidation (Scheme 129[235]; see also Section 3.1.3.2.) and subsequent cleavage of the resulting diols **132** or epoxides **16** using sodium metaperiodate ($NaIO_4$) (Scheme 127[251]) or periodic acid (HIO_4:$2H_2O$; H_5IO_6, Scheme 128,[255] Scheme 129[235]).

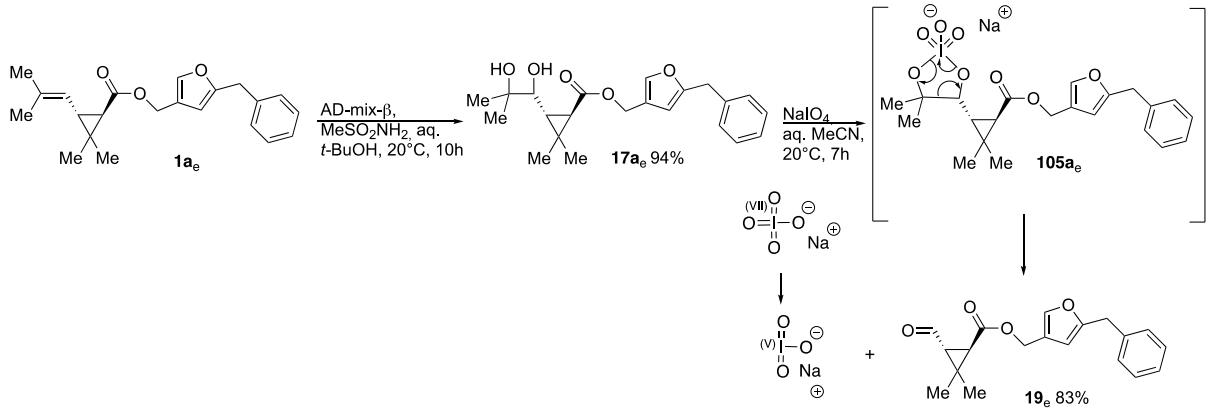
The oxidative cleavage of diols, the Criegee-Malaprade reaction, that has been pioneered by Criegee[301] and Malaprade[302] in the 1930's, proceeds usually with high efficiency and high functional group tolerance to provide

efficiently two carbonyl compounds. It however requires the use of stoichiometric amounts of high-valent iodine reagents or lead tetraacetate ($PbOAc_4$) that is also able to achieve the same transformation. These reagents are of high molecular weight, may generate stoichiometric hazardous waste[303] and are superseded by ruthenium[304-306] or silver(I)[303]-catalyzed reactions that are disclosed below. They possess the advantage to avoid overoxidation of aldehydes to carboxylic acids that often takes place with the previous methods.[303-306]

The mechanism of the high-valent iodine reaction is tentatively disclosed in Scheme 127. It implies[307] the intermediate formation from either *cis*- and *trans*-diols of a five-membered cyclic diester of iodo(VII) acid **105** that decomposes in a single-step reaction in which the three valence electron pairs are shifted simultaneously.

One of these shifted electron pairs ends up as a lone pair on iodine that change its valency from VII to V. The others allow the formation of the pi-bonds of the carbonyl compounds and achieve the cleavage of the sigma-C−C bond (Scheme 127).[307]

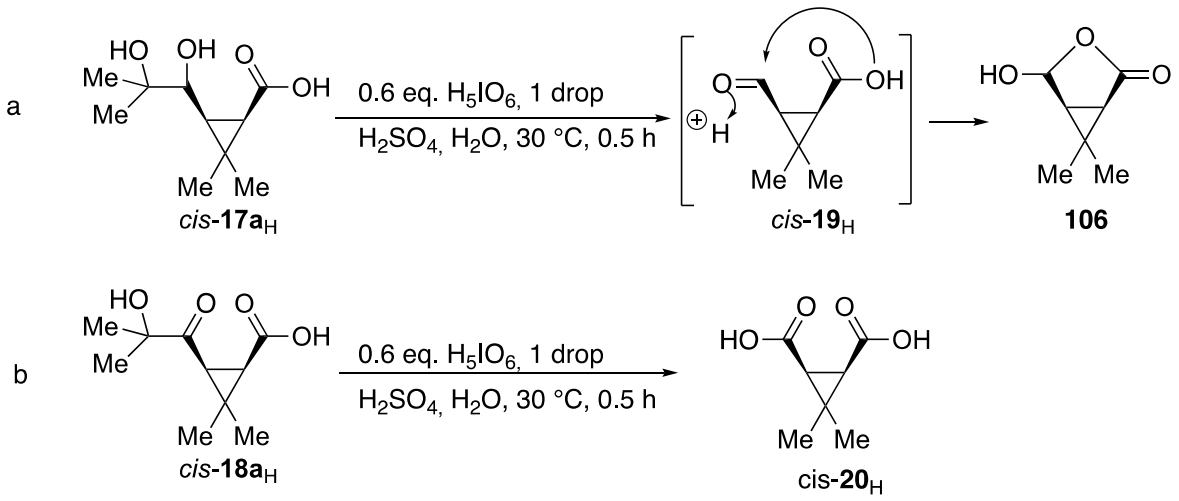
The two-steps process involving the formation and cleavage of vicinal diols is good alternative to the ozonolysis of resmethrin that indistinctly cleave the C=C double bond of the chrysanthemic part and that of the furan ring (Scheme 127).[251]



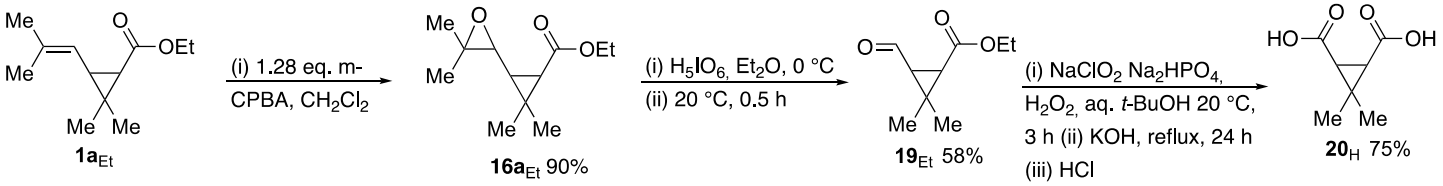
Scheme 127. Stepwise synthesis of hemicaronate involving the intermediate formation of diol and sodium periodate treatment.[251]

Periodic acid promotes the cleavage of the diol derived from the *cis*-chrysanthemic acid *cis*-**17a**$_H$ but does not lead to *cis*-hemicaronic acid *cis*-(**19**$_H$) but instead to the lactol **106** (biocartol) as the result of an intramolecular cyclization promoted by the acidic medium (Scheme 128, entry a).[255] Periodic acid also cleaves the ketoalchool *cis*-**18a**$_H$ but produces caronic acid *cis*-(**20**$_H$) (Scheme 128, entry b).[255]

The acidic medium also favors the epoxide ring opening of ethyl oxido-chrysanthemate (**16a**$_{Et}$) that promotes the concomitant cleavage leading to the ethyl hemicaronate (**19**$_{Et}$) (Scheme 129).[235] The latter has been further oxidized to ethyl caronate (**20**$_{Et}$) and finally transformed to caronic acid (**20**$_H$) on sequential treatment with sodium chlorite/hydrogen peroxide, saponification using potassium hydroxide then acidification.[235]

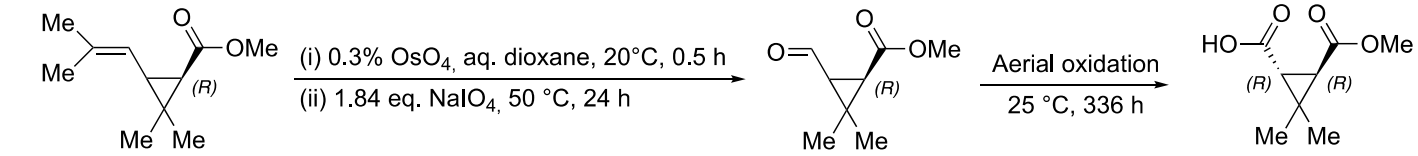


Scheme 128. Action of periodic acid on a diol and a beta-hydroxy ketone derived from *cis*-chrysanthemic acid.[255]



Scheme 129. Action of periodic acid on ethyl oxido-chrysanthemate and of sodium chlorite on the resulting hemicaronate.[235]

A more straightforward process, known as the Lemieux-Johnson oxidation,[308,309] has been used to achieve the one pot synthesis of methyl hemicaronate (**19**$_{Me}$) from methyl chrysanthemate (**1a**$_{Me}$). It uses catalytic amounts of osmium tetroxide and at least stoichiometric amounts of sodium periodate (Scheme 105).[51,310] The latter not only cleaves the diol but also recycles the reduced osmiate [Os(VI)] to the original osmium VII reagent. It not only dramatically reduces the cost and the dangerousness of the process but also shorten it (Scheme 130).



a (1*R*,3*R*)-*trans*-**1a**$_{Me}$
b (1*R*,3*S*)-*cis*-**1a**$_{Me}$

(1*R*,3*R*)-*trans*-**19**$_{Me}$ 68%[51,310]
(1*R*,3*S*)-*cis*-**19**$_{Me}$ 72%[310]

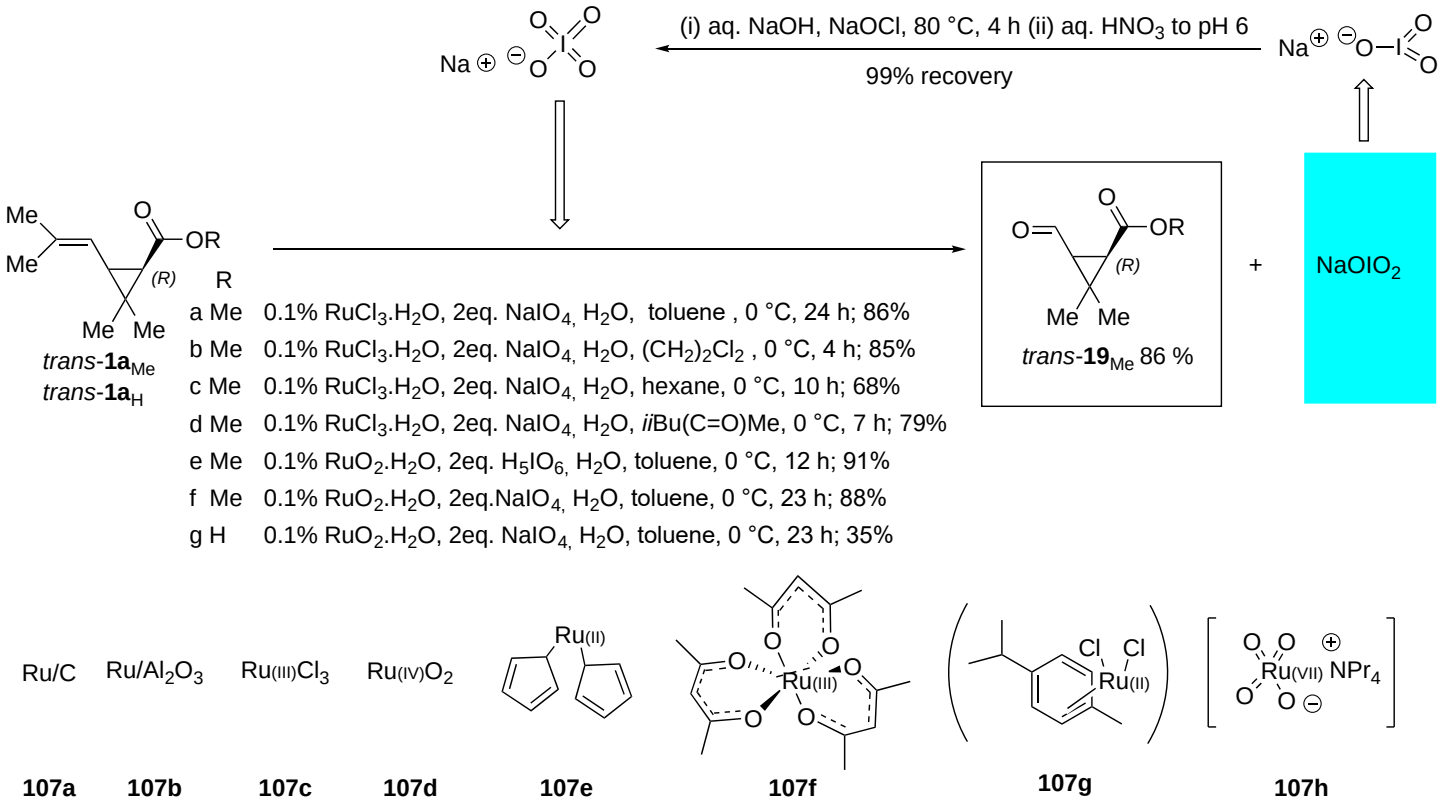
(1*R*,3*R*)-trans-**20**$_{Me}$ 85%[51]

Scheme 130. Synthesis of methyl hemicaronate form chrysanthemic acid and aerial oxidation to methyl caronate.[51,310]

In order to make the process "greener", another approach has been described (Scheme 131).[304] It uses ruthenium containing catalysts **107**, high-valent iodine (VII) compounds as final oxidants and an original solution to recycle the reduced iodine (V) by-products.[304]

It takes advantage of the previous work of Sharpless[305] and Yang,[306] who described that ruthenium(VIII) compounds have a high propensity to cleave the C=C double bond of alkenes as well as those belonging to aromatic compounds through a mechanism related to the one disclosed for OsO_4.[305,307] The reduced iodine (V) co-products have been then oxidized back to high-valent iodine (VII) compounds using a stoichiometric amount NaOCl[307] and avoids costly waste management (Scheme 131).[304]

Accordingly, several reagents and conditions have been tested on methyl *trans*-chrysanthemate *trans*-(**1a**$_{Me}$) and on *trans*-chrysanthemic acid *trans*-(**1a**$_H$). We have collected in Scheme 131 a few results among the many disclosed in the patent that are representative and allow comparisons.[304] The reaction has been successfully extended to the synthesis of ethyl-, propyl-, *i*-propyl-, butyl-, *i*-butyl- and *t*-butyl hemicaronates, among others.



Scheme 131. One-pot ruthemium catalyzed sodium periodate cleavage of [C=C] double bond of chrysanthemic acid and some of its esters.[304]

As general trends the reactions are carried out at 0 °C in a biphasic water-organic solvent mixture (usually toluene), using catalytic amounts (< 0.1 eq.) of Ru(II), Ru(III), Ru(IV) or Ru(VII) catalysts **107** and an excess of alkaline metal periodates (usually $NaIO_4$) or periodic acid as final oxidant.[304] They usually deliver methyl hemicaronates in good (65%) to extremely good (90%) yields. It has been found[304] that:

(a) ruthenium supported on carbon **107a** or on alumina **107b**, ruthenium(III) trichloride **107c** and ruthenium(IV) dioxide **107d** are less efficient than dicyclopentadienyl ruthenium(II) **107e**, tris(acetylacetonato)ruthenium(III) **107f**, dichloro(*p*-cymene)ruthenium(II) dimer **107g** or tetrapropylammonium perruthenate (VII) **107h** that are efficient catalysts (Scheme 131),

(b) dichloroethylene is a better solvent than toluene or hexane (Scheme 131, compare entry b to entries a,c),

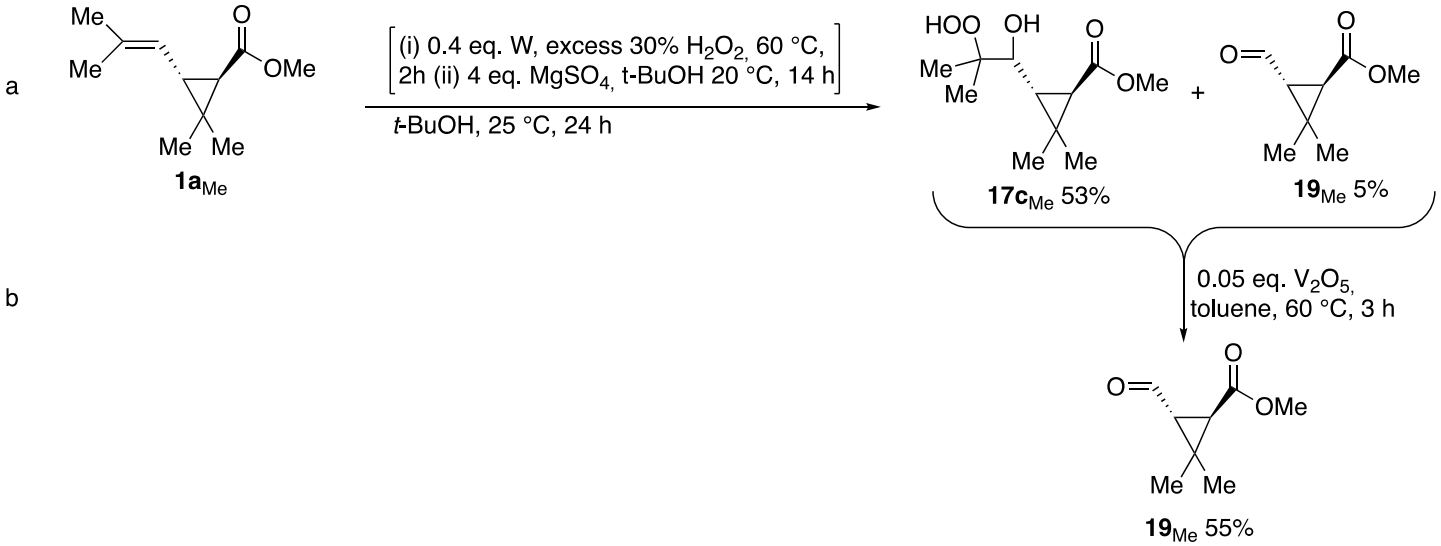
(c) the reactivity of periodic acid in the presence ruthenium(IV) oxide hydrate in toluene (Scheme 131, entry e, compare to entry a) surpasses that of sodium and potassium periodate and that lithium periodate is the least reactive of the series,

(d) far better yield is obtained from methyl *trans*-chrysanthemate *trans*-(**1a**$_{Me}$) than from the related acid *trans*-(**1a**$_{H}$) (Scheme 131 entries f,g) and, most importantly,

e) sodium iodate formed as co-product remains in the aqueous phase and is oxidized there by sodium hypochlorite in the presence of sodium hydroxide so sodium paraperiodate ($Na_2H_3IO_6$) deposits as crystals in up to 99% and can be recycled (Scheme 131).[304]

In almost all the cases methyl hemicaronate (**19**$_{Me}$) needed as starting material to produce homologuous chrysanthemic esters and explore their insecticidal behavior is produced in high yield. However, in some cases caronic acid (**20**$_{H}$) or methyl caronate (**20**$_{Me}$) have been produced from chrysanthemic acid (**1a**$_{H}$) or methyl chrysanthemate (**1a**$_{Me}$) as byproducts or voluntarily. For example, the synthesis of the overoxidized (**20**$_{H}$) and (**20**$_{Me}$) have been directly achieved using potassium permanganate (Scheme 109)[259] or through the intermediate formation of diols, using for example chromium trioxide,[208] or ketols (Scheme 128).[255] Transformation of hemicaronates to monoalkyl caronates has been also achieved by air oxidation (Scheme 130, entry a)[51] or better using pure dioxygen.[12]

3.2.4. Reactions involving hydrogen peroxide in the presence of a catalyst. We have already reported (Section 3.1.3.3.1.; Scheme 105) that the catalyst prepared from hydrogen peroxide and tungsten metal, in the presence of magnesium sulfate as dehydrating agent, reacts with methyl chrysanthemate (**1a**$_{Me}$) in *t*-butanol. The main product is beta-hydroxyperoxy alchohol **17c**$_{Me}$ in 50 to 60 % yield besides small amounts of methyl hemicaronate (**19**$_{Me}$) (5-6%, Scheme 132, entry a).[239] Although the yield of the latter can reach 30% using tungsten sulfide or tungsten silicide, (**19**$_{Me}$) is best produced [239] by reacting the crude mixture of **17c**$_{Me}$ and (**19**$_{Me}$) obtained above with vanadium pentoxide as described in Scheme 132, entry b.[239]



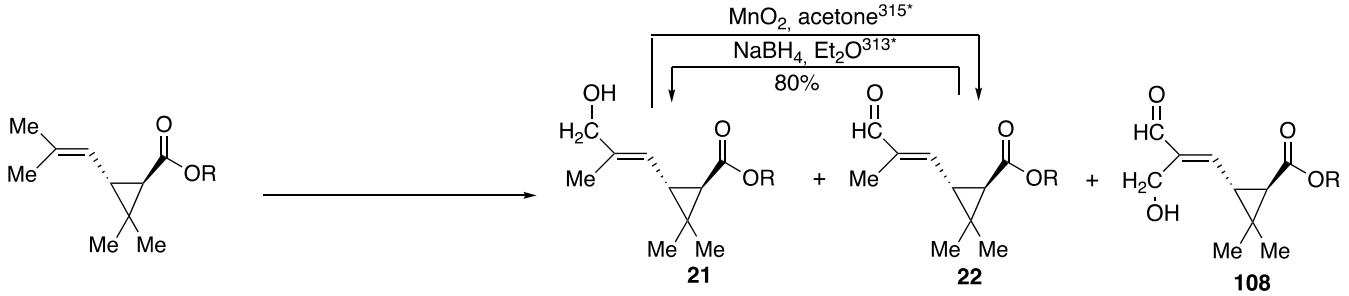
Scheme 132. Synthesis of methyl hemicaronate from chrysanthemic acid and hydrogen peroxide catalyzed by tungsten and vanadium oxides.[239]

The synthesis of methyl hemicaronate (**19**$_{Me}$) has been also achieved in a single step using a preformed reagent produced from hydrogen peroxide in the presence of larger amount of tungstic acid monohydrate (543 mg/ 4 g chrysanthemic acid 15 °C, 24 h, 55% yield of (**19**$_{Me}$)).[311] Performing the reaction using different conditions

and different metal catalysts such as tungsten trioxide, methylrhenium trioxide, molybdenum trioxide, on methyl, ethyl and *t*-butyl chrysanthemic esters, proved far less efficient producing methyl hemicaronate (**19**$_{Me}$) and gave much poorer yields.[311]

3.3. Reactions affecting the vinylic methyl groups

3.3.1. Reactions involving selenium dioxide. (Scheme 13, Route 27). Allylic oxidation of the vinylic methyl group of methyl- (**1a**$_{Me}$)[312] and *t*-butyl (**1a**$_{tBu}$),[54,313] chrysanthemates and phenothrin[12] (**1a**$_c$) have been effectively achieved using a stoichiometric or sub-stoichiometric amount of selenium dioxide at reflux of ethanol or dioxane (Scheme 133). Depending on the conditions, the reaction leads to the allyl alcohols **21**, the unsaturated aldehydes **22** or the overoxidized derivatives **108** in which each of the two methyl groups have reacted (Scheme 133). Allylic oxidation using selenium dioxide has been successfully extended to methyl *cis*-homochrysanthemate (**75a**$_H$) (from (1*S*,3*R*)-*cis*-chrysanthemic acid) and has been used as a key step in the synthesis of (−)-bertyadionol.[40]



a	1a$_{Me}$	R: Me	1.3 eq SeO_2, ethanol, reflux, 1 h	64%[312]	34%	66%	
b	1a$_{tBu}$	R: *t*-Bu	1.05 eq. SeO_2, dioxane, reflux, 1 h	79%[54]		41%	36%
c	1a$_c$	R: CH_2Ph-3-OPh	1.1 eq. SeO_2, dioxane, reflux, 1 h	80%[12]		100%	

Scheme 133. Selenium dioxide oxidation of alkyl chrysanthemates.[12,54,312,314]

Selenium dioxide, the Riley reagent has been discovered at Imperial Chemical Industries (ICI) in 1932 and has widely used due to its exceptional propensity to oxidize alkenes (the Guillemont reaction)[316] and carbonyl compounds at their alpha position. It however suffered poor reputation due to the production of bad-smelling selenium co-products that require extraction with mercury.[314]

Furthermore, although several mechanisms have been proposed, none of them proved to be suitable until the work of Sharpless who (i) disclosed its catalytic version[318,319] that uses *t*-butyl hydroperoxide[319] as final oxidant and (ii) proposed[314,317] in collaboration with Arigoni, the mechanism that has been, since then, widely accepted (Scheme 134).

The reaction takes place on a wide range of olefins producing allyl alcohols and/or α,β-unsaturated carbonyl compounds, without scrambling of the [C=C] double bond (Scheme 133, entries a,c). Anyhow, further reduction or oxidation of the resulting mixture for example with $NaBH_4$[313,320] or MnO_2[315] allows the synthesis of only one of these compounds (Scheme 133).[317] Over-oxidation is observed (Scheme 133, entry b)[54,314] often when the reactions are carried out with one equivalent of the reagent but for long time (10 h).[314,317]

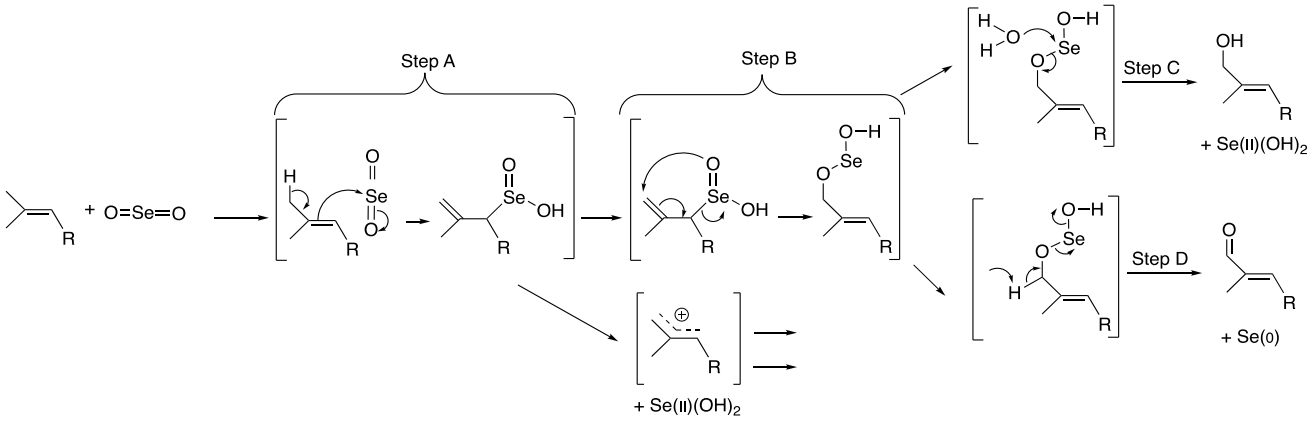
The reactivity of olefins follows their nucleophilicity. Terminal olefins are the least reactive and those bearing an isopropylidene moiety one of the most.[314,317]

In the case of (i) α,β-disubstituted olefins the methylene group is oxidized in priority to a methyl or a methine group and (ii) for trisubstituted olefins, not only oxidation occurs on the most substituted side of the

[C=C] double bond but also a methyl group is oxidized in priority to a methylene or a methine group. Furthermore, the reaction proceeds in this case with high stereocontrol producing almost exclusively the *E*-stereoisomer as it is the case with alkyl chrysanthemates **1a** (Scheme 133, entries a,c).[12,54,312]

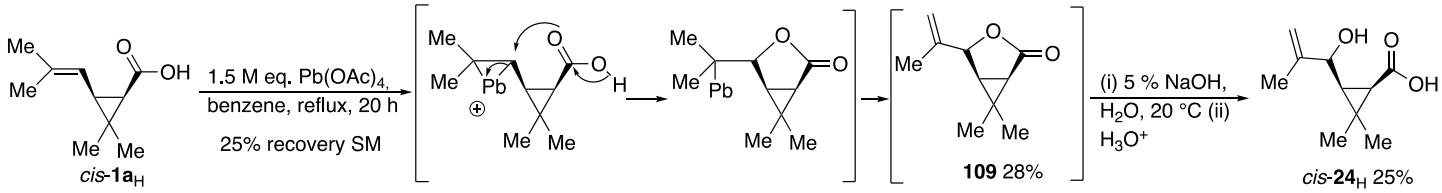
Selenium dioxide promoted allylic oxidation of alkenes proceeds in two successive steps (Scheme 134) [314,317,318] The first one is an ene-reaction that produces allyl seleninic acids (Scheme 134, step A).[317,318] These are prone to a subsequent [2,3] sigmatropic rearrangement that finally leads to seleninates (Scheme 134, step B).[317,318] *In situ* hydrolysis of the latter generates *E*-allyl alcohols (Scheme 134, step C)[318] whereas competing α-elimination leads to *E*-unsaturated carbonyl compounds (Scheme 134, step D).[314,318]

SeO_2-oxidation of chrysanthemates coupled with subsequent oxidation of the resulting compound(s) for example to the carboxylic acid or esters has been used as a valuable entry to pyrethric acid/esters possessing the correct stereochemistry of the C=C double bond, and precursors of pyrethrin II as it will be reported in the following Chapter (Chapter IVb).[11,51]



Scheme 134. Sharpless-Arigoni postulated mechanism of allylic oxidation of trisubstituted alkenes.[314,317]

3.3.2. Reaction involving lead tetraacetate (Scheme 13, Route 28). Reaction of *cis*-chrysanthemic acid *cis*-(**1a**$_H$) with 1.5 equivalent of lead tetraacetate in refluxing benzene for 20 h, affords the lactone **109** by intramolecular cyclization in 28% overall yield (Scheme 135).[217] The lactone ring is opened on further saponification with dilute sodium hydroxide and leads after acidification to the acid *cis*-**24**$_H$.[217]

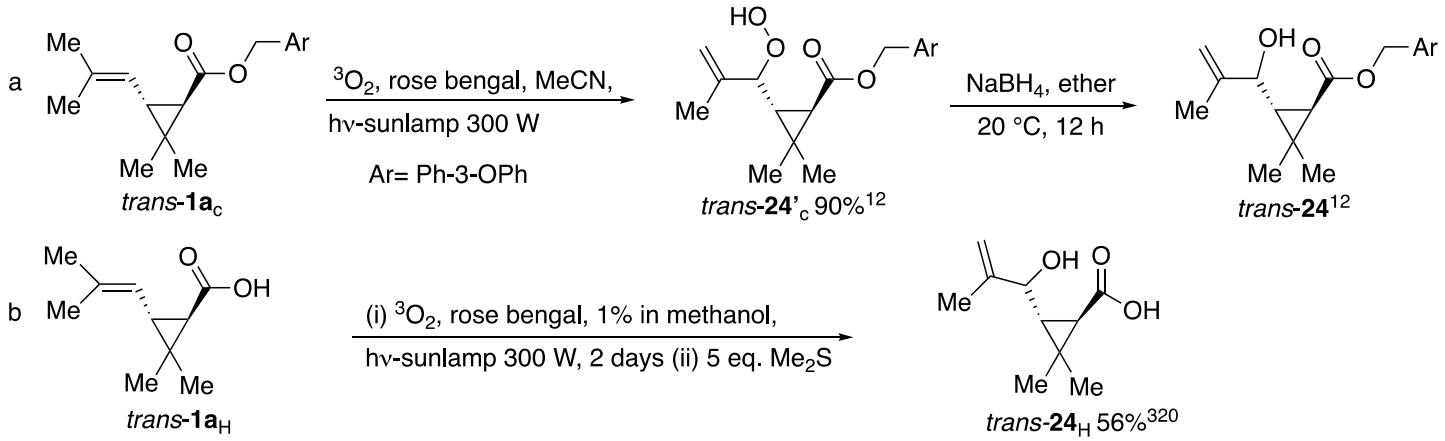


cis-**1a**$_H$ *cis*-**24**$_H$ 25%

Scheme 135. Lead tetraacetate oxidation of *cis*-chrysanthemic acid.[217]

3.3.3. Reactions involving photoxidation of chrysanthemic acid and some of its esters (Scheme 13, Route 28). Dye sensitized photooxygenation (rose bengal, sun lamp 300 W) has been efficiently achieved on phenothrin (**1a**$_C$) in acetonitrile (Scheme 136, entry a),[12] as well as with modest success on *trans*- (Scheme 136, entry b),[320] and *cis*- (Scheme 137)[320] chrysanthemic acid (**1a**$_H$) in methanol. The *trans*-isomers lead to allylic hydroperoxides **24'a** that result from the scrambling of the original trisubstituted C=C double bonds towards the terminus. The

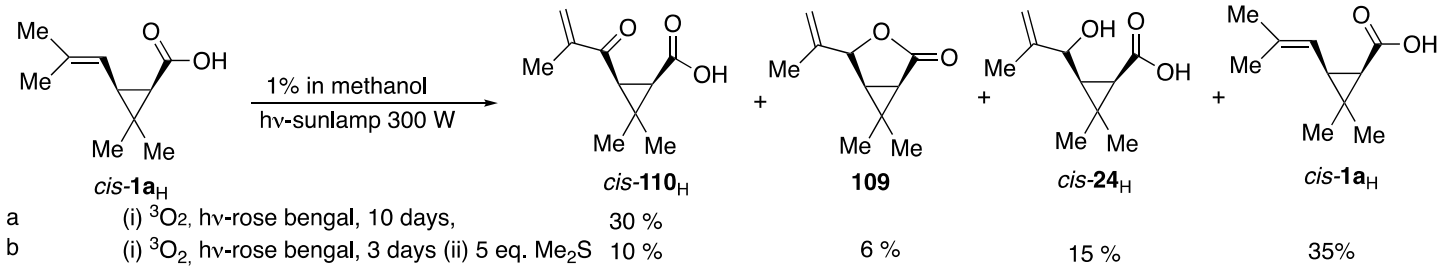
latter have been either reduced to the corresponding allylic alcohols, epimeric at their carbon using sodium borohydride (Scheme 136, entry a)[12] or dimethyl sulfide (Scheme 136, entry b, Scheme 137, entry b) to the corresponding allyl alcohol *trans*-**24a**$_H$.[320] These results should be compared to those disclosed in section 4.1. and are related the compounds observed in nature. These alcohols **24** are formally isomeric to those produced on reaction of chrysanthemic acid and alkyl chrysanthemates **1a** with selenium dioxide (**21**, Scheme 133).



Scheme 136. Photoxidation of *trans*-chrysanthemic acid and esters.[12,320]

The reaction implying *cis*-chrysanthemic acid *cis*-(**1a**$_H$) markedly differs from that of its *trans*-isomer since it is not only comparatively extremely slow (10 days instead of 2 days. Compare Scheme 137, entry b to Scheme 136, entry b)[320] but also because it delivers the enone *cis*-**110**$_H$ instead of the expected allylic hydroperoxide *cis*-**24**$_H$.

Trapping the reaction medium with an excess of dimethyl sulfide after 3 days,[320] still leads to the enone **110**$_H$ although in much lower amounts, besides substantial amount of unreacted *cis*-chrysanthemic acid (35%) but delivers also the allyl alcohol *cis*-**24**$_H$ and the product **109** probably resulting from its partial lactonization as the result of the proximity of the allylic hydroxy group and of the carboxyl moieties. This lactone **109** is similar to that produced from *cis*-chrysanthemic acid *cis*-(**1a**$_H$) and lead tetraacetate (Section 3.1.2.4, Scheme 135).[217]



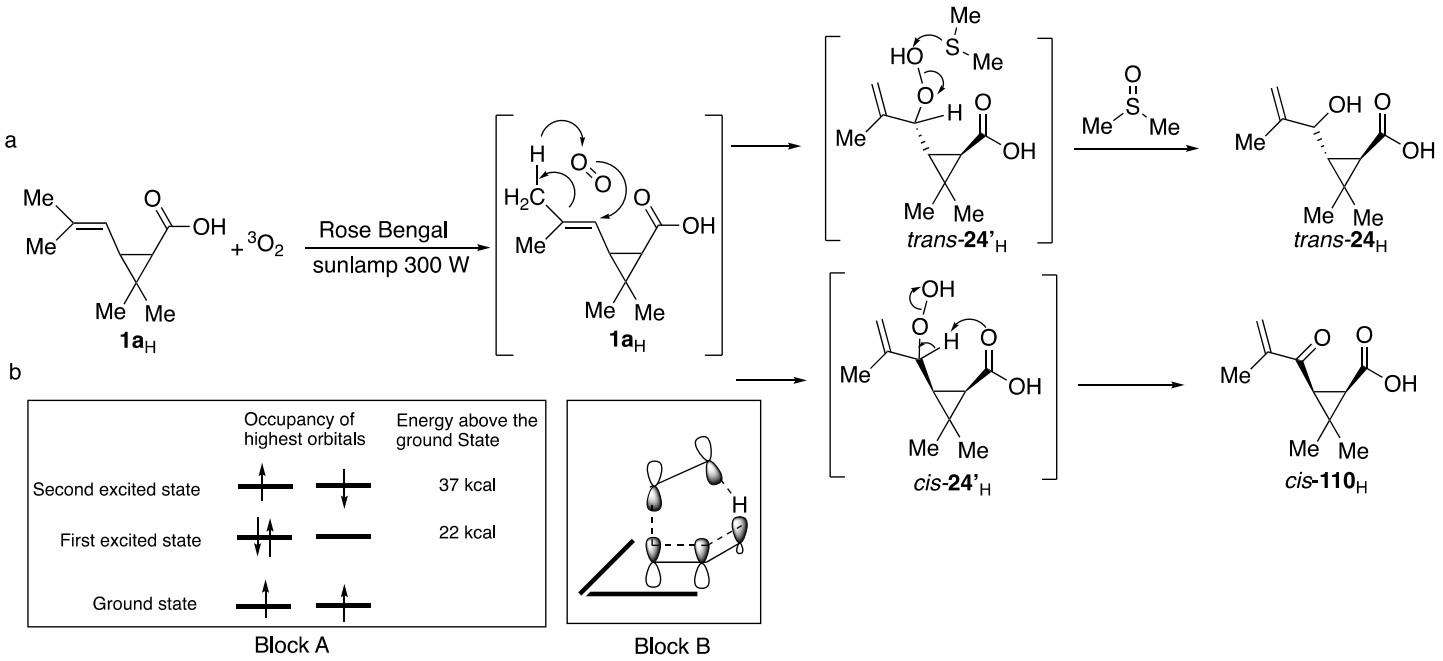
Scheme 137. Photoxidation of *cis*-chrysanthemic acid.[320]

Rose bengal, methylene blue or porphyrins photosensitized oxygenation of olefins containing at least one allylic hydrogen, provides allylic hydroperoxides.[321,322] The process involves singlet oxygen ($^1O_2$), resulting from energy transfer from the triplet sensitizer (rose bengal) to triplet oxygen ($^3O_2$) in a spin-allowed process. $^1O_2$ possesses an energy only 22 kcal above the ground state (Scheme 138, Block A) and resembles ethylene

electronically but is more electrophilic and is expected to undergo two-electron reactions.[322] Singlet oxygen can be also generated from sodium hypochlorite and hydrogen peroxide[323] and both the photochemical and the chemical method usually led to similar results.

This process is distinguishable from the radical oxidation initiated by sensitizers such as benzophenone which abstract hydrogen from alkenes and may also produce allylic hydroperoxides but differs in its reaction towards isopropanol. The latter remains unaffected by singlet oxygen but is very reactive towards hydrogen abstraction under radical process.[322]

The photosensitized oxygenation of olefins that is the subject of our interest is believed to proceed through a concerted ene-reaction involving a six membered cyclic transition state that includes singlet oxygen (Scheme 138, Block B) and leads to the allyl hydroperoxide **24'**$_H$ from chrysanthemic acid that is stable enough to generate the allylic alcohol **24**$_H$ in the *trans*-series on reaction with a reducing agent (Scheme 138, entry a)[320] or collapse to the enone *cis*-**110**$_H$ in the *cis*-series due to the proximity between the carbonyl of the carboxyl group and the allylic hydrogen on the side chain through an intramolecular elimination reaction proposed in Scheme 138, entry b.[320]



Scheme 138. Postulated mechanism of photoxidation of *cis*- and *trans*-chrysanthemic acids.[320,321,322]

4. Reactions Implying the Metalation of Alkyl Chrysanthemates

cis/*trans*- and *trans*/*cis*-Isomerization of chrysanthemic acid and alkyl chrysanthemates has been the subject of wide interest since the natural insecticides and (*S*)-bioallethrin belong to the *trans*-family of cyclopropane derivatives and their synthesis often leads to a *cis*/*trans*-mixture and that deltamethrin as well as the most active stereoisomers of cypermethrin possess the *cis*-configuration. So *cis*/*trans*-isomerization as well as *trans*/*cis*-isomerization is required to produce each series of compounds.

Most of the reactions involves the action of base on stereopure- or isomeric mixtures of alkyl chrysanthemates. It will be the subject of this section. *cis*/*trans*-isomerization of chrysanthemic acid has also

been carried out. It takes effectively place on its salts, generated for example using excess of potassium hydroxide in ethylene glycol but isomerization takes place under harsh conditions (> 225 °C). [51, 113,213,324,325-327]

4.1. *trans*/*cis*-Stereocontrolled epimerization of alkyl chrysanthemates

trans/*cis*-Isomerization, a contra-thermodynamic process, has been achieved through a kinetically controlled transformation involving a deprotonation using an excess of base in a non-protic solvent and reprotonation of the resulting carbeniate **12**$_{Li}$ or enolate **12'**$_{Li}$ by suitable acids (Scheme 139).[328] The electrophile is expected to attack the enolate/carbeniate from its least hindered side that leads to chrysanthemates in which the isobutylene and carboxylate moieties are *cis* to each other. Extension of this reaction allows the synthesis of methylated **112a**, allylated **112b** or methylthio-substituted **112c** methyl chrysanthemates (Scheme 140). [329] All these reactions do not lead to stereochemically pure chrysanthemates but as a mixture of stereoisomers in which the *cis*-stereoisomer often prevails (Scheme 139, Scheme 140).[328,329]

Metallation of esters has not always been a simple task and although alpha-metallated esters are long-known and widely used in the Reformatsky reaction,[330] they have been produced through an halogen-metal exchange reactions. Efficient metalation of esters, especially ethyl acetate, date back to 1970, when Rathke[331] described that lithium bis-(trimethylsilyl)amide) in tetrahydrofuran allows the quantitative formation of lithio ethyl acetate at -78 °C and that the latter is indefinitely stable at this temperature although it decomposes rapidly at 0 °C.

Successful metalation of esters requires strong bases such as lithium bis-(trimethylsilyl)amide[331] or lithium diisopropylamide[332] in THF to achieve rapid metalation of this poorly acidic derivatives (pKas methyl acetate/ acetone: 25/20) in order to avoid subsequent reaction of the metalated ester on the carbonyl group of the not yet metalated one's.

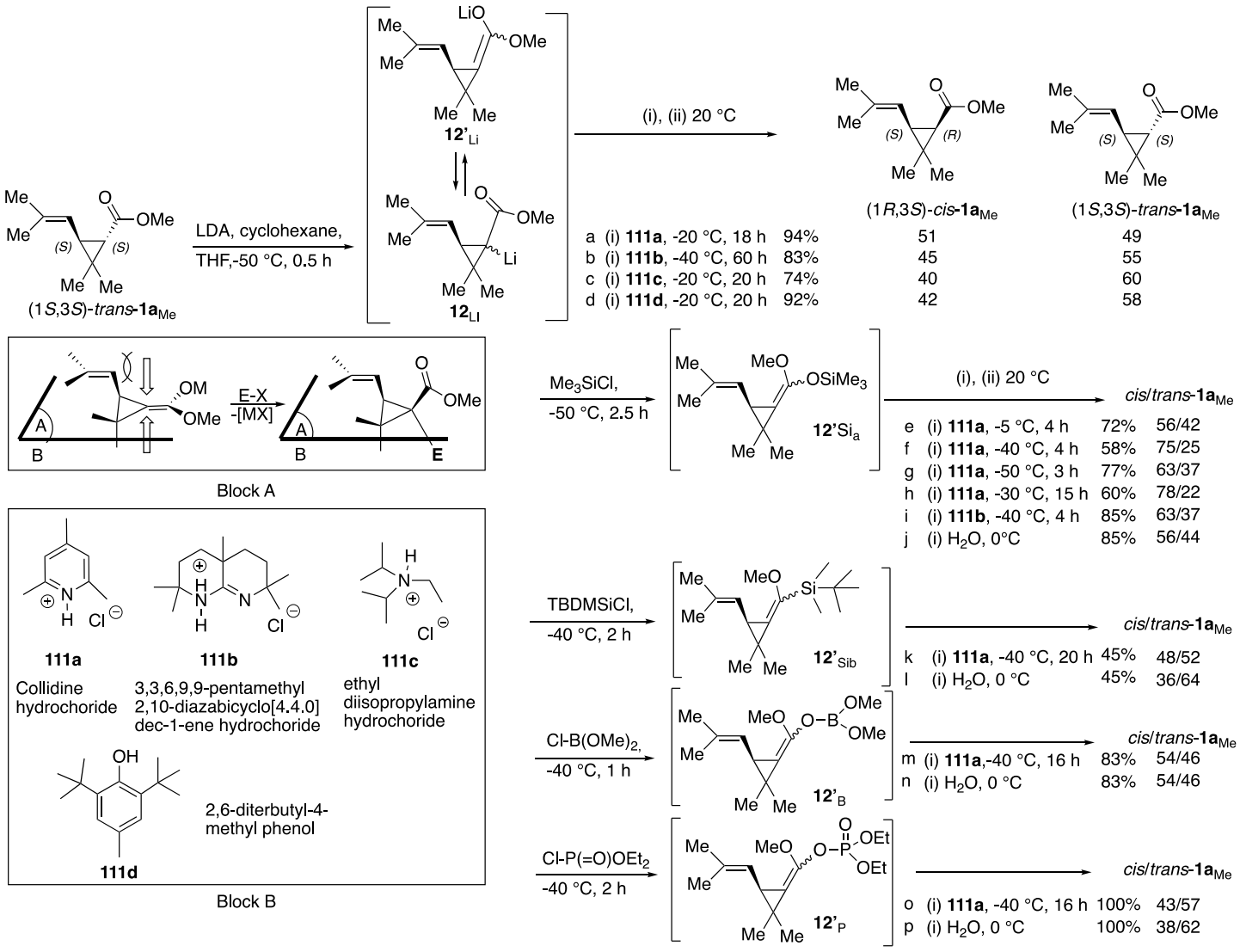
Furthermore, metalated esters are prone to lose their alkoxide leading to extremely reactive ketene in a highly temperature sensitive process. This elimination reaction does not take place with the lithium counter ion at -78 °C and is extremely rapid at 0 °C. The elimination is however already effective at-78 °C when potassium replaces the lithium cation, so potassium bases must be avoided.[331] Alkyl cyclopropane carboxylates are more difficult to metalate than alkyl acetates due to the poor contribution of the related enolates. This is also the case of generation of the related ketene due to the increasing strain involved in the cyclopropylidene concomitantly produced (Section 1.4., Scheme 14, Scheme 15).

The Rousell Uclaf team has published[328] different strategies to increase the percentage of the methyl *cis*-chrysanthemate from its *trans*-stereoisomer upon metalation/protonation process. Among these (i) increasing the size of the proton-donor **111** in an anhydrous environment and (ii) favoring the formation of enolates **12'**$_{Li}$ over the carbeniate **12** $_{Li}$ so the bulky proton donor can select the less hindered of its two faces leading to the *cis*-stereoisomers (Scheme 139, Block A: Face B instead of face A).

(i) Collidinium hydrochloride **111a** proved to be the more discriminant proton-donor among the other ammonium hydrochlorides **111b**, **111c**, the phenol **111d** or frozen water (Scheme 139 compare entry a to entries b-d; entries e-h to entries i,j; entry k to entry l; entry o to entry p), (ii) the trimethylsilyl enolate **12'**$_{Sia}$ delivers more *cis*-stereoisomer than its *t*-butyldimethylsilyl analogue **12'**$_{Sib}$, the dimethoxyboron- **12'**$_{B}$, or diethylphosphono- **12'**$_{P}$ enolates. Protonation of the trimethylsilyl enolate **12'**$_{Sia}$ is best achieved at -30 or -40 °C rather than at lower or higher temperatures (Scheme 139 compare entries f,h to entries e,g).

Due to the strain introduced, the C-lithiated compound (**12**$_{Li}$) is favored over the O-lithiated compound (enolate) (**12'**$_{Li}$) but the reaction with oxophilic reagents such as trimethylsilyl chloride, as expected, favors the formation of the required trimethylsilyl enolate **12'**$_{Sia}$. The stereochemical control disclosed in Scheme 139 seems to support its transient formation although it has not been proven and even in some cases the

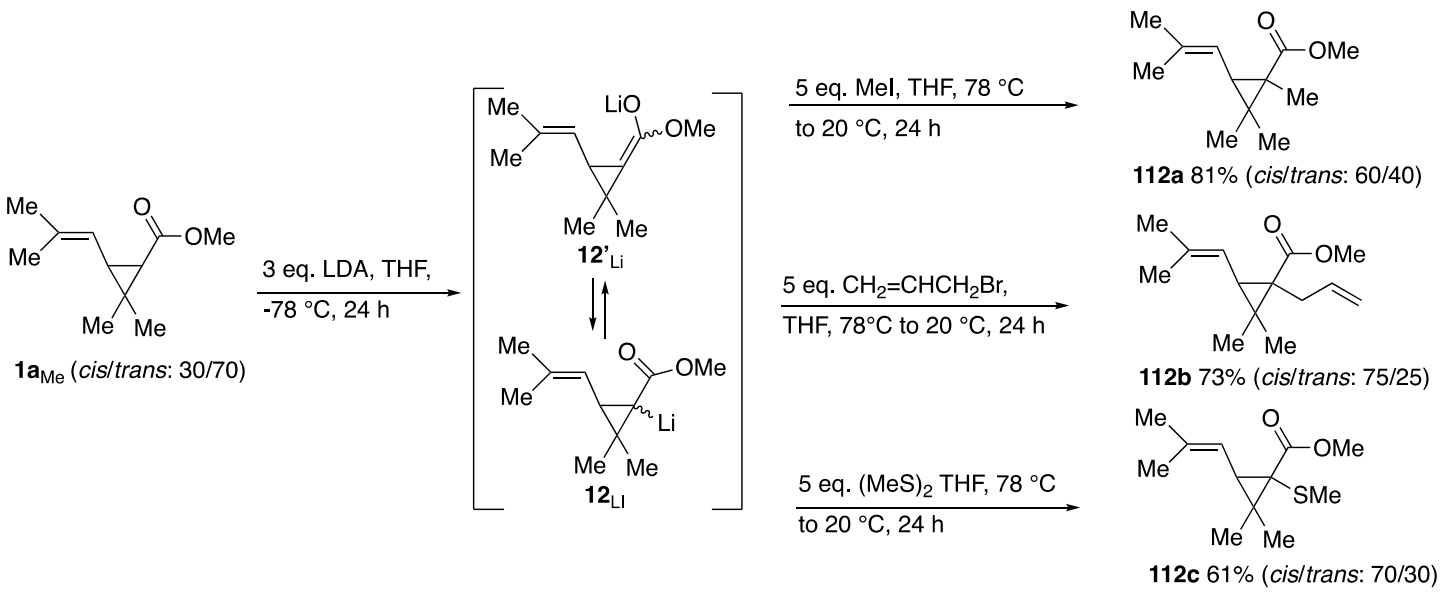
trimethylsilyl cyclopropane carboxylic acid has been isolated on sequential reaction of cyclopropane carboxylic acid with LDA (2eq.) in THF and trimethylsilyl chloride.[333]



Scheme 139. Stereochemistry of the products resulting from the metalation/protonation of methyl chrysanthemate under kinetically controlled conditions.[328]

Similarly, sequential reaction of methyl chrysanthemate (*trans*/*cis*: 7/3) with excess of LDA at -78 °C then with methyl iodide, allyl bromide or dimethyl disulfide affords good yields of C-alkyl or C-methylthio methyl chrysanthemates **112** in which the *cis*-stereoisomers prevail (Scheme 140).[329]

Related reactions, applied to *trans*-chrysanthemonitrile (**1a**$_{CN}$)[147] are not as *cis*-selective as disclosed for methyl chrysanthemate (**1a**$_{Me}$). Deuteration of the lithiated species (1.1eq. LDA, -78 °C, 0.3 h) leads to deuterated chrysanthemonitrile as a stereoisomeric mixture (80%, *trans*/*cis*: 53/47), sulfenylation with diphenyl disulfide generates phenylthio chrysanthemonitrile (31%, *trans*/*cis*: 65/35),[147] and hydroxylation by molybdenum peroxide-pyridine-hexamethylphosphoramide complex (MoOPH) leads exclusively to *trans*-hydroxy-chrysanthemonitrile (75%).[147]



1a$_{Me}$ (*cis*/*trans*: 30/70)

12'$_{Li}$

12$_{LI}$

112a 81% (*cis*/*trans*: 60/40)

112b 73% (*cis*/*trans*: 75/25)

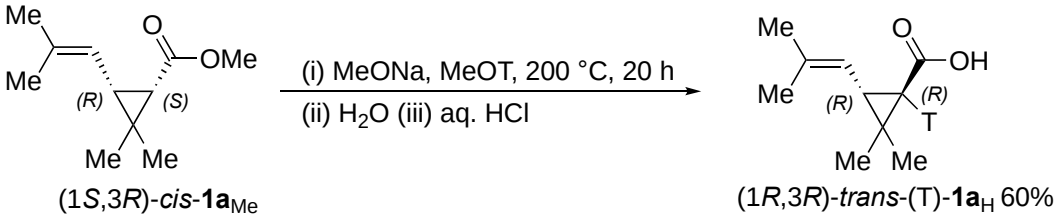
112c 61% (*cis*/*trans*: 70/30)

Scheme 140. Stereochemistry of the products resulting from the metalation/alkylation or thiomethylation of methyl chrysanthemate under kinetically controlled conditions.[329]

4.2. *cis*/*trans*-Stereocontrolled epimerization of alkyl chrysanthemates

cis/*trans*-Stereocontrolled epimerization of alkyl chrysanthemates is a key reaction to produce *trans*-chrysanthemates *trans*-**1a**$_R$ from their *cis*-stereoisomers *cis*-**1a**$_R$. The latter are produced from synthetic methods that deliver chrysanthemic acid from a five- or a six-membered cyclic intermediate or from a *trans*/*cis*-mixture (70/30 or 60/40) commercially available on reaction of diazoacetates with 2,5-dimethylhexadiene.[147] The reaction is usually performed with a small amount of base (B-M) in such way that the conjugated acid (B-H) is able to react with the resulting enolate **12'** to generate the alkyl chrysanthemate **1a**$_R$. Metalation is expected to occur faster on the *cis*-**1a$_R$** than on the *trans*-**1a$_R$** due to unfavorable steric interactions on the latter and delivers *trans*-**1a**$_R$ due to the conditions favoring a thermodynamic control (See below Scheme 142). [51,59,112,113,216, 325,334-338]

Reaction of methyl (1*S*,3*R*)-*cis*-chrysanthemate (1*S*,3*R*)-*cis*-(**1a**$_{Me}$) with sodium methylate in tritiated methanol allows the synthesis of methyl (1*R*,3*R*)-*trans*-chrysanthemate (1*R*,3*R*)-*trans*-(**1a**$_{Me}$) bearing a tritium atom at C-1 which unambiguously establishes that metalation has taken place at C-1 (Scheme 141).[339,340]

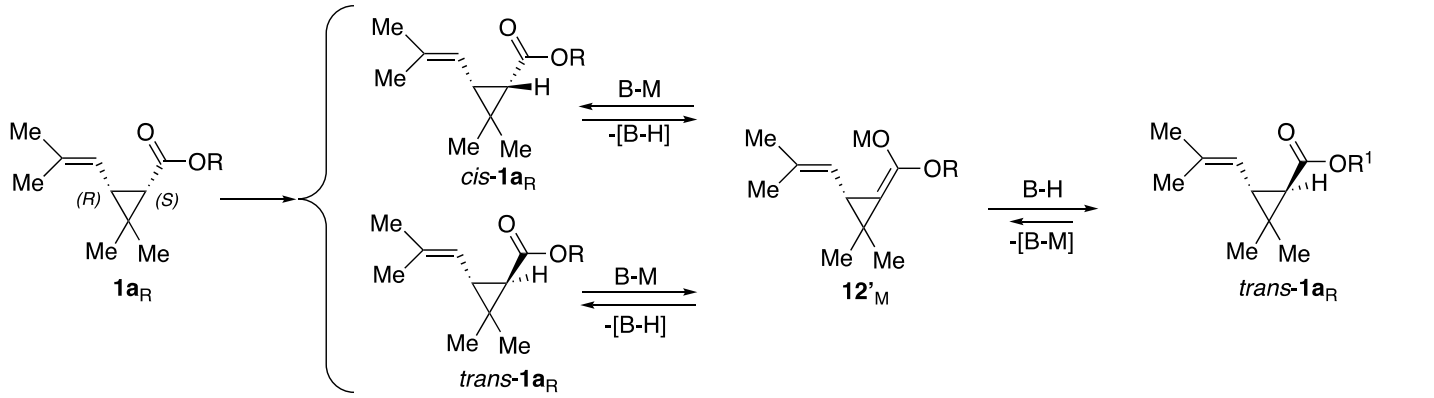


(1*S*,3*R*)-*cis*-**1a**$_{Me}$

(1*R*,3*R*)-*trans*-(T)-**1a**$_H$ 60%

Scheme 141. Structure and stereochemistry of the products resulting from the metalation/tritiation of methyl chrysanthemate under thermodynamically controlled conditions.[340]

Otherwise this transformation has been usually achieved under less drastic conditions gathered in Scheme 142.[11,51,59,113,141,147, 216,338,341]



	Starting material	Conditions	Major stereoisomer	Overall yield (*trans*/*cis*)
a	(1*S*, 3*R*)-*cis*-**1a**$_{Et}$	*cat*-EtONa, ethanol, sealed tube, 180 °C, 2 h	(1*R*, 3*R*)-*trans*-**1a**$_{Me}$	90% (100/0)[113]
b	*cis*-**1a**$_{Et}$	EtONa, EtOH, 100 °C, 65 h	(1*R*, 3*R*)-*trans*-**1a**$_{Et}$	86% (100/0)[216]
c	*cis*/*trans*-**1a**$_{Et}$ (40/60)	2.2 eq EtONa (1.9N), ethanol, reflux, 24 h	*trans*-**1a**$_{Et}$	90% (75/25)[51]
d	*cis*/*trans*-**1a**$_{Et}$ (40/60)	2.2 eq EtONa (1.9N), ethanol, reflux, 72 h	*trans*-**1a**$_{Et}$	90% (75/25)[51]
e	*cis*/*trans*-**1a**$_{Et}$ (40/60)	6 eq EtONa (3N), ethanol, reflux, 72 h	*trans*-**1a**$_{Et}$	85% (92/8)[51]
f	*cis*/*trans*-**1a**$_{Et}$ (40/60)	1.1 eq EtONa (0.4N), benzene, reflux, 6 h	*trans*-**1a**$_{Et}$	90% (85/15)[51]
g	*cis*/*trans*-**1a**$_{Et}$ (40/60)	1.25 eq EtONa (0.5N), toluene, reflux, 24 h	*trans*-**1a**$_{Et}$	81% (92/8)[51]
h	*cis*/*trans*-**1a**$_{Et}$ (40/70)	1.1 eq. *t*-AmylONa, benzene, reflux, 4 h	*trans*-**1a**$_{Et}$	30% (97/3)[51]
			trans-**1a**$_{tamyl}$	60% (97/3)[51]
i	*cis*/*trans*-**1a**$_{Et}$ (30/70)	1.3 eq. *t*-AmylONa, toluene, reflux, 0.8 h, 20 °C, 0.2 h	*trans*-**1a**$_{Et}$	73% (100/0)[147]
			trans-**1a**$_{tamyl}$	86% (100/0)[141,341]
j	*cis*/*trans*-**1a**$_{Me}$(41/59)	2 eq. *t*-BuOK, THF, 20 °C, 2 h	*trans*-**1a**$_{tBu}$	99% (93/7)[338]
k	(1*S*, 3*R*)-*cis*-**1a**$_{Et}$	Solid superbase (Na, NaOH-Al_2O_3), 60 °C	(1*R*, 3*R*)-*trans*-**1a**$_{Et}$	99% (99/1)[338]
l	(1*S*, 3*R*)-*cis*-**1a**$_{Et}$	Solid superbase (Na, NaOH-Al_2O_3), neat, 80 °C	(1*R*, 3*R*)-*trans*-**1a**$_{Et}$	98% (92/8)[11,338]
m	(1*S*, 3*R*)-*cis*-**1a**$_{Et}$	NaH, neat, 130 °C,	(1*R*, 3*R*)-*trans*-**1a**$_{Et}$	99% (91/9)[338]
n	(1*S*, 3*R*)-*cis*-**1a**$_{Et}$	EtONa, neat, 130 °C	(1*R*, 3*R*)-*trans*-**1a**$_{Et}$	- - (100/0)[59]
o	*cis*-**1a**$_{t\text{-}Bu}$	3 eq. *t*-BuOK, *t*-BuOH, reflux, 8.5 h	*trans*-**1a**$_{tBu}$	

Scheme 142. Structure and stereochemistry of the products resulting from the metalation/protonation of methyl chrysanthemate under various conditions.[11,51,59,113,141,147,216,338,341]

Accordingly, it has been found that *cis*/*trans* epimerization can be achieved with:

(i) an alcoholate in the related alcohol as the solvent such as sodium ethylate in ethanol (Scheme 142, entries a,b,c,d,e)[113,216,51] or potassium *t*-butoxide in *t*-butanol (Scheme 142, entry o)[59,337] at reflux. The reaction has been successfully carried out in the presence of the alcoholate in catalytic amounts (Scheme 142, entry a)[113] or stoichiometric or sub-stoichiometric amount (Scheme 142, entries b,c,d,e,n).[51,59,216,337]

(ii) sodium ethylate (Scheme 142, entries f,g)[51] or *t*-amylate (Scheme 142, entries h,i)[51] in benzene or toluene or potassium *t*-butylate in THF (Scheme 142, entry j),[141,341]

(iii) a neat base, such as sodium hydride (Scheme 142, entry m),[338] sodium ethylate (Scheme 142, entry n),[338] or better solid superbase, generated by mixing sodium, sodium hydroxide and alumina[342,343] (Scheme 142, entries k,l),[338]

In case the reaction is carried out with an alcoholate or in an alcohol, the alkoxy moiety of which is different from that of the ester, transesterification takes also place (Scheme 142, entries h,l,j).[51, 141,147,341]

It should be noticed that performing the *cis*/*trans*-isomerization using:

(i) stoichiometric or sub-stoichiometric amounts of a base offers the advantages of avoiding the need to perform the reaction at high temperature in a sealed tube but dramatically increases the reaction time (Scheme 142 compare entry e to a) [51,113]

(ii) benzene, toluene or even THF as solvents favor the epimerization relative to alcohols (Scheme 142 compare: entry g to entry d; [51] entry j to entry o [59, 141, 337, 341]). This is effectively the case of reaction involving potassium *t*-amylate (Scheme 142 compare entries h,i) and potassium *t*-butoxide[59,337] (iii) alcoholates bearing a tertiary alkyl group are more efficient to perform the isomerization than their primary-alkyl analogues (Scheme 142 compare entries f to g; compare h to f). However, transesterification takes concomitantly place on methyl or ethyl chrysanthemate (Scheme 142 compare entries h,i).

The transformation of these mixtures of methyl or ethyl chrysanthemate and a *t*-alkyl chrysanthemate to the corresponding chrysanthemic acid is not easy since it requires orthogonal methods:[51] (i) dealkylation or base-promoted dealkoxylation for primary alkyl chrysantemates[51] (ii) acid-catalysed dealkylation or thermal decomposition for *t*-alkyl chrysantemates.[51,59] It is therefore crucial to use conditions that produce quantitively and rapidly the *t*-alkyl chrysanthemates exclusively to avoid such problem but also because the interactions between the isobutenyl and the carboxy group are maximal and favor the *trans*-stereoisomer under thermodynamically controlled conditions (Scheme 142 entries j,o).[141,341]

Another solution involving superbases is highly suitable for industrial purposes (Scheme 142, entries k,l).[338] It offers the advantage to use cheaper and easily recycled reagent, in a process that can be performed neat and provides the *trans*-chrysanthemates *trans*-**1a**$_R$ in extremely good yield and with very high stereocontrol without concomitant *trans*-esterification. Related strong bases such as sodium hydride[11,338] or sodium ethylate,[338] used in neat form clearly proved to be less efficient (Scheme 142, entries m,n).

Superbases are compounds that have a high affinity for protons as a broad definition. However conflictual definitions exist: The IUPAC Gold Book mention of superbase only exists in the superacid definition and refers to reagents "as basic as lithium diisoproplamide";[344] or has been related to the definition of "proton sponge".[345] We rely on the definition of Caubère:[346] "a superbase is a basic reagent created by combining reagents leading to a new basic species that possesses basic properties that surpass that of each of its component". Accordingly, the term does not involve the notions of thermodynamic or kinetic neither of strength compared to any other reagent that is not part of the mixture. It applies to unimetal superbases (USB) that have been used by Caubère and in the case of chrysanthemates by Suzukamo (Na+NaOH supported on alumina) [338,342,343] as well as to multimetal superbases (MSB) promoted by Schlosser.[347]

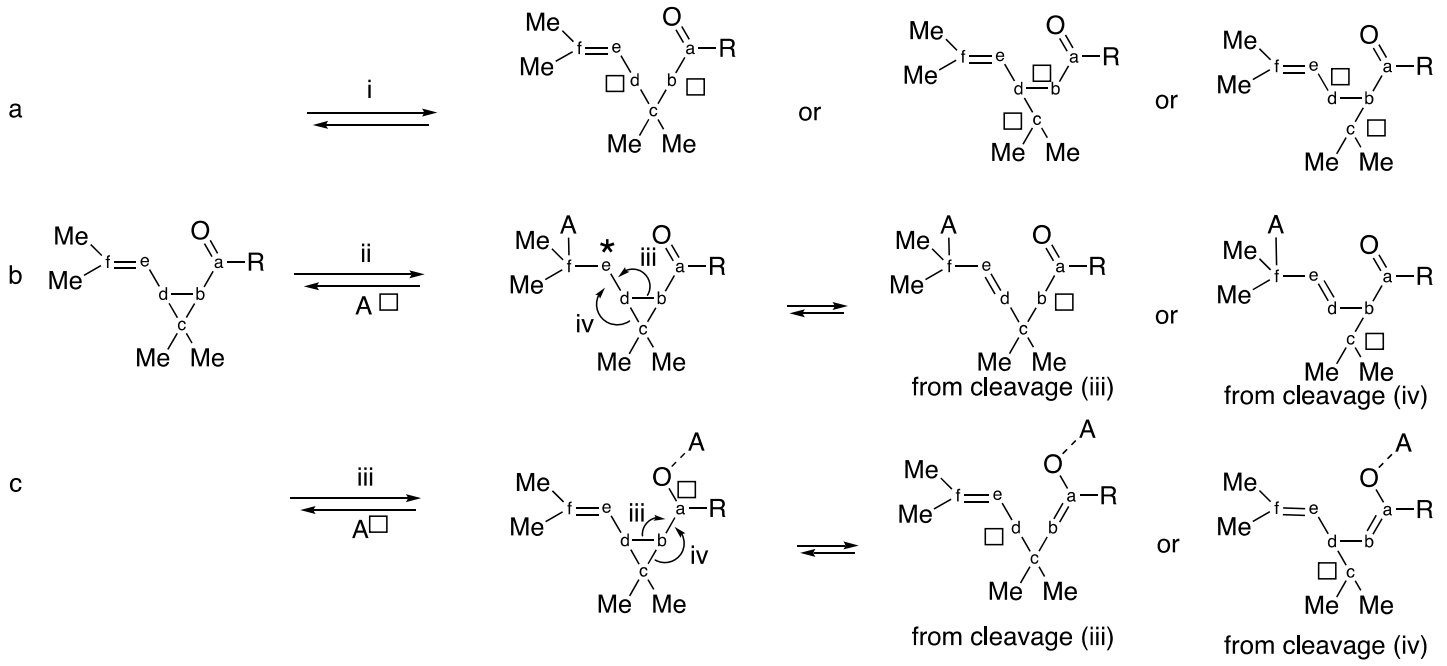
4.3. *cis*/*trans*-Stereocontrolled epimerization of chrysanthemic acid

As disclosed above *cis*/*trans*-isomerisation of *cis*-chrysanthemic acid *cis*-(**1a**$_H$) through metalation reaction is difficult and is achieved under drastic conditions that use excess of potassium hydroxide in ethylene glycol that require heating at more than 225 °C as we have disclosed at the beginning of this section. [113,51,324,325,213,326,327] The other approach, the basis of which has been discussed above takes advantage of the easy metalation/protonation under thermodynamic control of the related esters followed by transformation of the *trans*-chrysanthemates **1a**$_R$ to the *trans*-chrysanthemic acid (**1a**$_H$). Another approach that probably involves metalation at C-1 requires a three steps sequence from *cis*-chrysanthemic acid *cis*-(**1a**$_H$): (i) intermediate formation of its acid chloride *cis*-(**3a**$_{Cl}$) (ii) its transformation to the corresponding *cis*-pyridinium salt that isomerizes to *trans*-(**3a**$_{Cl}$) and (iii) delivers *trans*-chrysanthemic acid *trans*-(**1a**$_H$) on sequential treatment with potassium carbonate and hydrochloric acid (Scheme 27, entry c).[63] Another approach to *cis*/*trans*-isomerisation in this series involves the exceptional aptitude of the cyclopropane ring to be cleaved and reformed that will be discussed in the next section.

5. Reactions Implying the Cyclopropane Ring Opening of Chrysanthemic Acid and of Related Derivatives

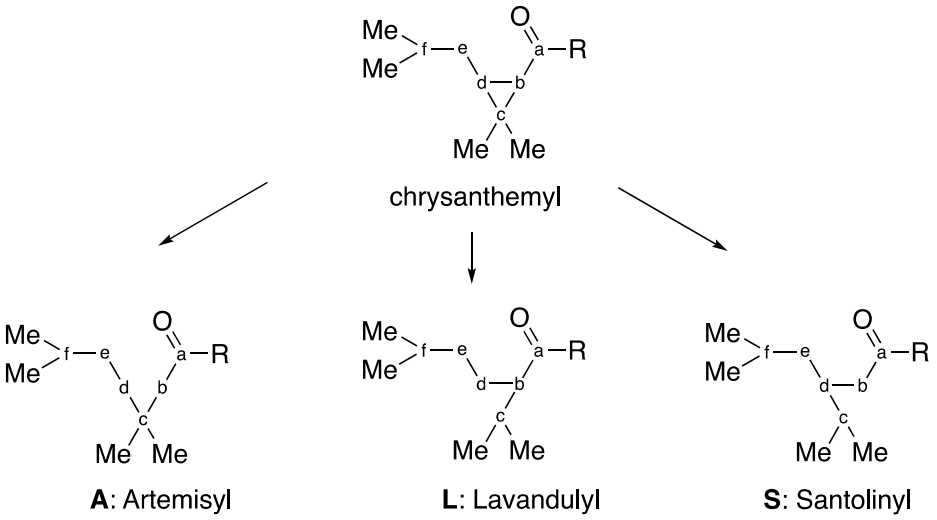
As previously discussed (Section 1.2.2.2.), the cyclopropane ring in the environments of chrysanthemic acid and its derivatives such as: alkyl chrysanthemates, chrysanthemoyl chloride, chrysanthemaldehyde, and homochrysanthemic acid, is fragile and has a propensity to be cleaved. This has been achieved (i) under the physical action such as light or heat (Scheme 143, entry a) or (ii) with reagents able to either add transiently to their [Ce,Cf] double bond (Scheme 143, entry b) or (ii) to activate their carbonyl group (Scheme 143, entry c). The basic aspects have been already covered in Section 1.2.2.2..

The cleavage of one of the bonds belonging to the cyclopropane ring, leads to reactive intermediates bearing radicals or charges at 1,3 positions that can either decompose through substitution or/and elimination processes or collapse and regenerate the three membered cycle. In such case, the stereochemistry of the product could be affected depending upon the stereochemistry of the starting material and the nature of the bond cleaved. The latter process is expected to involve the transition state with the lowest energy level and usually favors the production of the *trans*-stereoisomer. Thus, a radical or a positive charge should be well stabilized at [Cd] that bears a vinyl group and at [Cc] that bears two methyl groups whereas a negative charge should be stabilized at [Cd] that bears a vinyl group, and particularly well at [Cb] that bears a carboxy group.



Scheme 143. Regioselective cleavage of one of the [C-C] bond of the cyclopropane ring under ionic (+, -) or radical (·) processes.

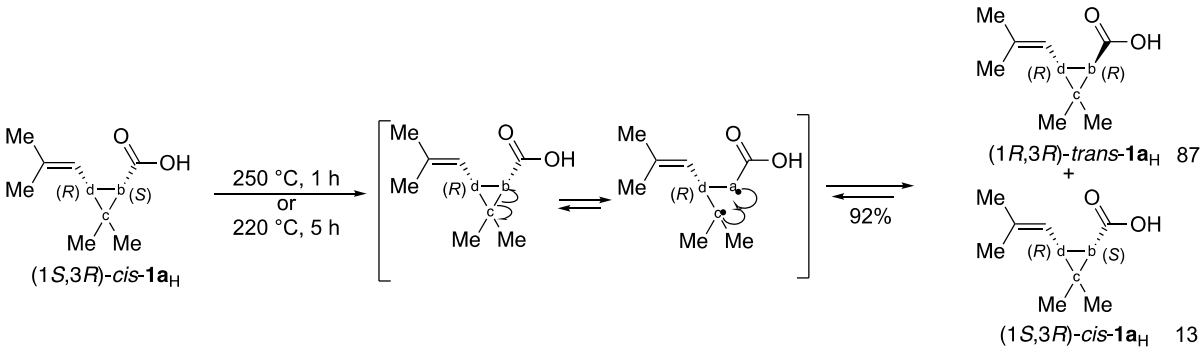
Among those products, we can refer to (i) polyenic compounds resulting from cyclopropane ring opening process possessing either artemisyl- (A), lavandulyl- (L) or santolinyl- (S)-skeletons (Scheme 144; these names refer to the arrangement of the [Ca] to [Cf] carbon frameworks wathever are functionalities present on the related compounds), resulting from loosing a hydrogen (ii) lactone ring containing compounds resulting of trapping of one of reactive species intramolecularly by the carboxy group (see below).



Scheme 144. Structures related to the artemisyl-, lavandulyl- or santolinyl-skeletons.

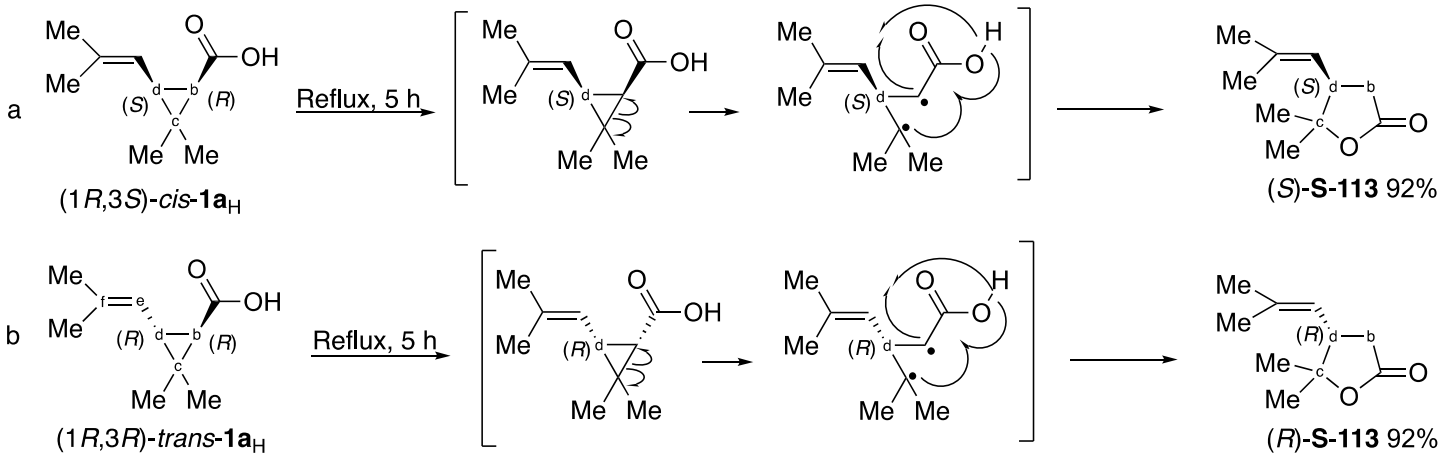
5.1. Cyclopropane ring opening under thermal conditions

Heating *cis*-chrysanthemic acid *cis*-(**1a**$_H$) around 200-250 °C allows clean *cis*/*trans*-isomerisation to produce *trans*-chrysanthemic acid *trans*-(**1a**$_H$) in very high yield and with good diastereoselectivity. The reaction takes place by formal inversion of configuration at [Cb] and complete retention of the configuration at [Cd], suggesting that it takes place by cleavage of the [Cb-Cc] bond (Scheme 145).[348]



Scheme 145. *cis*/*trans*-Thermal isomerization of *cis*-chrysanthemic acid.[348]

The reaction of *cis*-chrysanthemic acid (**1a**$_H$) takes another course when carried out at higher temperature and provides [71,72,349] instead pyrocine **S**-**113** (**S** refers to the santolinyl skeleton resulting from the nature of the σ bond destroyed in the process, Scheme 144) that contains a five membered cyclic lactone (Scheme 146). Its formation could involve trapping the diradical intermediate resulting from the [Cc-Cb] bond cleavage, by the hydroxyl group present on the carboxy moiety. The reaction is highly stereospecific and provides the pyrocine with complete retention of configuration at [Cd] (Scheme 146, compare entry b to entry a).[72,349]

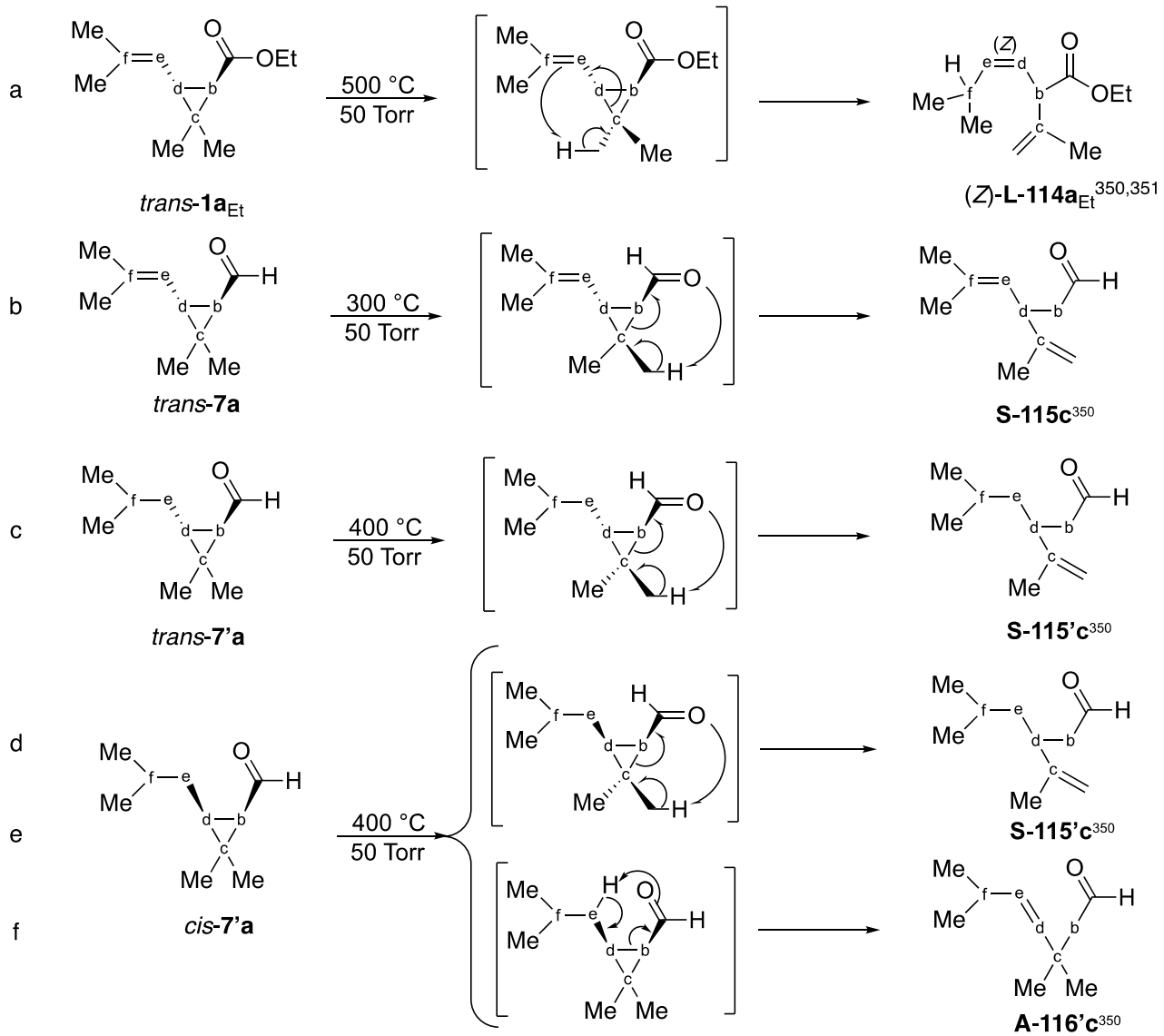


Scheme 146. Stereospecific thermal isomerization of chrysanthemic acid to pyrocine involving the regioselective cyclopropane ring opening.[72,349]

Performing the reaction of ethyl *cis*/*trans*-chrysanthemate (**1a**$_{Et)}$ at even higher temperature, under flash thermolysis (500 °C) at low pressure, leads instead to the dienyl ester(*Z*)-**L-114a**$_{Et}$ in low yield (Scheme 147, entry a). [350] Its skeleton belongs to the lavandulyl family (ethyl lavandulyl carboxylate, Scheme 144) and possesses the (*Z*)-[351] and not the (*E*)-stereochemistry [350] as erroneously described initially. This stereochemistry, ~~is~~ different from the one observed when the reaction is carried out under acid catalysis, suggests that (*Z*)-**L-(114a**$_{Et}$) is the result of a concerted intramolecular process involving the isobutenyl group and one of the hydrogens belonging to the methyl group at [Cc] and the concomitant cleavage of the [Cc−Cd] bond (Scheme 147).

A related process occurs on flash thermolysis of *trans*-chrysanthemal *trans*-**7a** (Scheme 147, entry b). The reaction not only proceeds at much lower temperature (300 instead of 500 °C) but it delivers[350] the diene **S-115c**, possessing the santolinyl skeleton, that could result from the cleavage of the [Cb−Cc] bond of **7a**.[350] This process substantially differs from that of the related ester (**1a**$_{Et}$) (Scheme 147, entry a)[350] or from the reaction of **7a** in an acidic media that delivers the dienal **A-69c** possessing the artemisyl skeleton instead (Scheme 84, entry b).[173]

It has been often noticed that presence of the isobutenyl group on cyclopropane ring plays an important role in the process disclosed above. For example, not only the thermolysis of dihydro *trans*-chrysanthemal *trans*-(**7'a**) takes place at a temperature substantially higher than that of (**7a**) (Scheme 147, entry c compare to entry b) [350] but also thermolysis of *cis*-dihydro chrysanthemal *cis*-(**7'a**) produces in complement to the unsaturated aldehyde **S**-(**115'c**) possessing the santolinyl skeleton (Scheme 147, entry d), its isomer **A-116'c** possessing the artemisyl skeleton instead (Scheme 147, entry f).[350] Apparently **S-115'c** results from a six-membered intermediate that involves the removal of the hydrogen located on the methyl group at at [Cc] *cis* to the carbonyl group (Scheme 147, entry c). The formation of **A-116'c** in competition with **S-115'c** results from the intermediate formation of a competing six-membered transition state that instead involves the removal of the methine hydrogen at [Ce] which is only accessible in the *cis*-stereoisomer *cis*-**7'a** (Scheme 147, entry f).



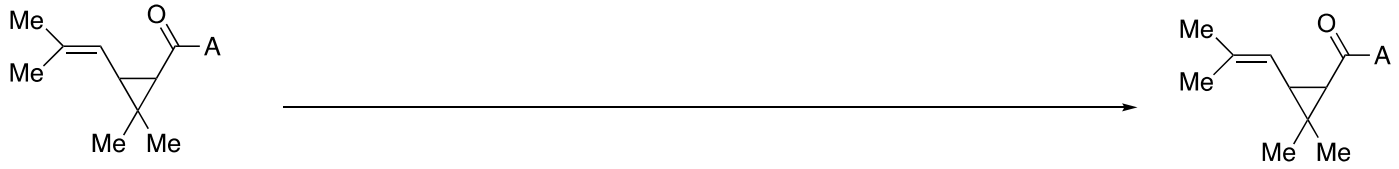
Scheme 147. Flash thermolysis of ethyl chrysanthemate, chrysanthemic aldehyde and dihydro chrysanthemic aldehyde.[350,351]

5.2. Cyclopropane ring opening implying light

5.2.1. Cyclopropane ring opening implying light in the presence of a sensitizer. Pyrethroids have been found to be sensitive to air under sunlight as reported in Section 1.4. of this review (Scheme 5[3] and Scheme 6),[13] It has been for example reported that (1*R*,3*R*)-*trans*-phenothrin (1*R*,3*R*)-(**1a**$_c$) on irradiation at 360 nm in degassed benzene or in solid phase under sunlight, is exclusively isomerized to its less stable *cis*-stereoisomer (*rac*)-*cis*-(**1a**$_c$) (Scheme 4).[12]

It has also been reported [59] that irradiation with a low pressure as well as with a high pressure mercury lamp of *t*-butyl *rac*-*trans*-chrysanthemate *trans*-(**1a**$_{tBu}$) in hexane for up to 10 h does not isomerize it to it *cis*-isomer (Scheme 148, entries a,b). This process can be however achieved on addition of a sensitizer such as acetophenone or isobutyrophenone,[59] with the latter being by far more efficient that the former especially in terms of velocity.[59] The reaction reached a steady-state after about 6 h in which the *cis*/*trans* ratio of isomers is about 36/64.[59] The same ratio (*cis*/*trans*:36/64) has been achieved under similar conditions starting from *t*-butyl *rac*-*cis*-chrysanthemate *cis*-(**1a**$_{tBu}$) (Scheme 148, entry e).[59] Related ratios have been observed for chrysanthemic

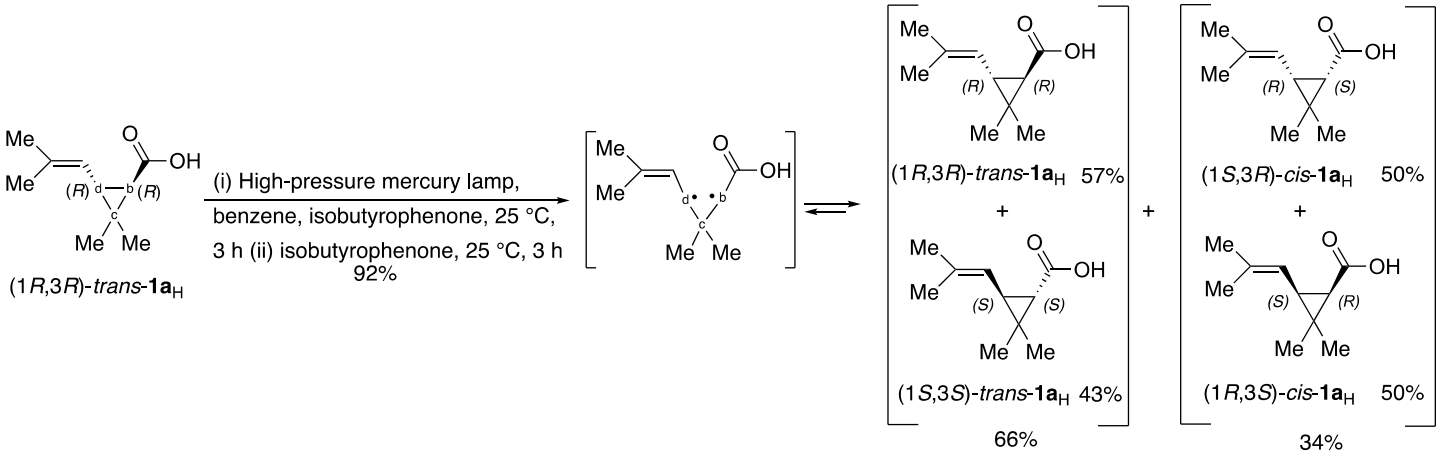
acid (**1a**$_H$) (*cis*/*trans*:34/66, Scheme 148, entries f,g)[59] and chrysanthemic amide (**5b**) (*cis*/*trans*:32/68, (Scheme 148, entry h)[59] and the process has been extended to *t*-butyl pyrethrate.



				cis	*trans*
a	*trans*-**1a**$_{t\text{-Bu}}$	A= O-*t*-Bu	Low-pressure mercury lamp, hexane	0%	- -
b	*trans*-**1a**$_{t\text{-Bu}}$	A= O-*t*-Bu	High-pressure mercury lamp, hexane	0%	- -
c	*trans*-**1a**$_{t\text{-Bu}}$	A= O-*t*-Bu	High-pressure mercury lamp, benzene, isobutyrophenone, 25 °C, 3 h	34%	66%
d	*trans*-**1a**$_{t\text{-Bu}}$	A= O-*t*-Bu	High-pressure mercury lamp, benzene, isobutyrophenone, 25 °C, 4 h	34%	66%
e	*cis*-**1a**$_{t\text{-Bu}}$	A= O-*t*-Bu	High-pressure mercury lamp, benzene, isobutyrophenone, 25 °C, 3 h	34%	66%
f	*trans*-**1a**$_H$	A= OH	High-pressure mercury lamp, benzene, isobutyrophenone, 25 °C, 3 h	34%	66%
g	*cis*-**1a**$_H$	A= OH	High-pressure mercury lamp, benzene, isobutyrophenone, 25 °C, 3 h	34%	66%
h	*trans*-**5b**	A= NH_2	High-pressure mercury lamp, benzene, isobutyrophenone, 25 °C, 3 h	32%	68%

Scheme 148. Photosensitized *cis*/*trans*-isomerization of chrysanthemic acid, *t*-butyl esters and chrysanthemamides.[59]

It has been suggested that such photosensitized *cis*/*trans*-isomerization takes place by cleavage of the [Cb-Cd] bond and recombination. The stereochemical information is therefore lost in the process when it is carried out for example on enantiopure (1*R*, 3*R*)-*trans*-chrysanthemic acid that effectively leads to racemized or partially racemized product (Scheme 149).[59]



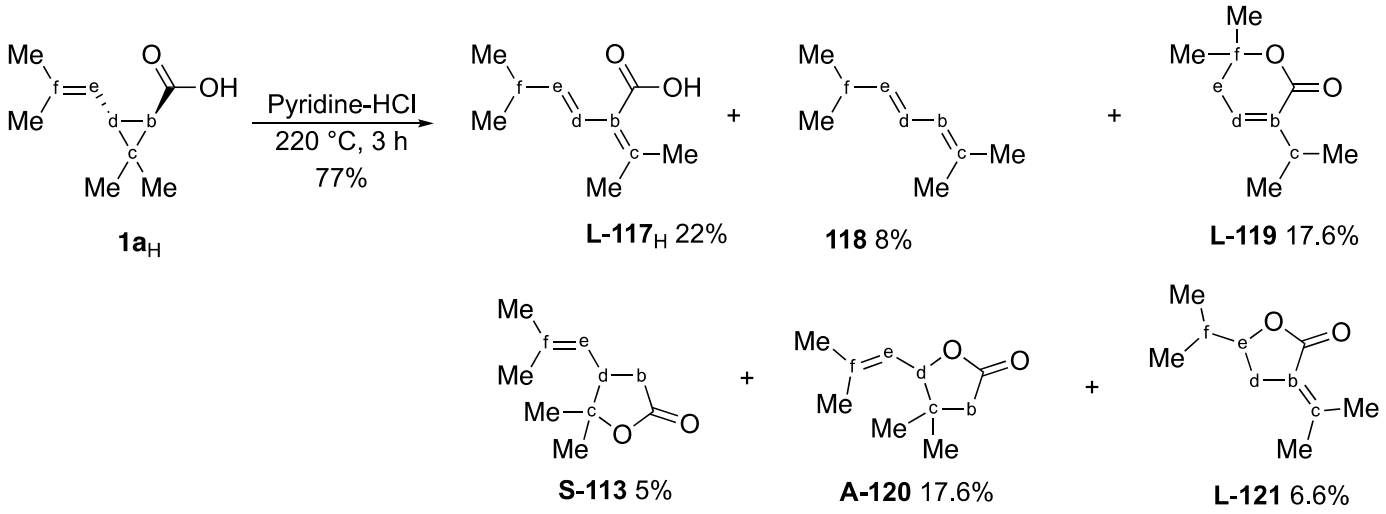
Scheme 149. Photosensitized *cis*/*trans*-isomerization of chrysanthemic acid implying the intermediate formation of a biradical intermediate possessing the artemisyl-skeleton.[59]

5.3. Cyclopropane ring opening involving protic acids catalysts

5.3.1. Reactions of chrysanthemic acid and alkyl chrysanthemates with protic acids. Brønstetd acids have been widely used to catalyze the esterification of chrysanthemic acid with alcohols (Section 2.1.2.1.1.). On several occasions however, addition across its [Ce=Cf] double bond (Scheme 151, route a; Section 3.1.2.) or cyclopropane ring opening (Scheme 151, route b) has been reported.

For example, it has been reported[214] that in boiling dilute sulfuric acid (i) hydration of (1*R*,3*S*) *trans*-chrysanthemic acid *trans*-(**1a**$_H$) occurs to give (1*R*,3*R*)-*trans*-δ-hydroxydihydrochrysanthemic acid **14a**$_H$[214] whereas lactonization takes place on (1R,3R)-*cis*-chrysanthemic acid *cis*-(**1a**$_H$) to produce (1*R*,3*R*)-*cis*-dihydrochrysanthemo-δ-lactone **25**.[214]

It has been also reported that reaction of *trans*-chrysanthemic acid *trans*-**1a**$_H$ with pyridinium hydrochloride, carried out at 220 °C, leads to a series of compounds resulting from the cyclopropane ring opening in 77% overall yield (Scheme 150).[352] The dienoic acid **L-117a**$_H$, possesses the lavandulyl skeleton (Scheme 144) and results from the [Cc−Cd] bond cleavage, and the diene **118** from a retroaldol reaction.[352] The five membered- **S-113**, **A-120** and six-membered- **L-119**, **A-120**, **L-121** lactones formation that includes pyrocine **S-113**, results from the effect of the high temperature on the different product resulting from the cyclopropane ring fission.[352]



Scheme 150. Compounds generated from the reaction at 220 °C of *trans*-chrysanthemic acid with pyridinium hydrochloride.[352]

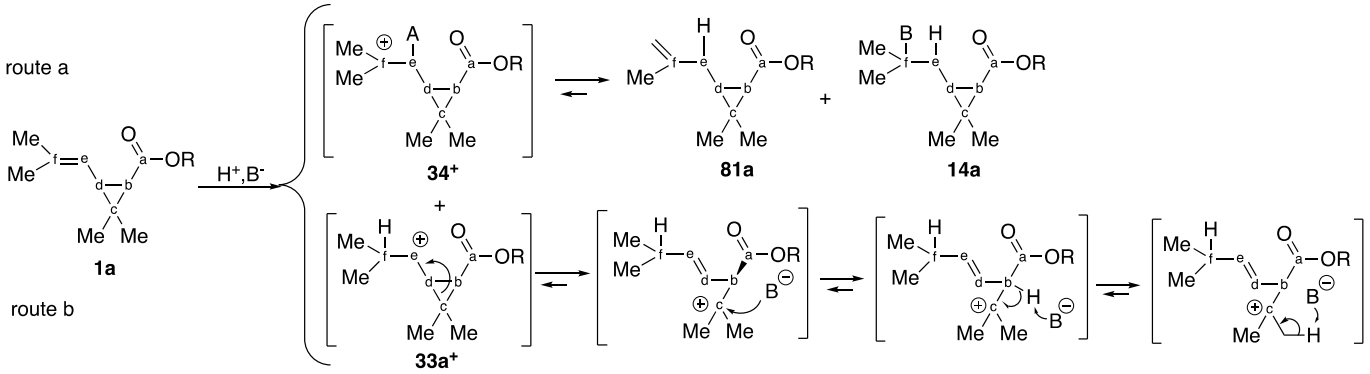
Alkyl chrysanthemates **1a$_R$** also react with different protic acids and among others sulfuric acid in a two phase system (hexane/water; Scheme 151, entries a-d),[90] *p*-toluenesulfonic acid in toluene (PTSA; Scheme 151, entry e),[152] or methanesulfonic acid in 1,2-dichloroethane (Scheme 151, entries f,g).[338,351] They deliver under conditions (70-110 °C; Scheme 151, entries a-c, e-g)[90,152,338,351] that are less drastic than those disclosed in Scheme 150,[352] mainly products possessing the lavandulyl (**L**)-skeleton (Scheme 144) that result from the [Cc−Cd] bond cleavage of their cyclopropane ring (Scheme 151, route b). Rising the temperature up to 130 °C drastically lowers the amount of the open chain products at the advantage of lactone derivatives (structure not disclosed).[90]

Reaction of **1a**$_R$ with aqueous sulfuric acid leads to (i) the dienes (*E*)-**L-117a**$_R$ and (*E*)-**L-114a**$_R$ that are produced from the carbocationic intermediate **33a**$^+$ by proton abstraction from [Cb] and [Cc], respectively, but also (ii) deliver the homoallyl alcohols (*E*)-**L-122a**$_R$ that result from the addition of an hydroxyl group to [Cc] on the same carbocationic intermediate **33a**$^+$ (Scheme 151, entries a-d).[90] The homoallyl alcohols (*E*)-**L-122a**$_R$ are missing when water is missing as in reactions involving sulfonic acids in organic solvents (Scheme 151, entries e-g).[152,338,351] It has been also been observed that:

(i) the amount of the thermodynamically more stable diene (*E*)-**L-117a** increases by increasing the reaction temperature or time (Scheme 151, compare entry e to f;[351,152] entry b to a[90]),

(ii) compounds (*E*)-**L**-**122a**$_R$, (*E*)-**L**-**117a**$_R$ and (*E*)-**L**-**114a**$_R$ exclusively possesses the *E*-stereochemistry that differentiate for example the diene (*E*)-**L**-**114**a$_{Me}$ generated from an acid treatment from the same compound formed under pyrolysis that exclusively possesses the (*Z*)-stereochemistry (Scheme 145),[348,350]

(iii) the transformation of methyl *cis*- or *trans*-chrysanthemate (**1a**$_{Me}$) proceeds stereospecifically keeping in the product (*E*)-**L**-**114**a$_{Me}$ the stereochemistry at [Ca] present originally on the cyclopropane ring of methyl *trans*-chrysanthemate (1*R*,3*S*)-*trans*-(**1a**$_{Me}$) (Scheme 151, entry g).[338,351,]



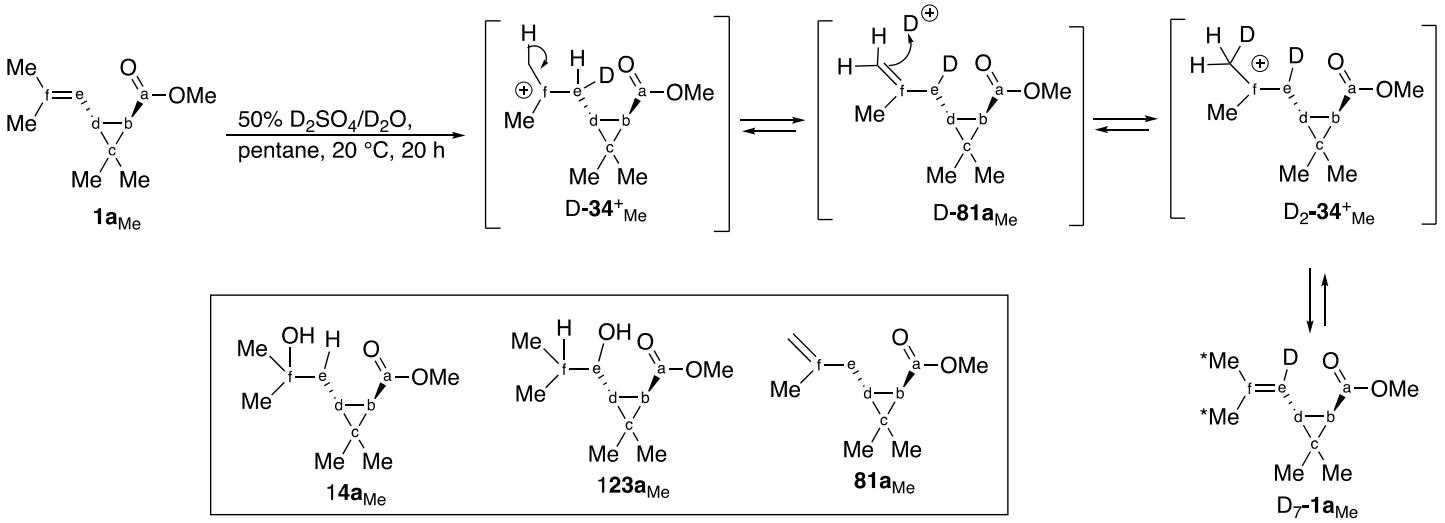
	R			(*E*)-**L**-**122a**	(*E*)-**L**-**117a**$_R$	(*E*)-**L**-**114a**$_R$	
a	Me	*trans*-**1a**$_{Me}$	50 % aq. H_2SO_4, hexane, 20 °C, 20 h	22%	3%	18%[90]	50%
b	Me	*trans*-**1a**$_{Me}$	50 % aq. H_2SO_4, hexane, 20 °C, 70 h	33%	15%	23%[90]	15%`
c	Me	*trans*-**1a**$_{Me}$	50 % aq. H_2SO_4, hexane, 20 °C, 180 h	28%	31%	18%[90]	7%
d	Me	*trans*-**1a**$_{Me}$	50 % aq. H_2SO_4, hexane, 130 °C, 1 h	4%	11%	22%[90]	33%
e	Me	*cis*-**1a**$_{Me}$	PTSA, toluene, reflux, 2h		88%[152]		
f	Et	*trans/cis*-**1a**$_{Et}$ (80/20)	0.37 eq. $MeSO_3H$, $(CH_2)_2Cl_2$, 70°C, 2h	- - - -	46%[351,338*]	47%[351,338*]	
g	Et	(1*R*,3*R*)-*trans*-**1a**$_{Et}$	0.37 eq. $MeSO_3H$, $(CH_2)_2Cl_2$, 70°C, 2h	- - - -	46%[351,338*]	47%[351,338*]	

Scheme 151. Compounds generated from the reaction of alkyl chrysanthemates with protic acids under different conditions.[90,152,351,338]

Careful monitoring of the reaction of methyl *trans*-chrysanthemate *trans*-(**1a**$_{Me}$) carried out at 20 °C with 50% aqueous sulfuric acid leads to the observation that alcohol (*E*)-**L**-**122a** is first formed [90] and then is transformed to the diene (*E*)-**L**-**114**a$_{Me}$ bearing a terminal double bond (Scheme 151, entry b) and finally to the more stable conjugated diene (*E*)-**L**-**117a**$_{Me}$ after longer reaction time (Scheme 151, entry c).[90]

In order to get further insight on the intimate mechanism of the reaction, methyl chrysanthemate **1a**$_{Me}$ has been reacted at room temperature using deuterated sulfuric acid in deuterated water (D_2SO_4-D_2O mixture, Scheme 152)[90] and leads to methyl D-chrysanthemate D_7-(**1a**$_{Me}$) exclusively labelled with deuterium at each of the two vinylic methyl groups and at [Ce]. This result suggests the formation in the process of the intermediates D-**34**$_{Me}^+$ bearing a carbenium ion at [Cf] then **81a**$_{Me}$ and D_2-**34**$_{Me}^+$ (Scheme 152).[90] It has also been reported that labelling is extremely rapid and the lavandulyl esters that are also formed in the process contain the label.

It has also been reported that none of the compounds that could have been expected (Scheme 152) to be produced such as methyl iso-chrysanthemate **81a**$_{Me}$, the tertiary alcohol **14a**$_{Me}$ and the cyclopropyl carbinol (**123a**$_{Me}$) that could have resulted from the isomerization of the C=C double bond or from the addition of water across the [Ce=Cf] double bond, have not been detected apparently because of the rapid interconversion back to the methyl chrysanthemate.

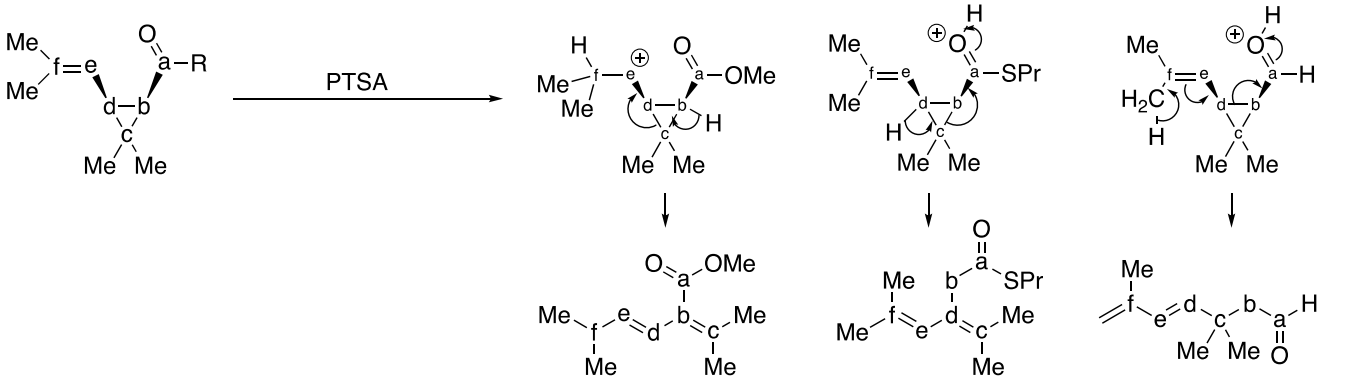


Scheme 152. Compounds generated from the reaction of chrysanthemic acid with deuterated acid in deuterated water.[90]

The tertiary carbenium ion **34**$_{Me}^{+}$ has however been successfully trapped by acidic methanolysis of methyl chrysanthemate leading to methyl methoxy-dihydrochrysanthemate besides lavandulic esters.[90]

5.3.2. Reactions of chrysanthemaldehyde and thiol esters with protic acids. *n*-Propylthio *cis*-chrysanthemate (**6a**) reacts with p-toluenesulfonic acid (PTSA) and delivers after refluxing in toluene for 7h, the diene **S-124e** (Scheme 153, entry b),[152] the carbon skeleton of which is different from the one produced when methyl *cis*-chrysanthemate (**1a**$_{Me}$) is reacted under the same conditions (Scheme 153 compare entry b to entry a). Those differences presumably account from a different initial site of protonation that is expected to take place (i) on the carbonyl group of the unsaturated thioester (**6a**) promoting the cleavage of its [Cb−Cc] bond (Scheme 153, entry b) or (ii) on the C=C double bond of methyl *cis*-chrysanthemate *cis*-(**1a**$_{Me}$) promoting the cleavage of its [Cc−Cd] bond (Scheme 153, entry a).

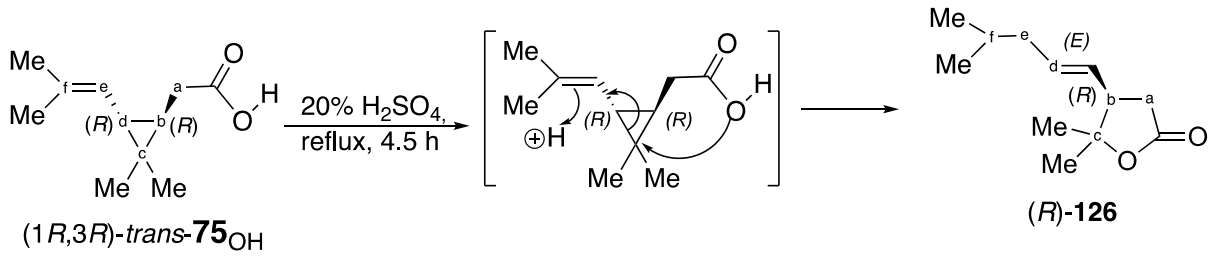
Under related conditions, *cis*-chrysanthemal *cis*-(**7a**) provides the unsaturated aldehyde **A-125c** that involves the last of the three possibilities in which the [Cb−Cd] bond cleavage of the cyclopropane ring takes place (Scheme 153, entry c).[173,353]



a *cis*-**1a**$_{Me}$ R= OMe Toluene, reflux, 2 h
b *cis*-**6a** R= SPr Toluene, reflux, 7 h
c *cis*-**7a** R= H Benzene, 70°C, 3 h

Scheme 153. Regioselective generation of dienes possessing the lavandulyl,[152] santolinyl,[152] artemisyl-[173,353] skeletons from a vinylcyclopropane-carboxylic ester, -carboxylic thioester, and -caboxaldehyde and PTSA.

5.3.3. Reaction of homochrysanthemic acid and homochrysanthemamide with protic acids. Homochrysanthemic acid *trans*-**75a$_{OH}$** also reacts with 20% sulfuric acid on heating at reflux for 4.5 h but it produces the butyrolactone **126** bearing an unsaturated side-chain at C-4 in 57% yield.[71] The same compound **126** is formed if homochrysanthemamide *trans*-**75a**$_{NH}$[71] is reacted under similar conditions.



Scheme 154. Rationalizing the behavior of homochrysanthemic acid towards hot sulfuric acid.[71]

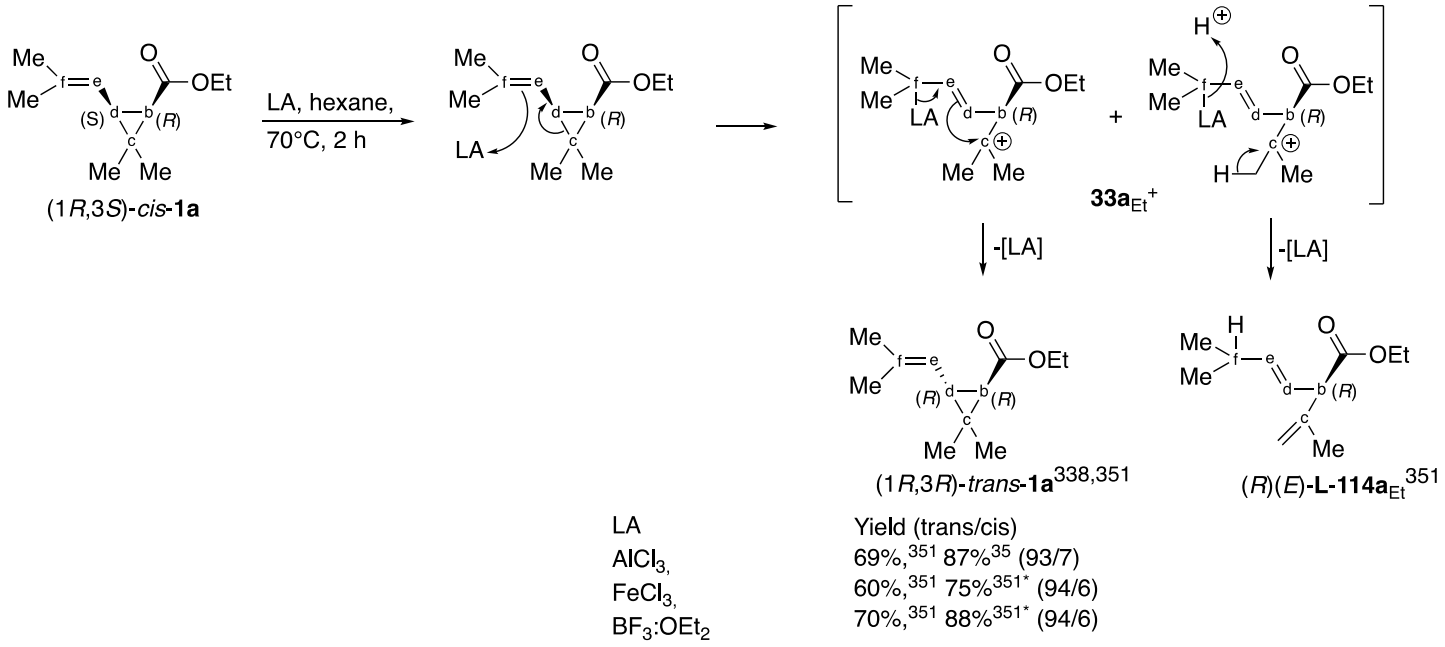
Performing the reaction on enantiomerically pure (1*R*,3*S*)-*trans*-homochrysanthemic acid (1*R*,3*S*)-*trans*-**75**$_{OH}$ leads to the butyrolactone (*R*)-**126** on which the stereochemistry at [Cb] is retained, probably due to a favorable anchimeric assistance (Scheme 154).[72] The results differ from those involving chrysanthemic acid (**1a**$_H$) that under closely related conditions mainly deliver dienes (Scheme 151)[90] and resemble the gross structure of the product resulting from the pyrolysis of chrysanthemic acid (**1a**$_H$) (Scheme 146)[72,349] that also possesses a butyrolactone. The latter bears an unsaturated side-chain at C-4 but its stereochemistry, supported by the mechanism proved different: [retention at [Cb] (Scheme 154)[72] instead of retention at [Cd] (Scheme 146)]. [72,349]

5.4. Cyclopropane ring opening involving Lewis acid catalysts

5.4.1. Reactions of alkyl chrysanthemates with Lewis acids. Reaction of alkyl chrysanthemates (methyl, ethyl, *n*-butyl) with catalytic amounts of aluminum trichloride, iron trichloride or boron trifluoride-etherate (up to 0.3 eq.) in hexane at 70 °C delivers in 0.5 to 3 h besides recovered isomerized alkyl *trans*-chrysanthemates **1a**$_R$ (60-88% yield),[338,351,354,355] some dienoate **L-114a** possessing the lavandulyl skeleton that retains at [Cb] the original stereochemistry present on the chrysanthemate (Scheme 155).[351]

The reaction performed on ethyl *cis*-chrysanthemate delivers the ethyl *trans*-chrysanthemate epimerized at [Cb] suggesting that the [Cb-Cc] bond cleavage selectively takes place in the process leading to a cationic intermediate. The latter recombines to produce the thermodynamically more stable ethyl *trans*-chrysanthemate (Scheme 155).[338,351,354] The dienoate **L-114a**$_{Et}$ is expected to be formed from the same intermediate by competing proton elimination from one hydrogen originating from one of the methyl group originally present on the cyclopropane ring (Scheme 155).[351] Typically,[354,355] ethyl (1*R*,3*S*)-*cis*-chrysanthemate (1*R*,3*S*)-*cis*-(**1a**$_{Et}$) in hexane on reaction with aluminum trichloride (0.4 eq.) heated at 70 °C for 3 h, leads to 88% of an isomeric mixture of ethyl chrysanthemate (**1a**$_{Et}$) in which the [(1*R*,3*R*)-*trans*-(**1a**$_{Et}$) prevails [(1*R*,3*R*)-*trans*: 88.4% *;* (1*S*,3*S*)-*trans*: 1.1%*;* (1*R*,3*S*)-*cis*: 10.5.% by weight].

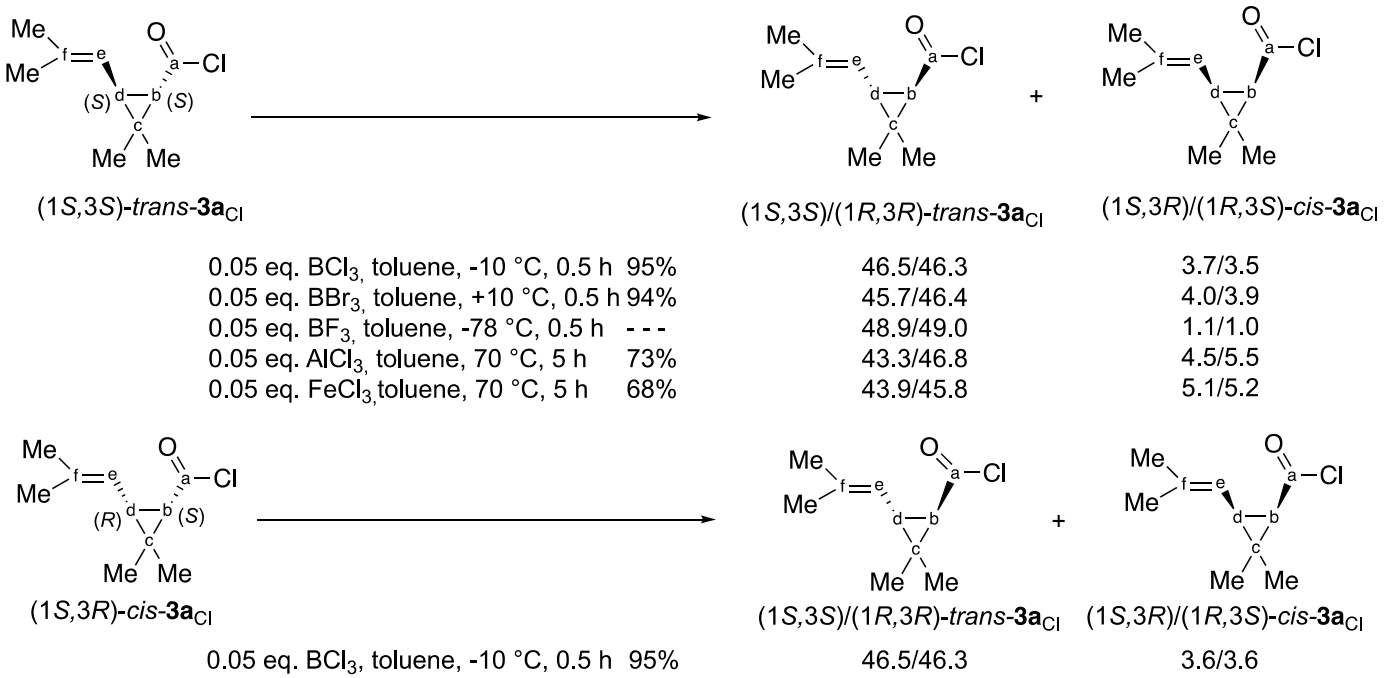
Therefore, Lewis acids behave towards alkyl chrysanthemates **1a**$_R$ differently than protic acids since not only (i) they induce the cleavage of the [Cb−Cd] bond of the cyclopropane ring (Scheme 155) whereas protic acids usually promote the [Cb−Cc] bond cleavage, but also (ii) they deliver alkyl chrysanthemates **1a**$_R$ (Scheme 155) whereas protic acids lead to ring opened compounds such as **L-117a** (Scheme 153, entry e). These features allow, for example, the convenient stereoselective isomerization of the alkyl *cis*-chrysanthemates *cis*-**1a**$_R$ to alkyl *trans*-chrysanthemate *trans*-**1a**$_R$ by specific epimerization at [Cd] leaving intact the stereochemistry at [Cb] on the cyclopropane ring (Scheme 155).[338,351,354,355]



Scheme 155. Lewis acids catalyzed *cis*/*trans*-isomerization of ethyl *cis*-chrysanthemate implying the formation of an intermediate possessing the lavandulyl skeleton.[338,351]

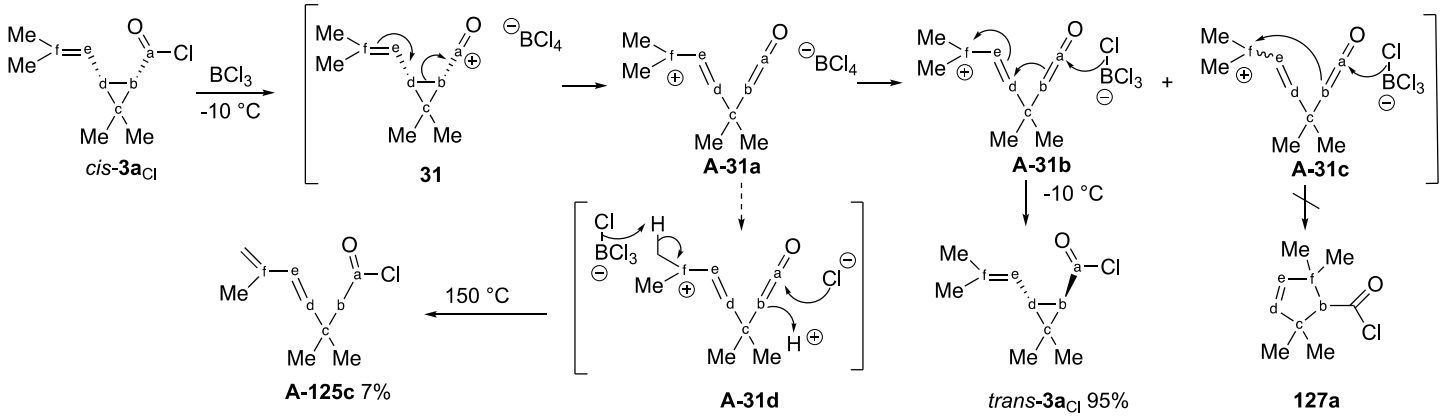
5.4.2. Reactions of chrysanthemoyl chloride, chrysanthemic acid anhydride, chrysanthemaldehyde and related compounds with Lewis acids. The reaction of enantiopure (1*S,*3*S*)-*trans*-chrysanthemoyl chloride and (1*S,*3*R*)-*cis*-chrysanthemoyl chloride (1*S,*3*R*)-*cis*-(3a$_{Cl}$) with Lewis acids leads in both cases to *rac*-*trans*-chrysanthemoyl chloride *trans*-(3a$_{Cl}$) (Scheme 156).[73,356] The reaction is favorably carried out[73,356] in aliphatic hydrocarbon such as hexane, an ethereal solvent such as dioxane, an aromatic solvent such as toluene or an halogen substituted hydrocarbon such as chloroform or trichloroethylene with the Lewis acid catalyst amounting 1/200 to 1/10 molar equivalent.[73] Although the crude mixture is conventionally treated with aqueous alkali and then with a mineral acid to deliver the completely racemized carboxylic acid, it can be directly subjected without hydrolysis to the reaction with pyrethrolone, allethrolone in the presence of a hydrogen halide-eliminating agent to obtain directly a bioactive ester.[73]

Racemization of (1*S*,3*S*)-*trans*-chrysanthemoyl chloride (1*S*,3*S*)-*trans*-(**3a**$_{Cl}$) with boron trichloride is over in less than 0.2 h when performed at -40 °C providing a racemic mixture in up to 93% yield and similar results are obtained when the reaction is performed at -20 or +20 °C (Scheme 156, entry a).[356,67] However the reaction is routinely achieved using boron trichloride in toluene at -10 °C, for 0.5 h (Scheme 156, entries a,f).[356] Boron tribromide reacts almost similarly but the transformation requires a higher temperature (Scheme 156, entry b compare to entry a).[356] Boron trifluoride is far more reactive (Scheme 156, entry c)[356] and aluminum or iron trichoride less reactive, the latter requiring much higher temperature and delivers much lower yields (Scheme 156, entries d,e).[356]



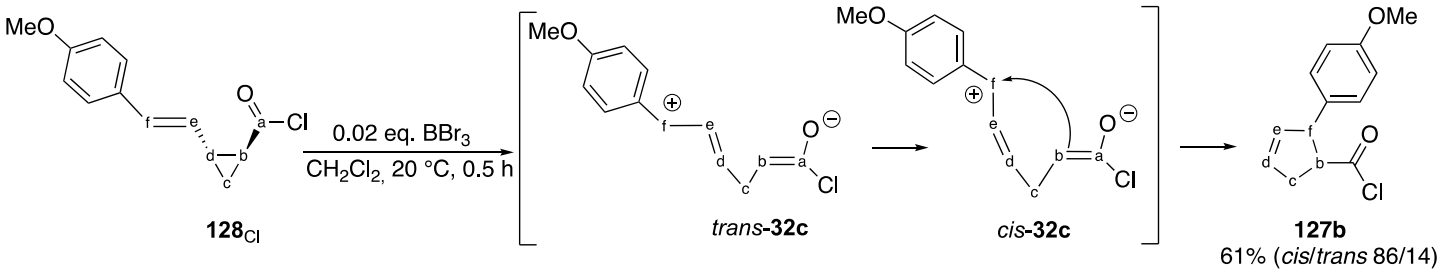
Scheme 156. Lewis acid catalyzed isomerization and racemization of enantiopure *trans*- and *cis*- chrysanthemoyl chloride.[73,356]

It has been found that the racemization rate of *cis*-chrysanthemic acid chloride *cis*-**3a**$_{Cl}$ in the presence of boron trichloride is independent of the configuration of the starting material and that the amount of *trans*-chrysanthemoyl chloride *trans*-(**3a**$_{Cl}$) increases over that of its *cis*-stereoisomer as the reaction temperature is lowered. Performing the reaction at low temperature offers also the advantage to avoid the formation of 3,3,6-trimethyl-hepta-4,6-dienoyl chloride **A-125**$_{Cl}$ that is competitively formed if the reaction is performed at high temperature (150 °C, 1 h, 7 %, Scheme 157).[356] Furthermore, it has been reported that the presence of the vinylcyclopropane moiety is required for successful ring cleavage that does not take place when a saturated side chain is attached at [Cd].[356] The racemization reaction is expected to proceed by selective cleavage of the [Cb,Cd] bond which simultaneously destroys both chiral centers present on the cyclopropane ring as described in Scheme 157 and benefit from the extra stabilization of the charge by delocalization on the isobutenyl moiety.[356]



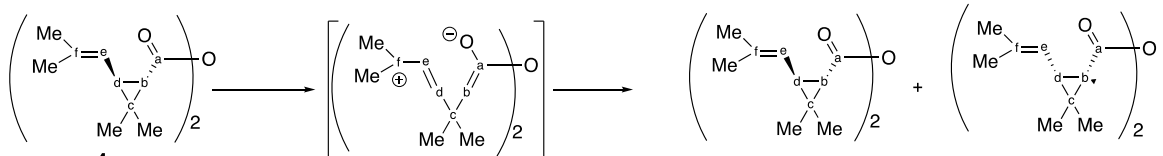
Scheme 157. Postulated mechanism for the boron trifluoride catalyzed isomerization of *cis*-chrysanthemoyl chloride.[356]

It is surprising that the reaction of the chloride ion on **31** produces exclusively a three membered cycle to the exclusion of the formation of some five membered compounds such as **127a** (Scheme 157).[356] It has however been reported that the styrenylcyclopropane carboxylic chloride **128**$_{Cl}$, that lacks the two methyl substituents at [Cc], expected to favor the formation of the three membered cycle from the open chain intermediate (Thorpe-Ingold effect),[368] reacts with boron tribromide at room temperature for 0.5 h, to deliver the 2-phenoxy cyclopentenyl acid chloride **127b** in 61% yield.[357] The presence of a *p*-methoxy-phenyl group on the vinylic moiety able to stabilize the developing carbocation at [Cf] and to allow the conformational changes that favor the proximity of [Cf] to [Cb] is crucial for the success of the competing process. Exchange of the methoxy-group by a methyl group on the aromatic ring that substantially lowers the stabilizing capabilities on the carbenium ion at [Cf] requires more drastic condition to take place. Furthermore, the interconversion proceeds in extremely poor yield if there is no substituent there and does not proceed with a chloro substituent on the aromatic ring.[357]



Scheme 158. Lewis acid catalyzed isomerisation of vinylcyclopropane carboxylic chloride to cyclopentene carboxylic chloride.[357]

Racemization has been also achieved on chrysanthemic acid anhydride (**4a**) catalyzed by aluminum trichloride or bromide (Scheme 159, entry a), iron trichloride (Scheme 159, entry b), tin tetrachloride (Scheme 159, entry c), titanium tetrachloride, zinc chloride and iodine that give the more favorable results (Scheme 159, entry d).[80]

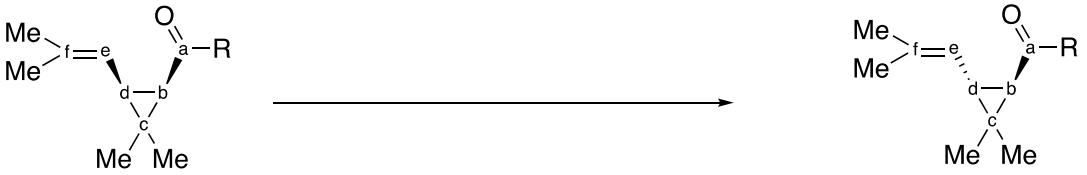


a	0.1 eq. $AlCl_3$, toluene, 100°C, 7h	48.7/40.5	6.7/4.0
b	0.12 eq. $FeCl_3$,dioxane, 70°C,1h	51.8/41.8	3.4/3.1
c	0.1 eq. $SnCl_4$,toluene, 50°C, 3h	54.1/43.1	1.5/1.3
d	0.12 eq. I_2, toluene, 60°C, 1h	46.5/44.4	3.9/5.2

Scheme 159. Racemization of chrysanthemic acid anhydride.[80]

cis- to *trans*-Chrysanthemal (**7**a) isomerization is even easier since it occurs quantitatively with zinc iodide in ether (Scheme 160, entry a), with methoxydimethyl sulfonium salt in DMSO (Scheme 160, entry c), or even on impregnation on silicagel (Scheme 160, entry b) for a day at room temperature.[353] Zinc chloride or bromide however, proved to be less efficient than zinc iodide,[353] lithium iodide is inefficient to promote any reaction,[353]

boron trifluoride catalysis leads to an intractable mixture of compounds,[353] and *p*-toluenesulfonic acid (PTSA) catalysis caused undesired ring opening (Scheme 153, entry c).[353]



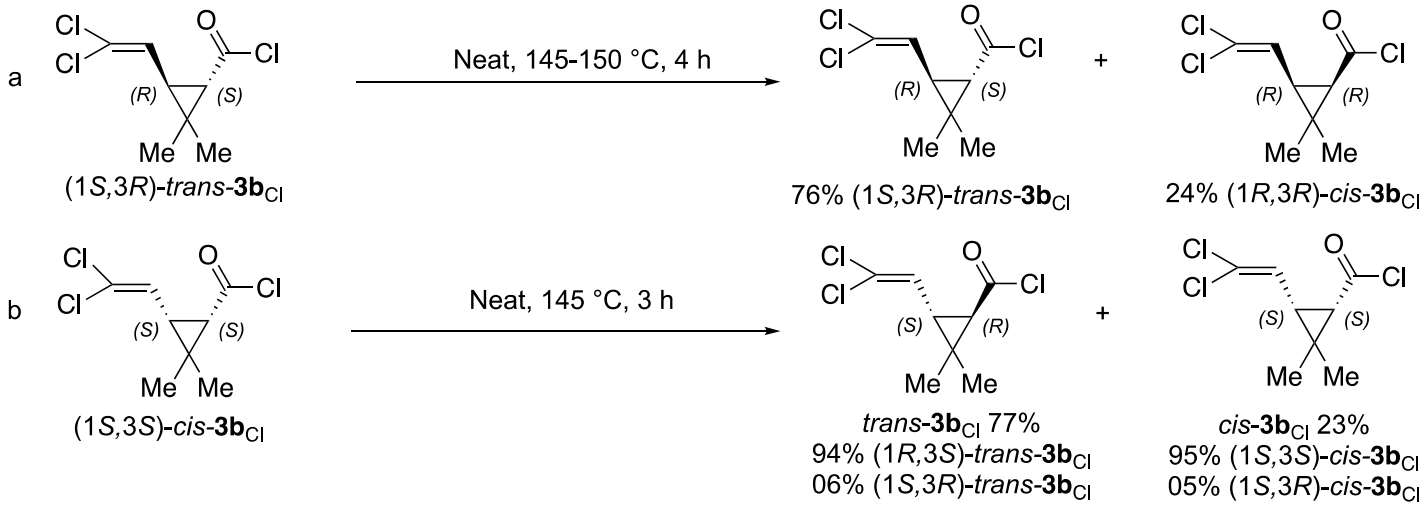
a	R: H *cis*-**7a**	0.5 eq. ZnI_2, Et_2O, 25 °C, 24 h	R: H *trans*-**7a** 100%
b	R: H *cis*-**7a**	SiO_2 (100 mesh), impregnation, 20 °C, 18 h	R: H *trans*-**7a** 100%
c	R: H *cis*-**7a**	1 eq. $MeOSMe_2.I$, DMSO, 25 °C, 24 h	R: H *trans*-**7a** 100%
d	R: Me *cis*-**8a**$_{Me}$	1 eq. $MeOSMe_2.I$, DMSO, 80 °C, 2 h	R: Me *trans*-**8a**$_{Me}$ 100%
e	R: Ph *cis*-**8a**$_{Ph}$	1 eq. $MeOSMe_2.I$, DMSO, 80 °C, 7 h	R: Ph *trans*-**8a**$_{Ph}$ 100%

Scheme 160. *cis*/*trans* Isomerization *cis*-chrysanthemal and related methyl and phenyl ketones catalyzed by methoxydimethyl sulfonium salt.[353]

It has been furthermore described, that the presence of the [Ce=Cf] double bond is essential for successful epimerization that let suggest that the reaction occurs by [Cb−Cd] bond cleavage.[353] This is further supported by the absence of deuterium incorporation when the reaction is carried out with methoxydimethyl sulfonium salt in deuterated DMSO.

Epimerisation is much less efficient when carried out under similar conditions with the related methyl- **8a**$_{Me}$ (Scheme 160, entry d) or phenyl- **8a**$_{Ph}$ (Scheme 160, entry e) ketones[353] that require heating at 80 °C for 2 or 7 h, respectively, to proceed.[353]

In conclusion[353] the most suitable conditions to achieve such epimerization reaction involve: (i) catalysts that do not coordinate too strongly (BF_3) or that are too weak (LiI), (ii) starting materials possessing at [Cb] a formyl rather than an acetyl or an arylcarbonyl group and at [Cc] an isobutenyl side chain rather than a phenyl group or a saturated side chain.[353]



(1*S*,3*R*)-*trans*-**3b**$_{Cl}$ — 76% (1*S*,3*R*)-*trans*-**3b**$_{Cl}$ + 24% (1*R*,3*R*)-*cis*-**3b**$_{Cl}$

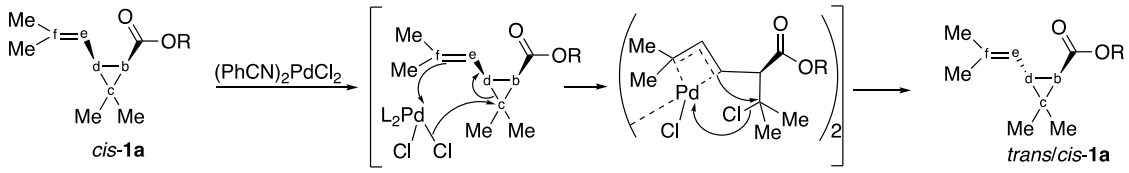
(1*S*,3*S*)-*cis*-**3b**$_{Cl}$ — *trans*-**3b**$_{Cl}$ 77% (94% (1*R*,3*S*)-*trans*-**3b**$_{Cl}$ 06% (1*S*,3*R*)-*trans*-**3b**$_{Cl}$) + *cis*-**3b**$_{Cl}$ 23% (95% (1*S*,3*S*)-*cis*-**3b**$_{Cl}$ 05% (1*S*,3*R*)-*cis*-**3b**$_{Cl}$)

Scheme 161. Heat promoted regioselective epimerization of *trans*- and *cis*-cypermethrinic acid chlorides at [C-1].[358]

It is interesting to notice that reacting cypermethrinic acid (**1b**$_H$) with an excess of thionyl chloride, and heating the residue after removal of the excess of thionyl chloride, at around 150 °C for 3-4 h leads to a 77/23 *trans*/*cis* mixture of cypermethrinoyl chloride (**3b**$_{Cl}$).[358] Performing the same reaction on (1*S*,3*R*)-*trans*-(**1b**$_H$) leads to a 76/24 mixture of 1*S*-*trans*/1*R*-*cis*-(**3b**$_{Cl}$) (Scheme 161, entry a)[358] whereas carrying out the reaction on the (1*S*,3*S*)-*cis*-(**1b**$_H$) leads[358] to a 77/23 mixture of 1*R*-*trans*/1*S*-*cis*-(**3b**$_{Cl}$) (Scheme 161, entry b)[358] suggesting that epimerization is almost exclusively taking place at C-1.[358]

5.5. Cyclopropane ring opening involving transition metal catalysts

Ethyl *cis*-chrysanthemate *cis*-(**1a**$_{Et}$) (Scheme 162, entries a,b) and *cis*-chrysanthemic acid (**1a**$_H$) (Scheme 162, entries c,d) are cleanly isomerized at room temperature to their *trans*-derivatives on reaction with palladium complexes (L_2PdCl_2) in a homogeneous liquid phase such as benzene or chloroform.[348,359] Benzonitrile proved to be a better ligand than other nitriles (RCN, R: Me, Pr), and palladium dichloride that is insoluble in the medium is completely inefficient.[359] The reaction performed with 0.15 eq. of benzonitrile takes place with up to 35% conversion within the first 0.1 h and stopped after 15.5 h at which time 87% of *cis*-(**1a**$_{Et}$) is converted to its *trans*-isomer *trans*-(**1a**$_{Et}$) (TN 6.7) and addition of more catalyst resulted in additional conversion.[359] Use of less than 0.15 Mol% of catalyst resulted in lower turnovers whereas complete conversion to the *trans*-stereoisomer occurs in less than 0.6 h when one equivalents of catalyst is used.



a	*cis*-1a$_{Et}$	0.14 eq. $(PhCN)_2PdCl_2$, $CDCl_3$, 20°C, 15,5h	**1a**$_{Et}$	71%	87/13[359]
b	*cis*-1a$_{Et}$	1 eq. $(PhCN)_2PdCl_2$, $CDCl_3$, 20°C, 0.4h	**1a**$_{Et}$	100%	100/0[359]
c	*cis*-1a$_H$	0.16 eq. $(PhCN)_2PdCl_2$, $CDCl_3$, 20°C, 5,5h	**1a**$_H$		100/0[359]
d	(1*R*,3*S*)-*cis*-1a$_H$	0.30 eq. $(PhCN)_2PdCl_2$, $CDCl_3$, 20°C, 3h	(1*R*,3*R*)-*trans*-**1a**$_H$	71%	92/8[348]
e	(1*R*,3*S*)-*cis*-1a$_H$	0.15 eq. $(PhCN)_2PdCl_2$, $CDCl_3$, 50°C, 3h	(1*R*,3*R*)-*trans*-**1a**$_H$	75%	79/21[348]
f	(1*R*,3*S*)-*cis*-1a$_H$	0.10 eq. $(PhCN)_2PdCl_2$, $CDCl_3$, 100°C, 3h	(1*R*,3*R*)-*trans*-**1a**$_H$	82%	63/37[348]

Scheme 162. Regioselective transition metal catalyzed epimerization of *cis*-chrysanthemic acid and related esters at [C-3].[348,359]

The reaction is highly stereoselective if carried out at 20 °C with no less than 0.3 equivalents of catalyst for 3 h. It occurs in 71% yield on enantiopure (1*R*,3*S*)-*cis*-(**1a**$_{Et}$) with almost complete retention of configuration at [Cb] and almost complete inversion at [Cd] suggesting the intermediate cleavage/recombination of the [Cc−Cd] bond (Scheme 162, entry d; *trans*/*cis* 92/08 ratio; trans(1*R*,3*R*)/(1*S*,3*S*): 90.7/1.6*; cis*-(1*R*,3*S*)*/*(1*S*,3*R*): 7.6/0.1).[348] The intimate mechanism of the transformation has not yet been established. We however suggest that it proceeds through the intermediate formation of a π-allyl complex[360] resulting from the cleavage of the [Cc−Cd] bond followed by recombination of the destroyed bond favoring the formation of the more stable *trans*-stereoisomer (Scheme 162).

If the same reaction is carried out with half the amount of catalyst, it requires a higher temperature (50 °C) to occur in the same time and although the reaction proceeds with almost the same yield the *trans*/*cis* ratio is much lower (Scheme 162, entry e; *trans*/*cis* 79/21 ratio; *trans*-(1*R*,3*R*)/(1*S*,3*S*): 74.3/4.4*; cis*-(1*R*,3*S*)*/*(1*S*,3*R*): 20.1/1.2).[348] The tendency is the same when the reaction is performed with an even lower amount of catalyst (10%, 100 °C, 3 h, 82% yield; Scheme 162, entry f; *trans*/*cis* 63/37 ratio; *trans*-(1*R*,3*R*)/(1*S*,3*S*): 60.6/2.4*; cis*-(1*R*,3*S*)*/*(1*S*,3*R*): 37.0/0).[348] Those results clearly show that the percentage of *cis*/*trans*-isomerization of the

vinylcyclopropane moiety is directly related to the amount of catalyst used and culminates with 1 equivalent. Interestingly, even at high temperature (100 °C, 3 h) the stereochemistry at [Ca] either on the *cis*- or the *trans*-chrysantemic acid is not affected.

5.6. Cyclopropane ring opening promoted by radicals

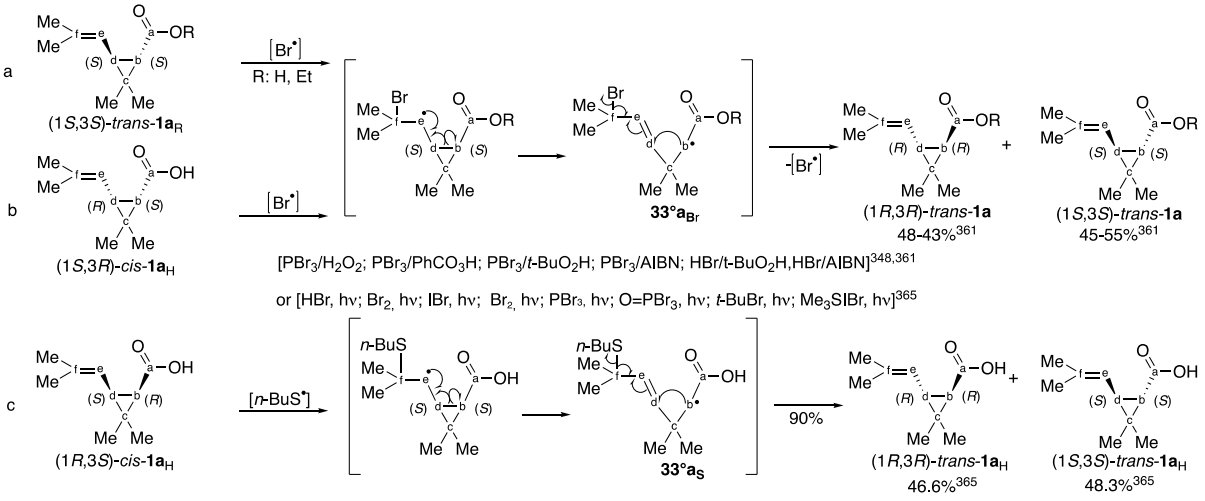
5.6.1. Cyclopropane ring opening promoted by radical initiator produced thermally. *cis*-Chrysanthemic acid enantiopures and racemic mixture of *cis*- and *trans*-chrysanthemic acid (**1a**$_H$) and the related ethyl ester *trans*-(**1a**$_{Et}$) have been transformed to their *trans*-stereoisomers as racemates on reaction with a series of reagents susceptible to generate a bromine radical (Scheme 163, entries a, b). [348,361]

This has been effectively achieved by using 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 phosphoryl bromide ($O=PBr_3$) 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-*t*-Bu) or azobisisobutyronitrile (AIBN).[348,361,362]

The reactions have been performed in dioxane, toluene, carbon tetrachloride, acetic acid, at 0 °C, room temperature, or at 80 °C, usually for about 0.5 h.[348,361,362]

cis- and *trans*-Chrysanthemic acid, as well their ethyl or butyl esters including enantiomerically enriched ones, have been successfully transformed to racemic *trans*-chrysanthemic acid with catalytic amounts of aluminum bromide in the presence of *t*-butyl hydroperoxide at room temperature[364] or azobisisobutyronitrile at 80 °C[363] in toluene or dioxane for 0.5 to 1 h.

Typically (1*S*,3*R*)-*cis*-chrysanthemic acid (1*S*,3*R*)-*cis*-(**1a**$_H$) when reacted with gaseous hydrobromide (0.15 eq.) in the presence of 0.05 eq. *tert*-butyl hydroperoxide in toluene at 20 °C for 0.5 h (Scheme 163, entry b), delivers in 90% yield (1*R*,3*S*)-*cis*-(**1a**$_H$) (2.3%)/(1*S*,3*R*)-*cis*-(**1a**$_H$) (2.1%)/(1*R*,3*R*)-*trans*-(**1a**$_H$) (44.3%)/(1S,3S)-*trans*-(**1a**$_H$) (51.3%).[348,361]



Scheme 163. Radical promoted racemisation of chrysanthemic acid.[348,361,365]

Otherwise, similar racemization has been also achieved from :
(i) (1*S*,3S)-*trans*-chrysanthemic acid on reaction with phosphorus tribromide and azobisisobutyronitrile (AIBN), benzene 80 °C, 0.3 h) or phosphorus pentabromide and (AIBN), benzene 70 °C, 0.3 h); hydrobromic acid and *t*-butyl hydroperoxide (HBr, t-BuO_2H, AcOH-toluene, 20 °C, 0.5 h),[361]

(ii) Ethyl (1*S*,3*S*)-*trans*-chrysanthemate on reaction with phosphorus tribromide and hydrogen peroxide (PBr_3, t-BuO_2H, dioxane, 20 °C, 0.5 h; or CCl_4, 0 °C, 1 h), phosphorus pentabromide and (AIBN), benzene 80 °C, 0.5 h) or hydrobromic acid and AIBN (HBr, AIBN, AcOH-dioxane, 80 °C, 0.5 h),[361]

(iii) Butyl (1*S*,3*S*)-*trans*-chrysanthemate (mainly 70%) on reaction with phosphorus tribromide and *t*-butylhydroperoxide, dioxane, 20 °C, 1 h, 90% (1*R*-*trans*/1S-*trans*/ 1*R*-*cis*/1*S*-*cis* 46.1/47.9/2.6/3.4).[362]

5.6.2. Cyclopropane ring opening promoted by radical initiator produced photochemically. Chrysanthemic acid, alkyl chrysanthemates, chrysanthemoyl chloride and chrysanthemic acid anhydride enantiomerically pure or as a mixture of enantiomers or diastereoisomers have been efficiently transformed to racemic mixture containing mainly the *trans*-stereoisomer on reaction with a series of bromo compounds used as pre-catalysts and decomposed by ultraviolet light (200-400 nm, Scheme 163).[365] The latter has been produced by a high pressure mercury lamp, a xenon lamp or a low pressure mercury lamp shaded in some cases by a Pyrex glass filter.[365]

The racemization proceeds[365,366] with hydrogen bromide, bromine or iodine monobromine but also with (i) phosphorus tribromide, phosphoryl bromide, (ii) boron and aluminum tribromide, carboxylic acid bromide, *tert*-butyl bromide, trialkylsilyl bromide that are all able to generate bromine radical (Scheme 163, entries a,b) as well as (iii) thiols such as phenylthiol, thiocresol, butanethiol as well as thiobenzoic acid, thiosalicylic acid that produce a thiyl radical (Scheme 163, entry c).[365-367]

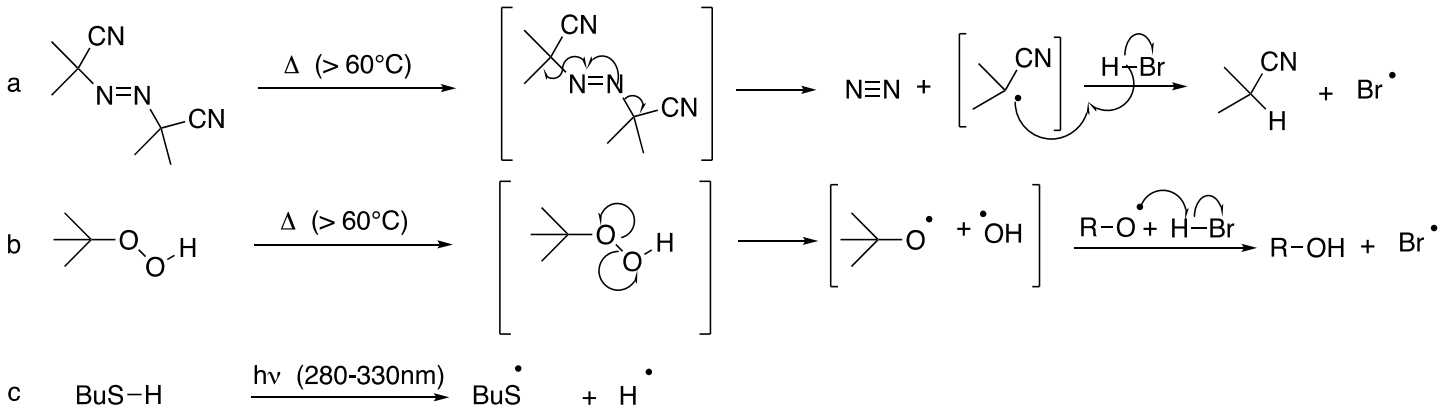
Thus (1*R*,3*R*)-*trans*-chrysanthemic acid and *cis*-chrysanthemic acid have been racemized on reaction with hydrogen bromide (25%) in toluene under irradiation with a xenon lamp (500 W) and a Pyrex glass filter[365] and (1*R*,3*S*)-*cis*-chrysanthemic acid has been racemized in 1 h on irradiation in the presence of 0.2 eq. n-butanethiol using a high pressure mercury lamp (100 W) leading to 90% yield of (1*S*,3S)-*trans*-(**1a**$_H$) (48.3%), (1*R*,3*R*)-*trans*-(**1a**$_H$) (46.6%), (1*R*,3*S*)-*cis*-(**1a**$_H$) (3%), (1*S*,3*R*)-*cis*-(**1a**$_H$) (2.7%).

The synthesis of bromine radical in the presence of azobisisobutyronitrile (AIBN) as radical initiator and generation of a thiyl radical upon irradiation are discussed below and shown in Scheme 164.

Free radical reactions[307] involve at their early stage the homolytic cleavage of a bond generating two radical species (homolysis). It can be achieved under heat, light or metal catalyzed reaction. Those reactions lead to compounds bearing a reactive single electron species that can initiate (initiation step) further processes such as substitution, addition or elimination-reactions that produce new radical that perpetuate the process through what is known as a radical chain reaction (propagation step). Reaction of two species each of them bearing a radical result in the formation of a compound and stops the chain process (termination step).

For example, the bromine radical is generated from hydrobromic acid and AIBN (Scheme 164, entry a) or *t*-butyl-hydroperoxide (Scheme 164, entry a) under thermal conditions that intermediary releases dinitrogen and the captodative carbon centered radical or the *tert*-butoxide and the hydroxide radicals, respectively.

Thiols absorb at short wavelengths (maximum of absorbance around 200 nm and a broad band centered at 235 nm for methanethiol), and different dissociation mechanisms may be involved.[367] Irradiation above 300 nm is thus rather inefficient in generating substantial amounts of thiyl radicals (Scheme 164, entry c). Nevertheless, in preparative chain reactions where only initiation is required, continuous irradiation using a sun lamp can be used, even through Pyrex glass (cutoff around 280 nm). In such cases, the slow but constant initiation is an advantage because the steady-state concentration of radicals remains low, diminishing the importance of termination reactions".[367]



Scheme 164. Postulated mechanism for production under thermal and photochemical processes of radical initiators from hydrobromic acid and butanethiol.

Anyhow, both the thermally and photochemically induced reactions are valuable for racemizing pyrethroids. Photochemical processes offer the advantage to be carried out even at low temperature but design of the reactor and selection of the light could be a problem that flow chemistry is changing.

6. Conclusions

Many reviews have reported the reactivity of a specific reagent or a specific transformation. Describing however the reactivity of a single substrate towards a variety of reagents is a rare exercise that we have intended to achieve in this review. Interestingly, this could be done due to the biological and commercial interest of chrysanthemic acid and its esters and because chrysanthemic acid and its lower esters has been used as a valuable starting material for the synthesis of similar compounds and analogues to synthesize related new compounds expected to possess exceptional biological properties and stability able to be patented and used.

Chrysanthemic acid and its esters concentrate on a ten-carbon basic skeleton an extremely high number of functional groups on which the high diversity of reagents disclosed react highly selectively. We can cite among others (i) thermal and photochemical processes including thermolysis (ii) reactions involving acids and bases (iii) reactions involving reducing agent, oxidant and without changing the oxidation level, (iv) concerted and non-concerted processes.

This is an original and interesting opportunity to rediscover the fundamental reactions of organic chemistry in a specific context. Moreover, several results come from patents and are industrially oriented that is quite uncommon in the academic literature. They offer however the advantage to be freely accessible! This paper involves experiment that can be performed on large scale, at low cost and for which green chemistry is more than just a label

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References

1. Krief, A. *Arkivoc* **2021**, *i*, 48-54. https://doi.org/10.24820/ark.5550190.p011.328
2. Krief, A. *Arkivoc* 2021, *i*, 55-77. https://doi.org/10.24820/ark.5550190.p011.482
3. Matsui, M.; Meguro, H. *Agr. Biol. Chem.* **1964**, 28, 27-31. https://doi.org/10.1080/00021369.1964.10858198
4. Elliott, M.; Janes, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473-505. https://doi.org/10.1039/CS9780700473
5. Ujihara, K. *J. Pestic. Sci.* 2019, **44**, 215-224. https://doi.org/10.1584/jpestics.D19-102
6. Matsuo, N. *Proc. Jpn. Acad., Ser. B* **2019**, *95*, 378-400 https://doi.org/10.2183/p jab.95.027
7. Krief, A. *Arkivoc* **2021**, *i*, 78-142. https://doi.org/10.24820/ark.5550190.p011.327
8. Staudinger, H.; Muntwyler, O.; Ruzicka, L.; Seibt, S. *Helv. Chim. Acta* **1924**, *7*, 390-406. https://doi.org/10.1002/hlca.19240070146
9. Schatz, P. F. *J. Chem. Educ.* **1978**, *55*, 468-470. https://doi.org/10.1021/ed055p468
10. Krief, A. *Arkivoc* **2021**, *i*, 378-470 https://doi.org/10.24820/ark.5550190.p011.427
11. Kawamoto, M.; Moriyama, M.; Ashida, Y.; Matsuo, N.; Tanabe, Y. *J. Org. Chem.* **2020**, *85*, 2984-2999, https://doi.org/10.1021/acs.joc.9b02767
12. Ruzo, L.O.; Smith, I.H.; Casida, J. E. *J. Agric. Food Chem.* **1982**, *30*, 110-115. https://doi.org/10.1021/jf00109a025
13. Ruzo, L.O.; Gaughan, L.C.; Casida, J. E. *J. Agric. Food Chem.* **1980**, *28*, 246-249. https://doi.org/10.1021/jf60228a015
14. Otera, J.; Nishikido, J. *Esterification: Methods, Reactions and applications*, Wiley VCH: Weinheim, 2nd Edn, 2010.
15. Markownikoff, W. *Annalen der Pharmacie* **1870***, 153*, 228-259. https://doi.org/10.1002/jlac.18701530204
16. Hughes, P. *J. Chem. Ed.* **2006***, 82*, 1152-1154. https://doi.org/10.1021/ed083p1152
17. Schleyer, P.v.R.; William, J.E.; Blanchard, K.R. *J. Am. Chem. Soc.* **1970**, *92*, 2377-2386 https://doi.org/10.1021/ja00711a030
18. Wiberg, K.B. *Acc. Chem. Res.* **1996**, *29*, 229-234. https://doi.org/10.1021/ar950207a
19. De Meijere, A. *Angew. Chem. Int. Ed. Engl.* **1979**, ***18***, 809-886. https://doi.org/10.1002/anie.197908093
20. Arca, H.A.; Mota, C.J.A. *Topics in Catalysis* **2018**, *61*, 616-622. https://doi.org/10.1007/s11244-018-0911-8
21. Roberts, J.D.; Mazur, R.H. *J. Am. Chem. Soc.* **1951**, *73*, 3542-3543. https://doi.org/10.1021/ja01151a550

22. Brown, H.C. "The Nonclassical Ion Problem" **1977,** ISBN: 978-1-4613-4118-5.
23. Olah, G.A., Reddy, V.P.; Prakash, G.K.S. *Chem. Rev.* **1992**, *92*, 69-98. https://doi.org/10.1021/cr00009a003
24. Choi, S.-Y.; Newcomb, M. *Tetrahedron* **1995**, *51*,657-664. https://doi.org/10.1016/0040-4020(94)00972-W
25. Itaya, N.; Kamoshita, K.; Mizutani, T.; Kitamura, S.; Nakai, S.; Kameda, N.; Fujimoto, K.; Okuno, Y. *United States of America Patent* US 3,669,789, 1972.
26. Martel, J.; Tessier, J.; Demoute, J. P. *United Kingdom Patent* GB 1 583 600, 1981.
27. Matsumoto, T.; Nagai, A.; Takahashi, Y. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 481-482. https://doi.org/10.1246/bcsj.36.481
28. Leigh, T. *Process for separating cis- and trans-isomers of cyclopropane carboxylic acids* US Pat. 4,306,077, 1981, December, 15.
29. Leigh, T. *Europan Patent* EP 0,010,874 A1, 1980, May, 14
30. Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, racemates, and resolutions* J. Wiley: New York, 1981.
31. Campbell, I. G. M.; Harper, S. H. *J. Chem. Soc.* **1945**, 283-286. https://doi.org/10.1039/JR9450000283
32. Campbell, I. G. M.; Harper, S. H. *J. Sci. Food Agric.* **1952**, *3*, 189-192. https://doi.org/10.1002/jsfa.2740030412
33. Matsui, M.; Horiuchi, F. *Agric. Biol. Chem.* **1971**, *35*, 1984-1985. https://doi.org/10.1271/bbb1961.35.1984
34. Itagaki, M.; Suzukamo, G.; Sasaki, K.; Fujita, K. US Pat. 6,268,525 B1 2001, July, 31.
35. Tessier, J. *Chem. Ind. (London)* **1984**, 199-204.
36. Kozsda-Kovacs, E.; Keseru, M.; Bockei, Z.; Szilagyi, I.; Simon, K.; Bertok, B.; Fogassy, E. *J. Chem. Soc., Perkin Trans.2* **2000**, 149-153. https://doi.org/10.1039/A904682H
37. Martel, J. *French Patent* FR 1,580,474, 1969; *Chem Abstr.* **1970**, *72*, 100136.
38. Rosini, G.; Ayoub, C.; Borzatta, V.; Marotta, E.; Mazzanti, A.; Righi, P. *Green Chem.* **2007**, *9*, 441-448. https://doi.org/10.1039/B615785H
39. Martel, J.; Buendia, J. *Swiss Patent* CH. 520,095, 1972; *Chem. Abstr.* **1970**, *73*, 109362.
40. Smith III, A. B.; Dorsey, B. D.; Visnick, M.; Maeda, T.; Malamas, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 3110-3112. https://doi.org/10.1021/ja00271a054
41. Kondo, K.; Suda, M. US Pat. 4,229,593, 1980, October 21.
42. Staudinger, H.; Ruzicka, L. *Helv. Chim. Acta* **1924**, *7*, 177. https://doi.org/10.1002/hlca.19240070124
43. Martel, J.; Huynh, C. US Pat. 3,711,555, 1973.
44. Sobti, R.; Dev, S. *Tetrahedron* **1974**, *30*, 2927-2929. https://doi.org/10.1016/S0040-4020(01)97467-8
45. Pohjala, L.; Alakurtti, S.; Ahola, T.; Yli-Kauhaluoma, J.; Tammela, P. *J. Nat. Prod.* **2009**, *72,* 1917-1926. https://doi.org/10.1021/np9003245
46. He, Z.-T.; Hartwig, J.F. *Nat. Commun.* **2019**, *10*, 4083-4097. https://doi.org/10.1038/s41467-019-12090-z
47. Lukashov, O. I. B; Sokolova, N. A. B.; Golosov, S. N. B; Kuzmina, N. E. B; Kazakov, P. V. B; Mirzabekova, N. S. B *Fluorine Notes* **2013**, *91*, 3-4.

48. Doyle, M. P.; Zhou, Q. L.; Simonsen, S. H.; Lynch, V. *Synlett* **1996**, 697-698. https://doi.org/10.1055/s-1996-5573
49. Lowenthal, R.E. ; Masamune, S. *Tetrahedron Lett.* **1991**, *50*, 7373-7376. https://doi.org/10.1016/0040-4039(91)80110-R
50. Suzukamo, G.; Fukao, M.; Nagase, T.; Toshioka, H. US Pat. 3,943,167 1976, March 9.
51. Crombie, L.; Doherty, C. F.; Pattenden, G. *J. Chem. Soc. (C)* **1970**, 1076-1080. https://doi.org/10.1039/J39700001076
52. De Vos, M.-J. *Ph.D. Thesis, Facultés Universitaires Notre-Dame de la Paix*, Namur, Belgium, 1981.
53. De Vos, M.-J.; Krief, A. *J. Am. Chem. Soc.* **1982**, *104*, 4282-4283. https://doi.org/10.1021/ja00379a055
54. Matsui, M.; Yamada, Y. *Agr. Biol. Chem*., **1963**, 27, 373-378. https://doi.org/10.1080/00021369.1963.10858107
55. Elliott, M.; Farnham, A. W.; Janes, N. F.; Needham, P. H.; Pulman, D. A. *Nature* **1973**, *244*, 456-457. https://doi.org/10.1038/244456a0
56. Elliott, M.; Janes, N.F.; Pulman, D. A.US Pat. 5,004,822, 1991.
57. Elliott, M.; Janes, N.F.; Pulman, D.A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2470-2474. https://doi.org/10.1039/P19740002470
58. Devos, M.-J.; Hevesi, L.; Bayet, P.; Krief, A. *Tetrahedron Lett.* **1976**, 3911-3914 https://doi.org/10.1016/0040-4039(76)80180-3
59. Ueda, K.; Matsui, M. *Tetrahedron* **1971**, *27*, 2771-2774. https://doi.org/10.1016/S0040-4020(01)98067-6
60. Brown, D. G.; Bodenstein, O.F.; Norton, S.J. *J. Agric. Food. Chem.* **1975**, *23*, 115-117. https://doi.org/10.1021/jf60197a031
61. Schneider, M.; Engel, N.; Boensman, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 64-66. https://doi.org/10.1002/anie.198400641
62. Nishizawa, M.; Shimizu, M.; Ohkawa, H.; Kanaoka, M. *Appl. Environ. Microbiol.* **1995**, 3208-3215.
63. Smejkal, J.; Farkas, J. *Coll. Czech. Chem. Commun.* **1963**, *28*, 481-486. https://doi.org/10.1135/cccc19630481
64. Murano, A. *Agric. Biol. Chem.* **1972**, *36*, 917-923. https://doi.org/10.1271/bbb1961.36.917
65. Ueda, K.; Matsui, M. *Agric. Biol. Chem.* **1970**, *34*, 1119-1125. https://doi.org/10.1271/bbb1961.34.1119
66. Martel, J. US Pat. 3,723,469 1973, March, 27.
67. Suzukamo, G.; Nagase, T. US Pat. 4,182,906, 1980 January, 8.
68. Elliott, M.; Janes, N.F.; Pulman, D.A. US Pat. 4,024,163. 1977, May 17.
69. Kanamaru, H.; Kamada, T.; Yoshitake, A. *Radioisotopes* **1986**, *35*, 109-114.
70. Guan, G.G.; Chen, X.; Xinzhuo, Z.Z. Chinese *J. Org. Chem.* **2009**, *29*, 589-594.
71. Staudinger, H.; Ruzicka, L. *Helv. Chim. Acta* **1924**, *7*, 201-211. https://doi.org/10.1002/hlca.19240070125
72. Crombie, L.; Crossley, J.; Mitchard, D. A. *J. Chem. Soc.* **1963**, *27*, 4957-4969. https://doi.org/10.1039/JR9630004957
73. Nagase, T.; Suzukamo, G. US Pat. 3,989,750, 1976 November, 2.
74. Poulter, C.D.; Marsh, L.L.; Hughes, J.M.; Argyle, J.C.; Satterwhite, D.M.; Goodfellow, R.J.; Moesinger, S.G. *J. Am. Chem. Soc.* **1977**, *99*, 3816-3823.

https://doi.org/10.1021/ja00453a050
75. Nesmeyanova, O. A.; Rudashevskaya, T. Y.; Dyachenko, A. I.; Savilova, S. F.; Nefedov, O. M. *Synthesis* **1982**, 296-297. https://doi.org/10.1055/s-1982-29786
76. Székely, I.; Zoltan, S.; Nagy, L.; Bertok, B.; Somfai, E.; Hidasl, G.; Imrei, L.; Lak, I.; Thurner, A. WO1992002482A1, 1992 February, 20.
77. Vilsmeier, A.; Haak, A. *Chem. Ber.* **1927**, *60*, 119-122. https://doi.org/10.1002/cber.19270600118
78. Meth-Cohn, O.; Stanforth, S.P. *The Vilsmeier-Haak reaction* In *Comprehensive Organic Synthesis* Elsevier, **1991**, *Vol 2*, 777-794. https://doi.org/10.1016/B978-0-08-052349-1.00049-4
79. Ash, M.L.; Pews, R.G. *United States of America Patent* US 4,423,222 **1983**, December 27.
80. Suzukamo, G.; Fukao, M. *United States of America Patent* US 4,485,257, **1984**, November 27.
81. Julia, S.; Julia, M.; Linstrumelle, G. *Bull. Soc. Chim. Fr.* **1966**, 3499-3507.
82. Sobti, R.; Dev, S. *Tetrahedron* **1974**, *30*, 2927-2929. https://doi.org/10.1016/S0040-4020(01)97467-8
83. Bailleul, D. *Ph.D. Thesis, Facultés Universitaires Notre-Dame de la Paix*, Namur, Belgium, 2004.
84. Noller, C.R.; Bergsteinsson, I. *Org. Synth.* **1935**, *15*, 3-5. https://doi.org/10.15227/orgsyn.015.0003
85. Hecht, S.M.; Kozarich, J.W. *J. Org. Chem.* **1973**, *38*, 1821-1824. https://doi.org/10.1021/jo00950a011
86. Huisgen, R. *Angew. Chem. Int. Ed.* **1963,** *2*, 633. https://doi.org/10.1002/anie.196306331
87. Krief, A. Gondal, H.G; Kremer A. *Chem. Comm.* **2008**, 4753-4755. https://doi.org/10.1039/B808695H
88. Crombie, L.; Harper, S. H.; Thompson, R. A. *J. Sci. Food Agric.* **1951**, *2*, 421-428. https://doi.org/10.1002/jsfa.2740020909
89. De Vos, M. J.; Denis, J. N.; Krief, A. *Tetrahedron Lett.* **1978**, *19*, 1847-1850. https://doi.org/10.1016/S0040-4039(01)94687-8
90. Goldschmidt, Z.; Crammer, B.; Ikan, R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2697-2705. https://doi.org/10.1039/P19840002697
91. McMurry, J.E. "Ester Cleavages via SN2-Type Dealkylation" *Organic Reactions* **1976**, volume 24. https://doi.org/10.1002/0471264180.or024.02
92. Le Châtelier, H.L. *Compt. Rend.* **1884**, 99, 786.
93. Quilez-Pardo, J. Solaz-Portolés *J. Res. Sci. Teach.* **1995**, *32*, 939-957. https://doi.org/10.1002/tea.3660320906
94. Oesper, R.E. *J. Chem. Ed.* **1931**, *8*, 442-461. https://doi.org/10.1021/ed008p442
95. Elliott, M.; Janes, N. F.; Pulman, D. A.; Soderlund, D. M. *Pestic Sci.* **1978**, *9*, 105-111. https://doi.org/10.1002/ps.2780090203
96. Wood, D.A. US Pat. 4,061,664, 1977, December 6.
97. "Conception de nouveaux insecticides pyrethrinoides à partir de produits naturels" Tessier J. *l'Actualité Chimique* **1986**, 5-14.
98. Sota, K.; Amano, T.; Aida,M.; Hayashi, A.; Tanaka, I. *Agr. Biol. Chem.* **1973**, *37*, 1019-1025.

https://doi.org/10.1271/bbb1961.37.1019
99. Makosza, M. *Pure Appl. Chem.* **2000**, *72*, 1399-1403. https://doi.org/10.1351/pac200072071399
100. Hashimoto, T.; Maruoka, K. *Chem. Rev*. **2007**, *107*, 5656-5682. https://doi.org/10.1021/cr068368n
101. Makosza, M.; Fedorynski, M. *Catalysts* **2020**, *10*, 1436-1442. https://doi.org/10.3390/catal10121436
102. Dehmlow, E. V. *Angew. Chem. Int. Ed.* **1977**, *16*, 493-505. https://doi.org/10.1002/anie.197704933
103. Starks, C.M.; Liotta, C.; Halper, M.E. *Phase-Transfer Catalysis: Fundamentals, applications and industrial perspectives* Springer: Dordrecht, 1994.
104. Roper, J. M. US Pat. 4,800,230, 1989.
105. Breslow R. Organic reaction mechanisms: An introduction W. A. Benjamin, 1966.
106. Martel, J.; Tessier, J. GB Pat. 1,548,474, 1979.
107. Martel, J.; Tessier, J. GB Pat. 1,535,157, 1978.
108. Sukumaran, J.; van Gool, J.; Hanefeld, U. *Enzyme Microb. Technol.* **2005**, 37 254-260.
109. Fischer, E.; Speier, A. *Chem. Ber.* **1985**, 28, 3252-3258. https://doi.org/10.1002/cber.189502803176
110. Hiroshi, S.; Kazunori, I. EP 1 227 077 B1 published 2002 01 24.
111. Hiroshi, S.; Kazunori, I. US Pat. Appl. *2002/0151741 A1* published 2002, October 17
112. Matsui, M.; Yoshioka, H.; Sakamoto, H.; Yamada, Y.; Kitahara, T. *Agric. Biol. Chem.* **1967**, *31*, 33-39. https://doi.org/10.1271/bbb1961.31.33
113. Matsui, M.; Yoshioka, H.; Yamada, Y.; Sakamoto, H.; Kitahara, T. *Agric. Biol. Chem.* **1965**, *29*, 784-786. https://doi.org/10.1271/bbb1961.29.784
114. Yoshioka, H.; Matsui, M.; Yamada, Y.; Sakamoto, H. *Ind. Chim. Belg.* **1967**, *32*, 890-892.
115. Clinton, R.O.; Laskowski, S.C. *J. Amer. Chem. Soc.* **1948**, *78*, 3135-3136. https://doi.org/10.1021/ja01189a501
116. Harper, S. H.; Reed, H. W. B. *J. Sci. Food Agric.* **1951**, *2*, 414-420. https://doi.org/10.1002/jsfa.2740020908
117. Katsuda, Y. US 3,932,470, 1976, January, 13.
118. Katsuda, Y.; Chikamoto, T.; Ogami, H.; Hirobe, H.; Kunishige, T. *Agr. Biol. Chem.* **1969**, *33*, 1361-1362. https://doi.org/10.1080/00021369.1969.10859476
119. Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140-1142. https://doi.org/10.1126/science.290.5494.1140
120. Elliott, M.; Farnham, A.W.; Janes, N.F.; Needham, P.H.; Pulman, D. A. *Nature* **1974**, *248*, 710-711. https://doi.org/10.1038/248710a0
121. Neises B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, 522-524. https://doi.org/10.1002/anie.197805221
122. Wakasugi, K.; Iida, A.; Misaki, T.; Nishii, Y.; Tanabe, Y. *Adv. Synth. Catal.* **2003**, *345*,1209-1214. https://doi.org/10.1002/adsc.200303093
123. Ray, R.; Matteson, S. *Tetrahedron Lett.* **1980**, *21*, 449-450. https://doi.org/10.1016/S0040-4039(00)71429-8
124. Shan, G.; Hammer, R.P.; Ottea, J. A. *J. Agric. Food. Chem.* **1997**, *45*, 4466-4473. https://doi.org/10.1021/jf970408o

125. Atago, T.; Tanaka, A.; Kawamura, T.; Matsuo, N.; Tanabe, Y. *Tetrahedron: Asymm.* **2009**, 20, 1015-1019. https://doi.org/10.1016/j.tetasy.2009.02.060
126. Jaszay, Z.M.; Petnehazy, I.; Tökc, L. *Synthesis* **1989**, 745-747. https://doi.org/10.1055/s-1989-27380
127. LaForge, F. B.; Barthel, W. F. *J. Org. Chem.* **1947**, *12*, 199-202. https://doi.org/10.1021/jo01165a024
128. Chen, Y.L.; Barthel, W.F. *J. Amer. Chem. Soc.* **1953**, *75*, 4287-4289. https://doi.org/10.1021/ja01113a041
129. Staudinger, H.; Ruzicka, L. *Helv. Chim. Acta* **1924**, *7*, 448-458.
130. Berry, D.J.; DiGiovanna, C.V.; Metrick, S.S.; Murugan, R. *Arkivoc*, **2001**, *i*, 201-226. https://doi.org/10.3998/ark.5550190.0002.114
131. Höfle, G., Steglich, W., Vorbrüggen, H. *Angew. Chem. Int. Ed.* **1978**, *17*, 569-583. https://doi.org/10.1002/anie.197805691
132. Hatch, C.E.; Baum, J. S.; Takashima, T. *J. Org. Chem.* **1980**, *45*, 3281-3285. https://doi.org/10.1021/jo01304a028
133. LaForge, F.B.; N. Green, N. Schechter, M.S. *J. Org. Chem.*, **1954**, *19*, 457-462. https://doi.org/10.1021/jo01368a027
134. Nozaki, M.; Okada, K.; Matsui, M. *Agric. Biol. Chem.* **1979**, *43*, 379-381. https://doi.org/10.1271/bbb1961.43.379
135. Coelho, P.; Meinhold, P.; Chen, M.M.Y. US Pat. 9487471B1 **2016** November, 8.
136. Roos, J.; Stelzer, U.; Effenberger, F. *Tetrahedron: Asymmetry* **1998**, *9*, 1043-1049. https://doi.org/10.1016/S0957-4166(98)00047-0
137. Leigh, T. GB Pat. 1 584 245, 1981, February 11.147.
138. Leigh, T. GB Pat. 1 584 246, 1981, February 11.
139. Krief, A; Froidebise, A. *Mini-Reviews in Organic Chemistry* **2005**, 4, 299-312. https://doi.org/10.2174/157019305774322680
140. Krief, A.; Froidebise, A. *Tetrahedron* **2004**, *35*, 7637-7658. https://doi.org/10.1016/j.tet.2004.06.035
141. Krief, A.; Jeanmart, S.; Gondal, U.; Kremer, A. *Helv. Chim. Acta* **2012**, *95*, 2123-2167. https://doi.org/10.1002/hlca.201200393
142. Iwakura, K.; Souda, H.; Takagaki, M.-s.; Yamada, Y. US Pat.Appl. /2002/0052525 A1, 2002, May 2.
143. Iwakura, K. Souda, H. personal communication, 2001.
144. Souda, H., Iwakura, K. US Pat. 6441220 B1 2002 August 27.
145. Iwakura, K.; Souda, H.; Takagaki, M.; Yamada, Y US Pat. Appl. 6706910 B2 2004, March, 16.
146. Makinson, G.K.; Schofield, D. US Pat. 4,116,998. 1978, September 26.
147. Van Cantfort, C.K.; Coates, R.M. *J. Org. Chem.* **1981**, *46,* 4331-4339. https://doi.org/10.1021/jo00335a002
148. Berteau, P.E; Casida, J.E. *J. Agr. Food Chem.* **1969**, *17*, 931-938. https://doi.org/10.1021/jf60165a009
149. Miller, D.C.; Choi, G., J.; Orbe, H.S.; Knowles, R.R. *J. Am. Chem. Soc.* **2015**, *137*, 13492−13495. https://doi.org/10.1021/jacs.5b09671
150. DE. Yang, Z.; Li, P.; He, Y; Luo, J.; Zhou, J.; Wu, Y.; Chen, L. *Chem. Zvesti* **2020**, *74*, 1621-1632. https://doi.org/10.1007/s11696-019-01012-4
151. Yang, Z.; Li, P.; He, Y.; Luo, J.; Zhou, J.; Wu, Y.; Chen, L. *J Heterocyclic Chem.* **2020**; 57, 81-88.

https://doi.org/10.1002/jhet.3750
152. Elmore, N.F.; Roberts, J.E.; Whitman, G.H. *J. Chem. Res. (S)* **1985**, 98-99.
153. Mills, F.D.; Mills, G.D.; Brown, R.T. *J. Agric. Food Chem.* **1989**, *37*, 501-507. https://doi.org/10.1021/jf00086a051
154. Edgewater, J.H.P. US Pat. 4,206,230 1980 June, 3.
155. Fiorito,D.; Folliet, S.; Liu, Y.; Mazet, C. *ACS Catal.* **2018**, *8*, 1392-1398. https://doi.org/10.1021/acscatal.7b04030
156. Rubottom, G. M.; Kim, C. *J. Org. Chem.* **1983**, 48, 1550-1552. https://doi.org/10.1021/jo00157a038
157. Li, H.; Fiorito, D.; Mazet, C. *ACS Catal.* **2017**, *7*, 1554-1562. https://doi.org/10.1021/acscatal.6b03376
158. Jorgenson, M. J. "Preparation of ketones from the reaction of organolithium reagents with carboxylic acids" *Org. React.* (N.Y.) **1970**, *18*, 1. https://doi.org/10.1002/0471264180.or018.01
159. Eastman, R.H.; Freeman, S.K. *J. Am. Chem. Soc.* **1955**, *77*, 6642-6644. https://doi.org/10.1021/ja01629a076
160. Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Amer. Chem. Soc.* **1963**, *85*, 207-222. https://doi.org/10.1021/ja00885a021
161. Szmuszkovicz, J. in "Advances in Organic Chemistry. Methods and Results," Vol. IV, p. 25. Interscience, New York, 1963.
162. Ivanov, A.S *"Meldrum's acid and related compounds in the synthesis of natural products and analogs". Chem. Soc. Rev.* **2008***, 37,* 789-811. https://doi.org/10.1039/B716020H
163. Brooks, D. E.; Lu, L. D.-L.; Masamune, S. *Angew. Chem. Int. Ed.*, **1979**, *18*, 72-74. https://doi.org/10.1002/anie.197900722
164. Bailey, W.J.; Daley, J.J Jr. *J. Org. Chem.* **1964**, 29, 1249-1251. https://doi.org/10.1021/jo01028a503
165. Krapcho A.P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, *13*, 957-960. https://doi.org/10.1016/S0040-4039(00)72461-0
166. McMurry J.E.; Wong, G.B. *Synth. Commun.* **1972**, 2, 389-394. https://doi.org/10.1080/00397917208081785
167. Manchand, P.S. . *Chem. Soc. D* **1971**, 667-667. https://doi.org/10.1039/C29710000667
168. Müller, P.; Siegfried, B. *Tetrahedron Lett.* **1973**, 14, 3565-3568. https://doi.org/10.1016/S0040-4039(01)86971-9
169. Greene, A.E.; Cruz, A.; Crabbé, P. *Tetrahedron Lett.* **1976**, *17,* 2707-2708. https://doi.org/10.1016/S0040-4039(00)77802-6
170. Mills, F. D. *Synth. Commun.* **1986**, *16*, 905-909.
171. Takai, K.; Nawate, K.; Okabayashi, T.; Nakatsuji, H.; Iida, A.; Tanabe, Y. *Tetrahedron* **2009**, *65*, 5596-560. https://doi.org/10.1016/j.tet.2009.02.084
172. Garayalde, D.; Gomez-Bengoa, E.; Huang, X.; Goeke, A.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 4720-4730. https://doi.org/10.1021/ja909013j

173. Dufour, S.; Castets,P.; Pickett, J.A.; Hooper, A.M. *Tetrahedron* **2012**, *68*, 5102-5108. https://doi.org/10.1016/j.tet.2012.04.037
174. Bergmann, J.; Tapia, J.; Bravo, M.; Zaviezo, T.; Flores, M.F. *Nat. Prod. Res.* **2019**, *33*, 303-308. https://doi.org/10.1080/14786419.2018.1446136
175. Inouye, Y.; Ohno, M. *Agr. Chem. Soc. Japan* **1956**, *20*, 25-28. https://doi.org/10.1080/03758397.1956.10857299
176. Galin, F.Z., Rakhimov, R.G., Vyrypaev, E.M.; Bogdanov, M.P.; Amirkhanov, D.V.; Furlei, I.I.; Tolstikov, G.A. *Russ. J. Electrochem.* **2000**, *36***,** 826-835. https://doi.org/10.1007/BF02757439
177. Romano, C.; Mazet, C. *J. Am. Chem. Soc.* **2018**, *140*, 4743-4750. https://doi.org/10.1021/jacs.8b02134
178. Berk, S.C.; Kreutzer, K.A.; Buchwald, S.L. *J. Am. Chem. Soc.* **1991**, *113*, 5093-5095. https://doi.org/10.1021/ja00013a075
179. Berk, S.C.; Buchwald, S.L. *J. Org. Chem.* **1992**, 57, 3751-3753. https://doi.org/10.1021/jo00040a001
180. Reding, M.T.; Buchwald, S.L. *J. Org. Chem.* **1995**, 60, 7884-7890. https://doi.org/10.1021/jo00129a031
181. Breeden, S.W.; Lawrence, N.J. *Synlett* **1994**, 833-835. https://doi.org/10.1055/s-1994-23022
182. Spasyuk, D.; Vicent, C.; Gusev, D.G. *J. Am. Chem. Soc.* **2015**, *137*, 3743-3746. https://doi.org/10.1021/ja512389y
183. Kajiwara, T.; Inouye, Y.; Ohno, M. *Bull. Inst. Chem. Res., Kyoto University,* **1971**, 49, 179-199. http://hdl.handle.net/2433/76364
184. Moore, P.W.; Read, C.D.G.; Bernhardt, P.V.; Williams, C.M. *Eur. J. Chem.* **2018***, 24,* 4556-4561. https://doi.org/10.1002/chem.201800531
185. Attenburrow, J.; Cameron, A.F.B; Chapman, J.H.; Evans, R.M.; Hems, B.A.; Janssen, A.B.A.; Walker, T. *J. Chem. Soc.* **1952,** 1094-1111. https://doi.org/10.1039/JR9520001094
186. Goldman, I. M. *J. Org. Chem.* **1969**, *34*, 1979-1981. https://doi.org/10.1021/jo01258a106
187. Han, X.; Zhang, F.; Meng, Q.; Sun, J. *J. Amer. Ceram. Soc.*, **2010**, 93, 1183-1186. https://doi.org/10.1111/j.1551-2916.2009.03567.x
188. Fetizon, M.; Golfier, M. *Compt. Rend. Serie C* **1968**, *276*, 900-901.
189. Kakis, F.J.; Fetizon, M.; Douchkine, N.; Golfier, M.; Mourgues, P.; Prange, T. *J. Org. Chem.* **1974**, *39*, 523-533. https://doi.org/10.1021/jo00918a024
190. Ferguson, L. M. *J. Chem. Educ.* **1970**, *47,* 46-53. https://doi.org/10.1021/ed047p46
191. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165-185. https://doi.org/10.1055/s-1981-29377
192. Tidwell, T. T. "Oxidation of alcohols to carbonyl compounds via alkoxysulfonium ylides: The Moffatt, Swern, and related oxidations". *Org. React.* **1990**, **39**, 297-572. https://doi.org/10.1002/0471264180.or039.03
193. Tidwell, T. T. *Synthesis* **1990**, 857-870.

https://doi.org/10.1055/s-1990-27036
194. Ley, S. V.; Norman, J.; Griffith, W. P.; Mardsen, S. P. *Synthesis* **1994**, 639-666. https://doi.org/10.1055/s-1994-25538
195. Lybaert, J.; Maes. B.; Abbaspour Therani, K.; De Wael K. *Electrochim. Acta* **2015**, 693-698. https://doi.org/10.1016/j.electacta.2015.09.107
196. Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Chellé-Regnaut, I.; Urch, C. J.; Brown, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 12661-12662. https://doi.org/10.1021/ja973227b
197. Bleloch, A.; Johnson, B. F. G.; Ley, S. V.; Price, A. J.; Shephard, D. S.; Thomas, A. W. *Chem. Commun.* **1999**, 1907-1908. https://doi.org/10.1039/A906354D
198. Karimi, B.; Elhamifar, D.; Yari, O.; Khorasani, M.; Vali, H.; Clark, J. H.; Hunt, A. J. *Chem. Eur. J.* **2012**, 18, 13520-13530. https://doi.org/10.1002/chem.201200380
199. Wiberg, K. B.; Hutton, W. *J. Am. Chem. Soc.* **1956**, *78*, 1640-1645. https://doi.org/10.1021/ja01589a039
200. Meier, H.; Zeller, K.-P. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 32-43. https://doi.org/10.1002/anie.197500321
201. Ye, T.; McKervey, M.A. *Chem. Rev.* **1994**, *94*, 1091-1160.
202. Sasaki, T.; Eguchi, S.; Ohno, M. *Tetrahedron* **1969**, *25*, 2145-2153. https://doi.org/10.1016/S0040-4020(01)82765-4
203. Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297-368. https://doi.org/10.1021/cr00084a001
204. Ghosh, A. K.; Brindisi, M.; Sarkar, A. *ChemMedChem* **2018**, *13*, 2351-2373. https://doi.org/10.1002/cmdc.201800518
205. Wallis, E. S.; Lane, J. F. "The Hofmann Reaction" *Organic Reactions* **1946**, *3*, 267-306. https://doi.org/10.1002/0471264180.or003.07. ISBN 9780471005285
206. Yamamoto, R. *J. Chem. Soc. Japan* **1923**, *44*, 311-330.
207. Matsui, M.; Uchiyama, M. *Agric. Biol. Chem.* **1962**, *26*, 532-534 https://doi.org/10.1080/00021369.1962.10858003
208. Matsui, M.; Yamashita, K.; Miyano, M.; Kitamuka, S.; Suzuki, Y.; Hamuro, M. *Bull. Agr. Chem. Soc. Japan* **1956**, *20*, 89-94. https://doi.org/10.1080/03758397.1956.10857311
209. Sugiyama, T.; Kobayashi, A.; Yamashita, K. *Agric. Biol. Chem.* **1974**, *38*, 979-985. https://doi.org/10.1080/00021369.1974.10861259
210. Hughes, P. *J. Chem. Educ.* **2006**, *83*, 1152-1154. https://doi.org/10.1021/ed083p1152
211. Lewis, D. E. *Bull. Hist. Chem.* **2010**, *35*, 115-124
212. Hofmann, A. W. *Philos. Trans. Royal Soc.* **1851,** *141*, 357-398. https://*doi.org/10.1098/rstl.1851.0017. S2CID 108453887*
213. Torii, S.; Inokuchi, T.; Oi, R. *J. Org. Chem.* **1983**, *48*, 1944-1951. https://doi.org/10.1021/jo00160a002
214. Harper, S. H.; Thompson, R. A. *J. Sci. Food Agric.* **1952**, *3*, 230-234. https://doi.org/10.1002/jsfa.2740030508

215. Matsui, M.; Miyano, M. *Bull. Agr. Chem. Soc.* **1955**, *19*, 159-160. https://doi.org/10.1080/03758397.1955.10857279
216. Lehmkuhl, H.; Mehler, K. *Liebigs Ann. Chem.* **1978**, 1841-1853. https://doi.org/10.1002/jlac.197819781117
217. Sasaki, T.; Eguchi, S.; Ohno, M. *J. Org. Chem.* **1968**, *33*, 676-679. https://doi.org/10.1021/jo01266a043
218. Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045-4048. https://doi.org/10.1021/ja01192a022
219. Honda, T.; Itaya, N., Higo, A.; Horiuchi, F. US Pat. 3,989,654, 1976, November 2.
220. Hassner, A.; Fibiger, R. F. *Synthesis* **1984**, 960-960. https://doi.org/10.1055/s-1984-31037
221. Lu, Z.; Zeng, X.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc.* **2017**, *139*, 18202-18205. https://doi.org/10.1021/jacs.7b12704
222. Xu, B., Lu, Z.; Hammond, G. B. US Pat. Appl. 2019/0176134A 2019, June 13.
223. Lu, Z; Bajwa, B.S.; Okoromoba, E.O.; Hammond, G.B.; Bo Xu, B. *Green Chem.* **2019**,*21*, 2224-2228. https://doi.org/10.1039/C8GC03166E
224. Cantet, C.; Gesson, J.-P.; Renoux, B.; Jouannetaud, M.P. *Tetrahedron Lett.* **2007**, *48*, 5255-5260. https://doi.org/10.1016/j.tetlet.2007.05.137
225. Sasaki, T.; Eguchi, S.; Ohno, M. *J. Org. Chem.* **1970**, *35*, 790-793. https://doi.org/10.1021/jo00828a055
226. Büchi, G.; Inman, C. G.; Lipinski; E. S. *J. Am. Chem. Soc.* **1954**, *76*, 4327-4331. https://doi.org/10.1021/ja01646a024
227. Thompson, M. P.; Agger, J.A.; Wong, L.S. *J. Chem. Educ.* 2015, 92, 1716-1720. https://doi.org/10.1021/acs.jchemed.5b00129
228. Coleman, G. H.; Johnstone, H. F. *Org. Synt.* 1925, 5, 31-32. https://doi.org/10.15227/orgsyn.005.0031
229. Osterberg, A. E.; Kendall, E. C. *J. Am. Chem. Soc.* **1920**, *42*, 2616-2626.
230. Matsui, M.; Uchiyama, M.; Yoshioka, H. *Agric. Biol. Chem.* **1963**, *27*, 549-561. https://doi.org/10.1080/00021369.1963.10858141
231. Borden, W. T.; Hoffmann, R. H.; Stuyver, T.; Chen, B. *J. Am. Chem. Soc.* **2017**, *139*, 9010-9018. https://doi.org/10.1021/jacs.7b04232
232. Krief, A.; Dumont, W.; Bailleul, D. *Synlett* **2005**, 2688-2690. https://doi.org/10.1055/s-2005-917091
233. Chen, Y.; Reymond, J.-L. *Tetrahedron Lett.* **1995**, *36*, 4015-4018. https://doi.org/10.1016/0040-4039(95)00702-E
234. Lane, B. S.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 2933-2934. https://doi.org/10.1021/ja004000a
235. Ito, M.; Kobayashi, C.; Himizu, A.; and Ikariya, T. *J. Am. Chem. Soc.* **2010**, *132*, 11414-11415. https://doi.org/10.1021/ja105048c
236. Lane, B. S.; Vogt, M.; DeRose, V. J.; Burgess, K. *J. Am. Chem. Soc.* **2002**, *124*, 11946-11954. https://doi.org/10.1021/ja025956j
237. Payne, G. B.; Deming, P. H.; Williams, P. H. *J.Org. Chem.* **1961**, *26*, 659-663. https://doi.org/10.1021/jo01062a004
238. Singleton, D. A.; Merrigan, S. R.; Liu, J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 3385-3386.

https://doi.org/10.1021/ja963656u
239. Hagiya, K.; Takano, N; Kurihara, A. US Pat. Appl. 2002/0025906A1, **2002**, February, 28.
240. Schroeder, M. *Chem. Rev.* **1980**, *80*, 187-213. https://doi.org/10.1021/cr60324a003
241. Castillo-Colaux C. *Ph. D. Thesis, Facultés Universitaires Notre-Dame de la Paix,* Namur, Belgium, 2002.
242. Criegee, R.; Marchand, B.; Wannowius, H. *Justus Liebigs Ann. Chem.* **1942**, *550*, 99-133. https://doi.org/10.1002/jlac.19425500106
243. Vanrheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973-1976. https://doi.org/10.1016/S0040-4039(00)78093-2
244. Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968-1970. https://doi.org/10.1021/ja00214a053
245. Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K.B. *Chem. Rev.* **1994**, *94*, 2483-2547. https://doi.org/10.1021/cr00032a009.
246. Sharpless, K. B. Nobel Lecture, **2001**, December 8. https://www.nobelprize.org/uploads/2018/06/sharpless-lecture.pdf
247. Milas, N. A.; Sussman, S. *J. Am. Chem. Soc.* **1936**, *58*, 7, 1302-1304. https://doi.org/10.1021/ja01298a065
248. Krief, A.; Castillo-Colaux C. *Synlett*. **2001**, 501-504. https://doi.org/10.1055/s-2001-12437
249. Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 11038-11053. https://doi.org/10.1021/ja961233m
250. Joergensen, K. A.; Hoffmann, R. *J. Am. Chem. Soc.* **1986**, *108*, 1867-1876. https://doi.org/10.1021/ja00268a026
251. Ferroni, C.; Bassetti, L.; Borzatta, V.; Capparella, E.; Gobbi, C.; Guerrini, A.; Varchi, G. *Pest. Manag. Sci.* **2015**, *71*, 728-736. https://doi.org/10.1002/ps.3842
252. Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem. Int. Ed.* **1985**, 1-30. https://doi.org/10.1002/anie.198500013
253. Wiberg, K. B.; Saegebarth, K. A. *J. Am. Chem. Soc.* **1957**, *79*, 2822-2824. https://doi.org/10.1021/ja01568a042
254. Yamamoto R. *J. Chem. Soc. Japan* **1923**, *44*, 323.
255. Matsui, M.; Yoshioka, H. *Agric. Biol. Chem.* **1964**, 28, 32-37. https://doi.org/10.1271/bbb1961.28.32
256. Matsui, M.; Uchiyama, M.; Yoshioka, H. *Agric. Biol. Chem.* **1963**, *27*, 554-557. https://doi.org/10.1271/bbb1961.27.554
257. Srinivasan, N.S.; Lee, D.G. *Synthesis* **1979**, 520-521. https://doi.org/10.1055/s-1979-28738
258. Jeanmart, S. *Ph.D. Thesis, Facultés Universitaires Notre-Dame de la Paix*, Namur, Belgium, 2004.
259. Moldovan, R.-P.; Teodoro, R.; Gao, Y.; Deuther-Conrad, W.; Kranz, M.; Wang, Y.; Kuwabara, H.; Nakano, M.; Valentine, H.; Fischer, S.; Pomper, M. G.; Wong, D. F.; Dannals, R. F.; Brust, P.; Horti, A.G. *J. Med. Chem.* **2016**, *59*, 7840-7855. https://doi.org/10.1021/acs.jmedchem.6b00554
260. Milewska, M. J.; Gdaniec, M.; Poloński, T. *Tetrahedron: Asym.* **1996**, *7*, 3169-3180.

https://doi.org/10.1016/0957-4166(96)00419-3
261. Coleman, J. E.; Ricciuti, C.; Swern, D. *J. Am. Chem. Soc.* **1956**, *78*, 5342-5345.
262. Lee, D. G.; Chang, V. S. *J. Org. Chem.* **1978**, 43, 1532-1536. https://doi.org/10.1021/jo00402a009
263. Jensen, H. P.; Sharpless, K. B. *J. Org. Chem.* **1974**, *39*, 2314-2314. https://doi.org/10.1021/jo00929a050
264. Sharpless, K. B; Lauer, R. F.; Repic, O.; Teranishi, A. Y.; Williams, D. R. *J. Am. Chem. Soc.* **1971**, *93*, 3303-3304. https://doi.org/10.1021/ja00742a045
265. Starks, C. M. *J. Am. Chem. Soc.* **1971,** *93*, 195-199. https://doi.org/10.1021/ja00730a033
266. Wolfe, S.; Ingold, C. F. Lemieux, R. U. *J. Am. Chem. Soc.* **1981**, *103*, 938-939. https://doi.org/10.1021/ja00394a037
267. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370. https://doi.org/10.1021/ja0214882
268. Lipshutz, B. H.; Ghorai, S.; Leong, W. W. Y; Taft, B. R.; Krogstad, D. V. *J. Org. Chem.* **2011**, *76*, 12, 5061–5073. https://doi.org/10.1021/jo200746y
269. Criegee, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 745-752. https://doi.org/10.1002/anie.197507451
270. Geletneky, C.; Berger, S. *Eur. J. Org. Chem.* **1998,** 1625-1627. https://doi.org/10.1002/(SICI)1099-0690(199808)1998:8<1625::AID-EJOC1625>3.0.CO;2-L
271. Breugst, M.; Reissing, H.-R. *Angew. Chem. Int. Ed.* 2020, 59, 12293-12307. https://doi.org/10.1002/anie.202003115
272. Ornum, S. G.; Champeau, R.M.; Pariza, R. *Chem. Rev.* **2006**, 106, 2990-3001. https://doi.org/10.1021/cr040682z
273. Bailey, P. S. *Chem Rev.* **1958**, *58*, 925-1010. https://doi.org/10.1021/cr50023a005
274. Schönbein, C.F. *Ber. Verh. Nat. Ges. Basel* **1847**, *7*, 4-7.
275. Rubin, M. B. *Bull. Hist. Chem.* **2001**, *26*, 40-56.
276. Rubin, M. B. *Bull. Hist. Chem.* **2002**, *27*, 81-106.
277. Rubin, M. B. *Bull. Hist. Chem.* **2009**, *34*, 39-49.
278. Rubin, M. B *Helv. Chim. Acta* **2003**, **1958**, 930-940. https://doi.org/10.1002/hlca.200390111
279. C. Harries, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 1933-1936. https://doi.org/10.1002/cber.190303602101
280. Bailey, P. S. *J. Org. Chem.* **1957**, *22*, 1548-1551. https://doi.org/10.1021/jo01363a003
281. Knowles, W. S.; Thompson, Q.E. *J. Org. Chem.* **1960**, *25*, 1031-1033. https://doi.org/10.1021/jo01076a044
282. Gupta, D.; Soman, R., Dev. S. *Tetrahedron* **1982**, *38*, 3013-3018. https://doi.org/10.1016/0040-4020(82)80187-7
283. Taylor, W. G. *Synthesis* **1980**, 554-555. https://doi.org/10.1055/s-1980-29118

284. Brown, D. G.; Bodenstein, O. F.; Norton, S. J. *J. Agric. Food. Chem.* **1973**, *21*, 767-769. https://doi.org/10.1021/jf60189a044
285. Pappas, J.J.; Keaveney, W.P.; Gancher, E.; Berger, M. *Tetrahedron, Lett.* **1966**, *7*, 4273-4278. https://doi.org/10.1016/S0040-4039(00)76049-7
286. Fisjer, E. E. US Pat. 2,733,270, 1956.
287. Sousa, J. A.; Bluhm, A. L. *J. Org. Chem.* **1960**, *25*, 108-111. https://doi.org/10.1021/jo01071a031
288. Corey, E. J. Burke, H. J. *J. Am. Chem. Soc.* **1956**, *78*, 174-180. https://doi.org/10.1021/ja01582a050
289. Kulkarni, G. H.; Toke, S. M. *Synth. Commun.* **1989**, *19*, 13-19. https://doi.org/10.1080/00397918908050947
290. Ruzo, L.O.; Kimmel, E.C.; Casida, J.E. *J. Agric. Food Chem.* **1986**, *34*, 937-940. https://doi.org/10.1021/jf00072a002
291. Ruzo, L.O.; Casida, J. E. *J. Agric. Food Chem.* **1982**, *30*, 963-966. https://doi.org/10.1021/jf00113a037
292. Nobis, M. Roberge, D. M. *Chemistry Today* **2011**, 29, 56-58.
293. Armesto, D.; Ortiz, M. J.; Agarrabeitia, A. R. *J. Org. Chem.* **1999**, *64*, 1056-1060. https://doi.org/10.1021/jo981965s
294. Unpublished, Laboratoire de chimie organique, *Facultés Universitaires Notre-Dame de la Paix*, Namur, Belgium, 1980.
295. Nakamura, S.; Watanabe, Y.; Toru, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3403-3404. https://doi.org/10.1039/A908649H
296. Genet, J.- P.; Denis, A.; Charbonnier, F. *Bull. Soc. Chim. Fr.* **1986**, 793.
297. Ortiz de Montellano, P. R.; Dinizo, S. E. *J. Org. Chem.* **1978**, *43*, 4323-4328. https://doi.org/10.1021/jo00416a015
298. Sevrin M. *Master Thesis Facultés Universitaires Notre-Dame de la Paix*, Namur, Belgium, 1980.
299. Farkas, J.; Kourim, P.; Sorm, F. *Coll. Czech. Chem. Commun.* **1959**, *24*, 2230-2236. https://doi.org/10.1135/cccc19592230
300. Bell, J. M.; Kubler, D. G.; Sartwell, P.; Zepp, R.G. *J. Org. Chem.* **1965**, *30*, 4284-4292. https://doi.org/10.1021/jo01023a067
301. Criegee, R. *Chem. Ber*. **1931**, *64*, 260-266. https://doi.org/10.1002/cber.19310640212
302. Malaprade, L. *Bull. Soc. Chim. Fr.* **1934**, 3, 833-852.
303. Zhou, Z.-z.; Liu, M.; Lv, L.; Li, C.-J. *Angew. Chem. Int. Ed.* **2018**, *57*, 2616-2620. https://doi.org/10.1002/anie.201711531
304. Yoshikawa, K. WO 03/059861 A1 2003, July, 24.
305. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936-3938. https://doi.org/10.1021/jo00332a045
306. Yang, D.; Zhang, C. *J. Org. Chem.* **2001**, *66*, 4814-4818. https://doi.org/10.1021/jo010122p
307. Bruckner, R. "Advanced organic chemistry. Reaction Mechanism" Hacourt Science and Technolo-Company: London, 2002.
308. Pappo, R.; Allen, D.S., Jr.; Lemieux, R.U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478-479. https://doi.org/10.1021/jo01110a606

309. Travis, B. R.; Narayan, R. S.; Borhan, B. *J. Am. Chem. Soc.* **2002**, *124*, 3824-3825. https://doi.org/10.1021/ja017295g
310. Natatsuka, I.; Shono, F.; Yoshitake, A. *J. Labelled Compd. Radiopharm.* **1977**, *13*, 561-569. https://doi.org/10.1002/jlcr.2580130414
311. Hagiya, K.; Komoto, I.; Kurihara, A. *European patent* EP 1 120 393 A1 2001, January, 26
312. Brown, M. A.; Holden, I.; Glickman, A. H.; Casida, J. E. *J. Agric. Food. Chem.* **1985**, *33*, 8-13. https://doi.org/10.1021/jf00061a003
313. Seyden-Penne, J. in Reductions by the alumino- and borohydrides in organic synthesis Wiley VCH, 1997.
314. Krief, A.; Hevesi, L. *in Organoselenium Chemistry I*; Springer Verlag: Heidelberg **1988**, p. 115.
315. Fatiadi, A. J.; *Synthesis* **1976**, 65-104. https://doi.org/10.1055/s-1976-23961
316. Guillemonat, A. *Annali di Chimica Applicata* **1939**, *11*, 143-211. https://chemport.cas.org/cgi-bin/sdcgi?APP=ftslink&action=reflink&origin=wiley&version=1%2E0&coi=1%3ACAS%3A528%3ADyaA1MXjt1eqsw%3D%3D&md5=557a5bedbac7cd3afe0220eda04d9661
317. Arigoni, D.; Vasella, A.; Sharpless, K. B.; Jensen, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 7917-7919. https://doi.org/10.1021/ja00804a087
318. Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7154-7155. https://doi.org/10.1021/ja00775a050
319. Umbreit, M.A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526-5528. https://doi.org/10.1021/ja00458a072
320. Sasaki, T.; Eguchi, S.; Ohno, M. *Synthetic Commun.* **1971**, *1*, 75-80. https://doi.org/10.1080/00397917108081619
321. Greer, C. *Acc. Chem. Res.* **2006**, *39*, 797-804. https://doi.org/10.1021/ar050191g
322. Foote, C.S. *Acc. Chem. Res.***1968**, *1*, 104-110. https://doi.org/10.1021/ar50004a002
323. Foote, C.S.; Wexler, S. *J. Am. Chem. Soc.* **1964**, *86*, 3879-3880. https://doi.org/10.1021/ja01072a060
324. Arlt, D.; Jautelat, M.; Lantzsch, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 703-722. https://doi.org/10.1002/anie.198107033
325. Julia, M.; Julia, S.; Bemont, B.; Tchernoff, G. *C. R. Acad. Sci. Ser. II C.* **1959**, *248*, 242.
326. Ficini, J.; d'Angelo, J. *Tetrahedron Lett.* **1976**, *17*, 2441-2444. https://doi.org/10.1016/0040-4039(76)90014-9
327. Krief, A. GB Pat. 2,246,129A, 1992, January, 22.
328. Martel J.; Buendia, J.; Nierat, J. *French Patent* FR 2 507 596 **1981**, June, 16.
329. Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1985**, 650-652. https://doi.org/10.1002/jlac.198519850328
330. Rathke, M. W. "The Reformatsky Reaction" *Organic Reactions* **1975**, 22, 423-460. https://doi.org/10.1002/0471264180.or022.04. ISBN 0471264180
331. Rathke, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3222-3223. https://doi.org/10.1021/ja00713a071
332. Sun, X.; Kenkre, S. L.; Remenar, J. F.; Gilchrist, J. H.; Collumn, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 4765-4766. https://doi.org/10.1021/ja970406k

333. Warner, P.M.; Le, D. *J. Org. Chem.* **1982**, 47, 893-895. https://doi.org/10.1021/jo00344a030
334. Yoshioka, H.; Matsui, M.; Yamada, Y.; Sakamoto, H. *Ind. Chim. Belg.* **1967**, *32*, 890.
335. Matsui, M.; Yoshioka, H. *French Patent* FR 1,396,649, 1965.
336. Gopichand, Y.; Khanra, A. S.; Mitra, R. B.; Chakravarti, K. K. *Ind. J. Chem.* **1975**, *13*, 433.
337. Julia, M. *French Patent* FR 1,203,902, **1960**.
338. Suzukamo, G. *J. Synth. Org. Chem. Japan* **1982**, *40*, 930-938. https://doi.org/10.5059/yukigoseikyokaishi.40.930
339. Crombie, L. *Pestic Sci.* **1980**, *11*, 102-118. https://doi.org/10.1002/ps.2780110203
340. Pattenden, G.; Storer, R. *J. Labelled Compd. Radiopharm.* **1976**, *12*, 551-556. https://doi.org/10.1002/jlcr.2580120411
341. Froidebise, A. *Ph. D. Thesis Facultés Universitaires Notre-Dame de la Paix* 2002.
342. Nagase, T.; Suzukamo, G.; Fukao, M. *United State of America Patent* US 3,928,485 **1975**, December, 23.
343. Nagase, T.; Suzukamo, G.; Fukao, M.; Nishio, K. *United State of America Patent* US 3,808,152 **1974**, April, 30.
344. *IUPAC Compendium of Chemical Terminology, 2nd ed. (the "Gold Book").* Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997). Online version (2019-) created by S. J. Chalk. ISBN 0-9678550-9-8. https://doi.org/10.1351/goldbook
345. Pozharskii, A.F.; Ozeryanskii, V.A. *Mendeleev Communications* **2012**, *22*, 117-124. https://doi.org/*10.1016/j.mencom.2012.05.001*
346. Caubère, P. *Chem. Rev.* **1993**, *93*, 2317-2334. https://doi.org/10.1021/cr00022a012
347. Schlosser, M. *Pure&Appl. Chem.* **1988**, *60*, 1627-1634. http://dx.doi.org/10.1351/pac198860111627
348. Suzukamo, G.; Fukao, M.; Hagiya, K.; Sakito, Y. *Sumitomo Kagaku* **1989**, 35-42.
349. Ueda, K.; Matsui, M. *Agric. Biol. Chem.* **1970**, *34*, 1115-1118. https://doi.org/10.1271/bbb1961.34.1115
350. Ohloff, G. *Tetrahedron Lett.* **1965**, *6*, 3795-3800. https://doi.org/10.1016/S0040-4039(01)99566-8
351. Suzukamo, G.; Fukao, M.; Tamura, M. *Tetrahedron Lett.* **1984**, *25*, 1595-1598. https://doi.org/10.1016/S0040-4039(01)90020-6
352. Otieno, D.A.; Pattenden, G.; Popplestone, C.R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 196-201. https://doi.org/10.1039/P19770000196
353. Sasaki, T.; Eguchi, S.; Ohno, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1469-1470. https://doi.org/10.1246/bcsj.53.1469
354. Suzukamo, G.; Fukao, M. US Pat. 4,473,703, 1984, September 25.
355. Suzukamo, G.; Fukao, M. *European Patent* EP 0 062 979 A1 1982, March 22.
356. Suzukamo, G.; Fukao, M.; Nagase, T. *Chem. Lett.* **1984**, *13*, 1799-1802. https://doi.org/10.1246/cl.1984.1799
357. Sakito, Y.; Suzukamo, G. *Chem. Lett.* **1986**, 621-625. https://doi.org/10.1246/cl.1986.621
358. Montgomery, R. E.; Smeltz, L. PTC WO 98/16487, 1998, April 23

359. Williams, J. L.; Rettig, M. F. *Tetrahedron Lett.* **1981**, *22*, 385-388. https://doi.org/10.1016/0040-4039(81)80106-2
360. Parra-Hake, M.; Rettig, M. F., Wing, R.M. *Organometallics* **1986**, *5*, 1032-1040. https://doi.org/10.1021/om00136a034
361. Suzukamo, G.; Sakito, Y.; Shiga, F.M.; Fukao, M.; Hagiya, K. US Pat. 4,788,323, 1988, November.
362. Suzukamo, G.; Fukao, M. US Pat. 4,644,080, 1987, February 17.
363. Suzukamo, G.; Fukao, M. *European Patent* EP 0 235 940 B1 1990, June 25.
364. Suzukamo, G.; Fukao, M. *European Patent* EP 0 165070 B1 1990, June 13.
365. Suzukamo, G.; Sakito, Y.; Fukao, M.; Hagiya, K. *European Patent* EP 0 299 760 A1 1988, July 14.
366. Suzukamo, G.; Sakito, Y.; Fukao, M.; Hagiya, K. US Pat. 4.898.655, 1990, February 6.
367. Dénès, F.; Pichowicz, M.; Povie, G.; Renaud, P. *Chem. Rev.* **2014**, *114*, 2587-2693. https://doi.org/10.1021/cr400441m
368. Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.*, **1915**, *107*, 1080-1106. https://doi.org/10.1039/CT9150701080

Author's Biography

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.