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Inspired by flowers: Synthetic routes to scalemic deltamethrinic acid

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Honouring Professor Alan Katritzky at the occasion of his 80th birthday

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ABSTRACT

This review reports different syntheses of deltamethrinic acid, especially those originating from our laboratory.

Deltamethrinic acid is a synthetic compound whose structure is inspired from those present in the flower head of the plant *Chrysanthemum cinerariifolium*. Its ester 'deltamethrin' exhibits an extremely high insecticidal activity (DDTx35.000) and an extremely low toxicity to mammals.

1. Introduction

1.1. Flowers and human interactions

Two main threats have challenged human civilization, the fear of hunger and the fear of illness. Man has used plant for these purposes very early and evidence of use of herbal remedies goes back to at least 60,000 years in Iraq.[1] Flowers, the reproductive structure of a plant,[2] do not derogate to such statement. Some are used as a source of food (broccoli, cauliflower and artichoke), spices (saffron, carper and clove) and are valuable ingredients in some beverages (hops flowers to give flavor to beer). Furthermore, opium poppy 'more than other medicinal species, has been used and misused from the early days of history'[3] and has been source a of inspiration for pain relieving medicines.[4]

Flowers occupy a place of choice in human civilization. They have long been admired and used by humans, for their beauty as well as in many cases for their fragrances (rose, violet and lavender). They have also been used for a wide range of events and functions that, cumulatively, encompass one's lifetime[2] such as at the occasion of new births, weddings and funerals; as tokens of love or esteem; as a gift of remembrance. Finally, floral emblems have been used in many countries (France: Lily flower; Italy: Cyclamen; Romania: rose).[5]

Chrysanthemums, perennial flowering plants in the family Asteraceae cumulate several of the above mentioned properties. They come in a wide variety of colors and flower forms, can grow to be 2–3 feet high. Chrysanthemum flowers possess great economical value. They are favorites of florists for arrangements, due to the longevity of their blooms and are widely used for decorating gardens and houses and even cemeteries on the occasion of All Saints' day because they bloom in fall. Chrysanthemum flowers used as greens, steamed or boiled are used in Chinese cuisine. They are also boiled to make 'chrysanthemum tea' which has many medicinal uses.

Chrysanthemum flowers have inspired several poets and painters such as Tao Qian,[6] Pierre Auguste Renoir[7] and Charles Monet.[7] White flowers are symbolic of: (i) death in Croatia, France, Japan, Korea, Poland, (ii) lamentation in China. A yellow chrysanthemum flower stylized as a central disc surrounded by a front set of 16 petals is used as an imperial seal in Japan[8] and the 'Supreme Order of the Chrysanthemum' is Japan's highest order. Finally some chrysanthemum or pyrethrum species such as *Chrysanthemum roseum* Adam, *C. coronarium* Linn from Persia and above all *Chrysanthemum cinerariifolium* which originates from the region of the Balkans possess insecticidal properties. These are known from antiquity since several dead insects were lying in the fields where such plants were growing. Insecticidal preparations date back to Persia, about 400 B.C.[9] White daisies have been cultivated from 1840 to 1918 in Dalmatia and thanks to the suitable climate *C. cinerariifolium* were

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also grown in Kenya, Rwanda, Tanzania, Papua New Guinea, Tasmania and Ecuador (Fig. 1).

1.2. Insecticide properties of pyrethrinoids from *C. cinerariifolium*

The ground yellow flower head which contains the active principle was introduced as 'Pyrethrum Powder' into the US (1860) and Japan (1885) and in 1919 kerosine extracts of pyrethrum started to replace the powder in home use. In 1919 the United States reached imports of up to 1000 tons per year whereas Japanese pyrethrum production reached a peak of 13,000 tons per year in 1938 (70% of the world's production at that time) and declined to only 1000 tons in 1965 at the time synthetic pyrethoids entered the market.

The active principle was isolated in 1909 by Fujitani[10] and the structure of its major and more active constituents, Pyrethrin I **1a** (Fig. 2), was determined by Staudinger and Rucizka.[11] Pyrethrin I is a scalemic ester of (1*R*)-*trans*-chrysanthemic acid (1*R*)-**2a** which possesses a vinyl cyclopropane carboxylic acid skeleton (Fig. 2). Pyrethrin I proved to be very attractive (i) thanks to the small doses needed to kill insects especially in the presence of piperonyl butoxide, a potent cytochrome P450 inhibitor (ii) its important knock-down effect which almost instantaneously paralyzes the insects, which avoids female insects to lay their eggs in fruits (iii) its insect repellent effect towards insect especially mosquitoes when used in less than fatal doses (iv) its very low toxicity to mammals compared to insects (Relative LD_{50}: 2 10^9 insects/albino female rats[12] and (v) its non persistence in the environment because it breaks down easily in the atmosphere on exposure to light and moisture. The latter features are particularly valuable for indoor use of pyrethrum extract and Pyrethrin I for domestic purposes but prevent their comparatively huge use outdoors in agriculture.

Figure 1. Picture of the flower head of *Chrysanthemum cinerariifolium* in which the insecticidal activity is concentrated.

1.3. Engenering pyrethrinoids insecticides to produce more active compounds: discovery of pyrethroids

Increased stability was required to avoid, in the field, very frequent spraying and that was achieved since the discovery by the scientists of NRDC[12] of synthetic pyrethroids such as cypermethrin **1b** or deltamethrin **1c** (Fig. 2). 1000 tons of these compounds are sprayed annually over 150 millions hectares (i.e., three times the area of France).

For both pyrethrin I **1a** and deltamethrin **1c,** the most active isomer is the one shown in Figure 2. Deltamethrin **1c** is sold as a scalemic compound and although cypermethrin **1b** is sold as a diastereoisomeric mixture, the most active compound has the same stereochemistry as the one disclosed for deltamethrin. Several reviews in journals and books have been published on pyrethroids, pyrethric acids and pyrethroic acids.[12a,13a–m]

We have been active in this field for the past thirty years and we have describe new synthetic routes to vinyl cyclopropane carboxylic acids **2**–**4** and related methyl-, ethyl- or *tert*-butyl esters which are precursors of the most active pyrethroids. In this presentation, we will concentrate on our own syntheses of the *cis*-stereoisomers and the strategy used, in the general context. In a brief introduction we will present the salient synthesis of deltamethrinic acids in the general context of synthesis of pyrethric acids (derived from natural products) and pyrethroic acids (synthetic analogues of the formers).

1.4. Mechanism of action

Deltamethrin acts toward insects by ingestion or simply by contact since is extremely lipophilic and easily penetrates their cuticles.[13d] Its typical effects are: hyperexcitation, loss of coordination, tremors, convulsions, tetanic spasms, knock-down effect, dehydration and finally death. Deltamethrin alters normal neuronal function by inhibiting ion movements across the nerve cell membrane. It is known to (i) modify the sodium channel in such a way as to prolong the tail current associated with step repolarization following a depolarizing pulse and (ii) alter in intracellular calcium ion concentrations and possibly by binding to GABA receptors.[13d]

In fact the primary target site is the voltage gated sodium channels associated with the membranes of nerve cells. Deltamethrin rapidly penetrates into the nerve fibers probably through a pre-

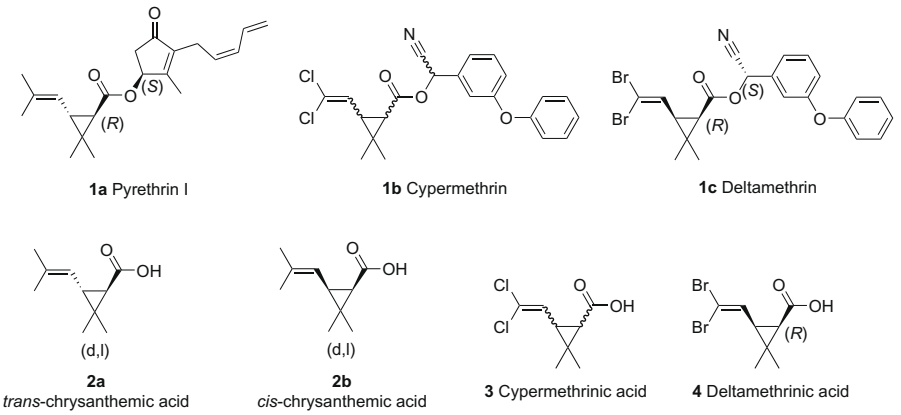


Figure 2. Structures of the most active pyrethrins and pyrethroids and the related pyrethric- and pyrethroic acids.

interaction with a specific receptor which has not yet been identified. It opens up, as other pyrethroids do, presynaptic sodium channels interfering with the transport between sodium and potassium cations, thereby disrupting the entire nervous system. Such process also takes place with DDT and therefore deltamethrin can be classified as biodegradable DDT.

Significant differences have been found to be associated with the absolute stereochemistry on the cyclopropane ring.[13j] Interestingly, the minimum effective concentration on membrane potential is ten time less for the (1*R*)-stereoisomers of deltamethrin than for the corresponding (1*S*)-stereoisomers regardless of the *cis* or *trans*-stereochemistry. The higher activity of the *cis*-isomer of deltamethrin is probably due to its lower propensity of its ester functional group to be hydrolyzed may be for steric reasons.

Interestingly, there is some discrimination between useful insects, such as bees, and harmful ones. Both are killed when deltamethrin is sprayed on them. However, although residual contact toxicity exists for both series of insects, it leads to death of the harmful ones whereas bees can recover from the initial knockdown effect. Therefore bees can stay alive if the deltamethrin is sprayed on the fields in the late afternoon (after five pm) at a time they are in the hive.

Lower toxicity of deltamethrin, as well as pyrethroids in general, to mammals is due largely to its rapid metabolism by nonspecific carboxyl esterases.

2. Description of syntheses of chrysanthemic acids and related compounds

2.1. Selected synthetic methods and strategies for chrysanthemic acid 2 and deltamethrinic acid 4 formation

2.1.1. Historical methods and interconversions

The first synthesis of chrysanthemic acid **2** (racemic mixture of *cis*- and *trans*-isomers, 8% yield) was achieved by Staudinger using ethyl diazoacetate, excess of 2,5-dimethyl-2,4-hexadiene and copper bronze catalyst.[14a] Enormous progress has been made since: in 1945 the same mixture was obtained in 64% overall yield and separation of the 'natural' enantiomer achieved (Scheme 1, entry a).[14b] The same approach is presently used by the Sumitomo Company to produce ton scale of racemic mixture of *cis*- and *trans*-chrysanthemic acids **2**. Slight modifications of this process which instead use a chiraly liganded copper catalyst and menthyl diazoacetate has been published by the same company and allows the synthesis at room temperature (1*R*)-*trans*-chrysanthemic acid **(1*R*)-2a** in high yield (72%) with reasonably high diastereocontrol (de 84%) and high enantioselectivity (94%).[14c,d]

Another industrial synthesis of racemic *trans*-chrysanthemic acid **2a** uses a quite different approach involving ethyl 3-methyl-2-butenoate, 3-methyl-2-butenylsulfone and ethyl Grignard reagent as starting materials[13d,e,l] (Scheme 1, entry b). Alternatively we have synthesized the same ethyl ester of $\mathbf{2a_{Et}}$ from ethyl γ-oxobutenoate and isopropylidene triphenylphosphorane (Scheme 1 entry c).[15]

The strategies disclosed in Scheme 1 imply the cyclopropanation of compounds possessing a C,C double bond in each of all the possible ways.

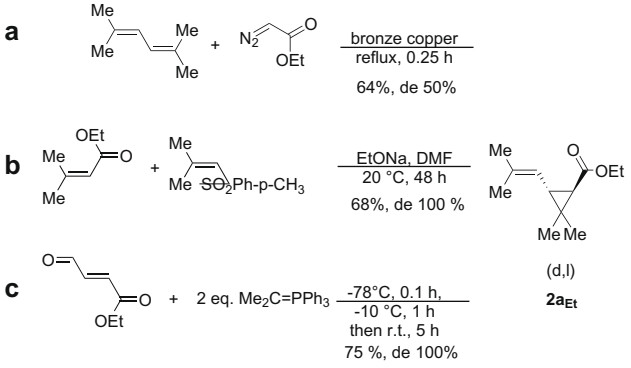
The synthesis of the desired (1*R*)-*trans*-chrysanthemic acid **(1*R*)-2a** has been successfully achieved after separation of the *cis*/*trans* diastereoisomeric mixtures in the first case (Scheme 1, entry a) followed by resolution of the *trans*-racemic **2a** mixture using 1-phenylethylamine,[14b] L-(*S*)-1-phenyl-2(*p*-tolyl)ethylamine[16] or even more conveniently the **d**-*threo* base derived from chloramphenicol ((1*R*,2*R*)-1-(4-nitro-phenyl)-2-dimethylaminopropane diol).[13d,f] The latter conditions have been used by the Roussel–Uclaf company on an industrial scale.[13d,e,17] The useless (1*S*)-*trans*-chrysanthemic acid (1*S*)-**2a** has been transformed by the same company, as described in Scheme 2, sequentially to (1*R*)-*cis*-chrysanthemic acid (1*R*)-**2b** then to deltamethrinic acid **4**.

The key step of this process is the contra-thermodynamic isomerization of (1*S*)-*trans*-chrysanthemic acid (1*S*)-**2a** to (1*R*)-*cis*-chrysanthemic acid (1*R*)-**2b**.[13d,e,17] It takes advantage of a base promoted epimerization at C-1 of the δ-hydroxy-ester **5** and subsequent lactonization which fixes the *cis*-stereochemistry there by leading to the γ-lactone **6** one of the isomers of **2**. Lewis acid catalyzed lactone ring opening of **6** to (1*R*)-**2b** followed by reductive ozonolysis, removes the isopropylidene moiety and produces the corresponding hemicaronic acid $\mathbf{7}_{cis}$ or its 5-membered ring lactol **8**.[13d,e] Modified Wittig reaction using carbon tetrabromide and triphenylphosphine allows the introduction of the dibromomethylene moiety leading to deltamethrinic acid **4**.[13d,e]

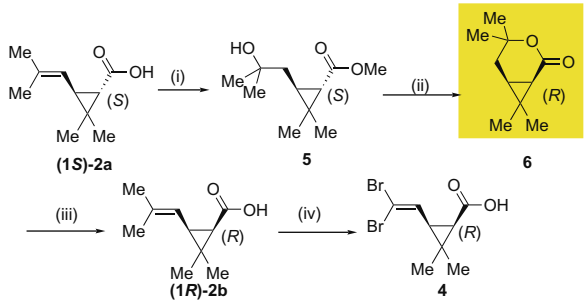
Alternatively (1*R*)-*trans*-chrysanthemic acid (1*R*)-**2a** has been transformed to deltamethrinic acid **4** by another sequence of reactions which use the same strategy but with a different sequence of events (Scheme 3).[13d,e,17] It requires formal epimerization at C-3 of chrysanthemic acid (1*R*)-**2a**. Reductive ozonolysis leads to the hemicaronic acid $\mathbf{7}_{trans}$ which is epimerized α- to the formyl group on reaction with base to produce $\mathbf{7}_{cis}$. The latter is then cyclized to the bicyclic five membered lactol **8** precursor of deltamethrinic acid **4**.

We have described a related strategy, disclosed in Scheme 4, which allows the synthesis of deltamethrinic acid **4** from methyl (*d,l*)-*cis*-caronic acid monomethyl ester **13**.[18] The key steps of this approach are:

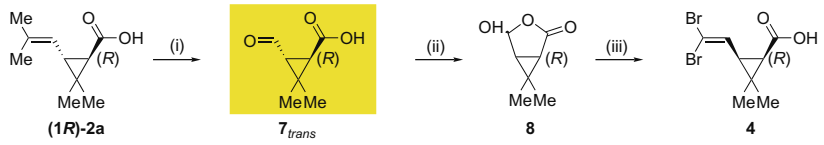
(i) Highly connective route to *trans*-diethyl caronate **10** available from diethylfumarate **9** or maleate and isopropylidene triphenylphosphorane[19] or from diethyl fumarate and isopropylidene diphenylsulfurane,[20] leading after some functional group manipulations to (*d,l*)-*cis*-caronic acid monomethyl ester **13**.



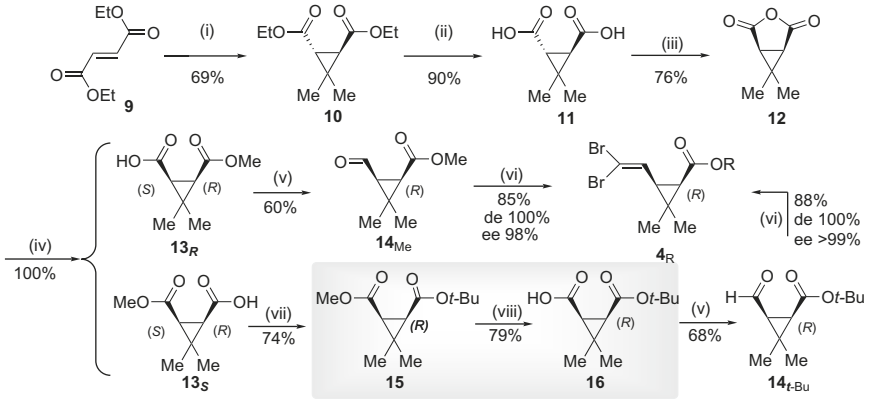
Scheme 1.



Scheme 2. Reagents and conditions: (i) (a) H_3O^+ (b) CH_2N_2; (ii) *t*-BuOK; (iii) $MgBr_2$, pyr., 125 °C, 14 h; (iv) (a) O_3, MeOH, −80 °C (b) Me_2S, −40 °C to 20 °C (c) aq AcOH, 80 °C, 0.25 h (d) CBr_4, PPh_3.



Scheme 3. Reagents and conditions: (i) (a) $SOCl_2$, pentane, 20 °C (b) MeOH, pyr. pentane, 20 °C, 48 h (c) O_3, −80 °C (d) Me_2S, −40 °C to 20 °C (e) AcOH; (ii) (a) MeONa, MeOH, 3 h (b) aq HCl (c) H_2O–dioxane, 2 h (iii) CBr_4, PPh_3, CH_2Cl_2.



Scheme 4. Reagents and conditions: (i) $2Me_2C{=}PPh_3$, THF, 20 °C, 2 h; (ii) KOH, EtOH, reflux, 20 h; (iii) Ac_2O, 220 °C, 6 h, sealed tube or Ac_2O, AcONa, distillation, 110 °C; (iv) (a) MeONa, MeOH, 0 °C, 0.1 h (b) H_3O^+ (c) (+)-(α)-methylbenzylamine, $Me_2C{=}O$ (0.23 M), 20 °C, 24 h, selective precipitation (d) K_2CO_3, 20 °C, 1 h (e) HCl, 1.01 equiv; 13*R*: 25% yield ee 98%; 13*S*: 25% yield ee 98%; (v) (a) BH_3–THF, THF, 20 °C, 3 h (b) CrO_3, pyr., HCl, CH_2Cl_2, 20 °C, 3 h (vi) CBr_4, PPh_3, CH_2Cl_2, 25 °C, 0.15 h; (vii) isobutene, trace of H_2SO_4, CH_2Cl_2, 20 °C; (viii) (a) K_2CO_3, MeOH–H_2O, 70 °C, 15 h (b) H_3O^+.

(ii) Efficient resolution of the latter using (+)-(α)-methylbenzylamine.[18]

(iii) Easy access in high de and ee, using almost the same strategy, to deltamethrinic acid **4** from each of the two enantiomers $\mathbf{13}_{\boldsymbol{R}}$ and $\mathbf{13}_{\boldsymbol{S}}$ of *cis*-caronic acid monomethyl ester.[18]

(iv) Original transformation of $\mathbf{13}_{\boldsymbol{S}}$ to its pseudo-enantiomer **16** taking advantage of the 'formal interchange' of the carboxyl and the alkyl carboxylate on the cyclopropane ring.[18]

(v) Chemoselective reduction of carboxyl group of **13** to the formyl group present on $\mathbf{14}_{\mathbf{Me}}$ or $\mathbf{14}_{\boldsymbol{t}\textbf{-Bu}}$ using a two steps process involving first borane–THF complex[18] which produces the carbinol which is then oxidized to the formyl group using chromium trioxide based reagents.[18]

Alternatively $\mathbf{13}_{\boldsymbol{S}}$ has been transformed to **4** by selective reduction of the methyl carboxylate, in the presence of the carboxyl group, using lithium borohydride[21] instead of borane–THF complex.[18]

An even simpler approach involves enantioselective ring opening of caronic anhydride **12** using achiral alcohols such as isopropanol and scalemic catalysts such as Ti-TADDOLates ((i)Ti(O*i*-Prop)$_4$, β-naphthyl-Taddol, THF, −30 °C, 120 h, ee 90%, Scheme 5, entry a)[22a] or more conveniently from methanol and quinidine (quinidine, MeOH, toluene–CCl_4, −55 °C, 60 h, ee 96%, Scheme 5, entry b).[22b] Other methods implying scalemic alcohols (Scheme 5, entries c–e) proved to be poorly selective.[22c]

		R	ee
a	Ti(O*i*-Pr)$_4$, β-naphthyl-Taddol, THF, -30 °C, 120 h	*i*-Pr	90%
b	Quinidine, MeOH, toluene-CCl_4, -55 °C, 60 h	Me	96%
c	Menthol, pyr., benzene, reflux, 16 h	Menthyl	5%
d	Li-menthylate, THF, -78 °C to 20 °C, 16 h	Menthyl	24%
e	Li-menthylate, THF-HMPA, -78 °C, 0.2 h, 20 °C, 0.5 h	Menthyl	19%

Scheme 5.

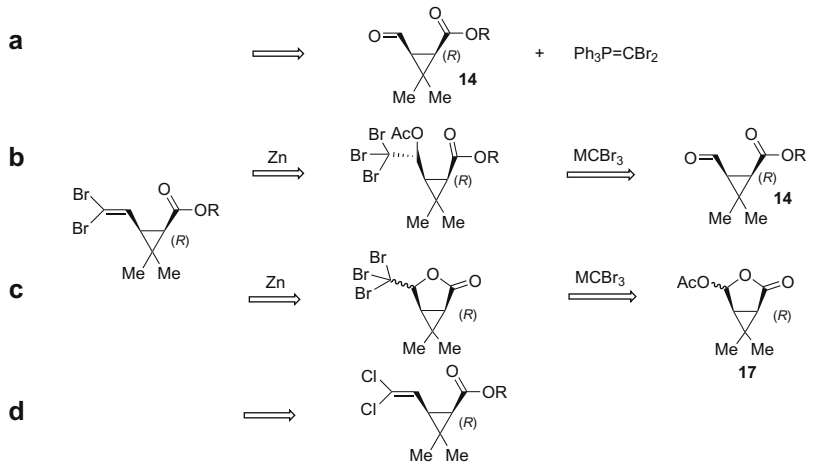
The synthesis of deltamethrinic acid **4** usually implies the formation, at the last stage of the synthesis, of the dibromovinyl moiety.

This has been achieved from (i) (1*R*)-*cis*-hemicaronic acid $\mathbf{7}_{\boldsymbol{cis}}$, or biocartol **8**, its cyclic isomer or related species such as its acetate **17**[13e,f,23a] or from alkyl (1*R*)-*cis*-hemicaronates such as **14** by introducing a carbon unit bearing at least two bromine atoms (Scheme 6, entries a–c) or (ii) *cis*-dichlorovinyl chrysanthemic acid by performing the Cl/Br exchange atoms (Scheme 6, entry d).[24]

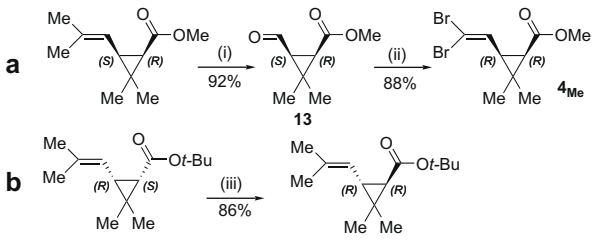
The reaction has been conveniently achieved from (1*R*)-*cis*-hemicaronic acid $\mathbf{7}_{\boldsymbol{cis}}$ or from alkyl (1*R*)-*cis*-hemicaronates such as **14** (Scheme 7, entry a) and the in situ generated dibromomethylene triphenyl phosphorane as outlined above (Scheme 6, entry a).[13e,f,23] This approach however is inappropriate for large scale operations due to the concomitant formation of stoichiometric amounts of triphenyl phosphine oxide. The three steps sequence shown in Scheme 6 (entries b and c) is however preferred. It involves (i) the reaction of metallo-tribromomethane which leads to the corresponding compounds bearing the β-hydroxy-tribromoalkyl moiety. The latter upon sequential esterification of the hydroxyl group and zinc promoted β-elimination reaction, leads to the formation of the dibromovinyl group (Scheme 6, entries b, c).[13e,f,23]

Accordingly we have found that *cis*-chrysanthemic **2b** is a better strategic target than its *trans*-stereoisomer **2a** to produce either deltamethrinic acid **4** or (1*R*)-*trans*-chrysanthemic acid (1*R*)-**2a** (Scheme 7). As a racemic mixture it can be resolved similarly to its *trans*-stereoisomer **2a** using (*l*)-quinine,[25a] 1-phenylethylamine[25] as well as *l*-*N*-methyl ephedrine.[25c]

- (1*R*)-*cis*-chrysanthemic acid (1*R*)-**2b** can be transformed to deltamethrinic acid **4** by sequential ozonolysis[14b,17,26] and Wittig reaction sequence (Scheme 7, entry a),
- (1*S*)-*cis*-chrysanthemic acid (1*S*)-**2b** can be transformed to (1*R*)-*trans*-chrysanthemic acid (1*R*)-**2a** by epimerization of the corresponding *t*-butyl ester using potassium *t*-butoxide in THF as the base (20 °C, 2 h, 86%, Scheme 7, entry b).[13m,27] The better *trans*/



Scheme 6.



Scheme 7. Reagents and conditions: (i) O_3, MeOH, −80 °C (b) Me_2S, −40 °C to 20 °C (c) aq AcOH, 80 °C, 0.25 h; (ii) CBr_4, PPh_3, CH_2Cl_2, 25 °C, 0.15 h (iii) *t*-BuOK, THF, 20 °C, 2 h.

cis ratio obtained from *t*-butyl- compared to related methyl- or ethyl esters[26] is probably due to the fact that the two groups on the adjacent carbon on the cyclopropane ring are large enough to favor the *trans*-stereochemistry under thermodynamic control.[13m,27] For example the *cis*/*trans*-isomerization of the methyl ester using sodium methoxide (130 °C, 99%) provides at best (1*R*)-*trans*-chrysanthemic acid **(1*R*)-2a** possessing only a 82.4% de.[28]

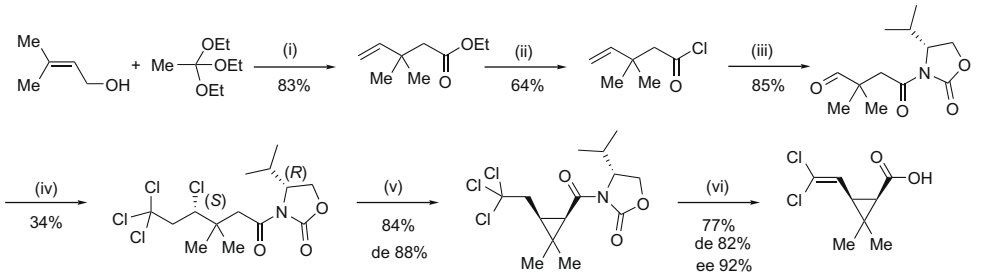
2.1.2. Deltamethrinic acid syntheses by cyclization of precursors containing its complete carbon skeleton

2.1.2.1. Using Sagami process. There are only very few cases where the cyclopropane ring is produced from a compound which already possesses the complete carbon skeleton of deltamethrinic acid. For example, to our knowledge, the method related to the 'Sagami process' which has been successfully applied to the synthesis of (1*R*)-*cis*-dichlorovinyl chrysanthemic acid (scalemic cypermethrinic acid),[29] has not been used for the synthesis of deltamethrinic acid (Scheme 8).

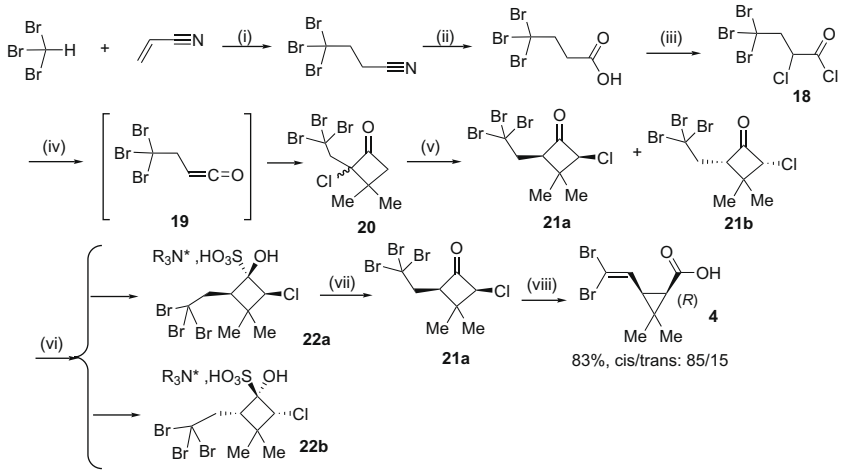
2.1.2.2. Using ketenes for the synthesis of cyclobutanone and Favorskii rearrangement to produce deltamethrinic acid. Nevertheless such type of approach has been effectively achieved in a process which is disclosed in Scheme 9.[30a] It allows the synthesis of deltamethrinic acid **4** by forming the cyclopropane ring from a compound which already possesses the complete carbon framework taking advantage of the Favorskii rearrangement of the scalemic chlorocyclobutanone **21a** which occurs with quite good diastereocontrol (de 70%). Nevertheless as described for the synthesis disclosed in Scheme 9, this process suffers from the quite tedious separation of the racemate **21a** + **21b**.

The chlorocyclobutanones **21a** and **21b** result from the elegant and highly diastereoselective 'cine rearrangement'[31] of the α-chlorocyclobutanone **20** which is formed as a racemic mixture on cycloaddition between the ketene intermediate **19** and isobutylene (Scheme 9). It is interesting to notice that the same process has been used to synthesize scalemic cypermethrinic acid[30] from the tetrachloro derivative analogous to **22a**. In the latter case the author recycled the enantiomer analogous to **22b** by a process which allows its racemization and resolution of the resulting mixture. This process has not been published in case of deltamethrinic acid synthesis.

2.1.2.3. Syntheses of deltamethrinic acid involving hemicaronaldehyde. 2.1.2.3.1. Strategies. So in most of the cases (1*R*)-hemicaronaldehyde **A** or related cyclic isomers **C** have been used, as outlined above, as starting materials for the synthesis of deltamethrinic acid **4**.

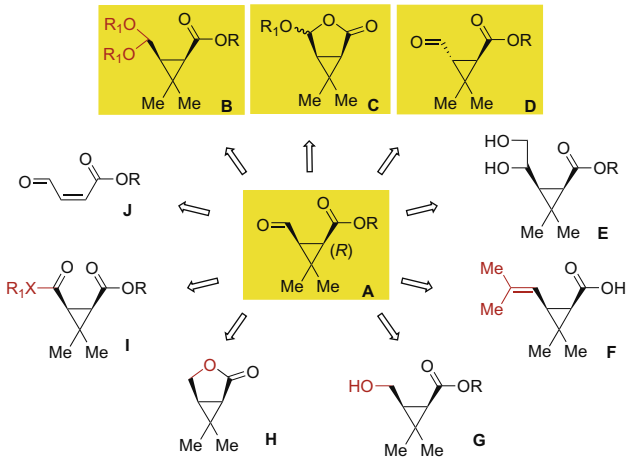


Scheme 8. Reagents and conditions: (i) (a) Propionic acid, 130 °C, 11 h (b) H_2SO_4, H_2O, 0 °C, 17 h; (ii) (a) NaOH, EtOH–H_2O, 5 °C, 1 h then 20 °C, 4 h (b) H_3O^+ (c) $SOCl_2$, DMF, benzene, reflux, 2.5 h; (iii) (*R*)-(−)-4-(1-ethylmethyl)-2-oxazolidinone, NaH, THF, 20 °C, 24 h; (iv) $Fe(CO)_5$, CCl_4, reflux, 6 h (the major diastereoisomer isolated in 60% yield after chromatographic purification gives (1*S*)-dichlorovinylchrysanthemic acid); (v) NaH, THF–DMF, 20 °C, 48 h, *cis*/*trans*: 94/6, ee *cis*: 96%; (vi) (a) aq KOH, THF–EtOH, 20 °C, 24 h (b) HCl, H_2O, *cis*/*trans*: 91/9 due to fractionation which occured upon chromatographic purification.



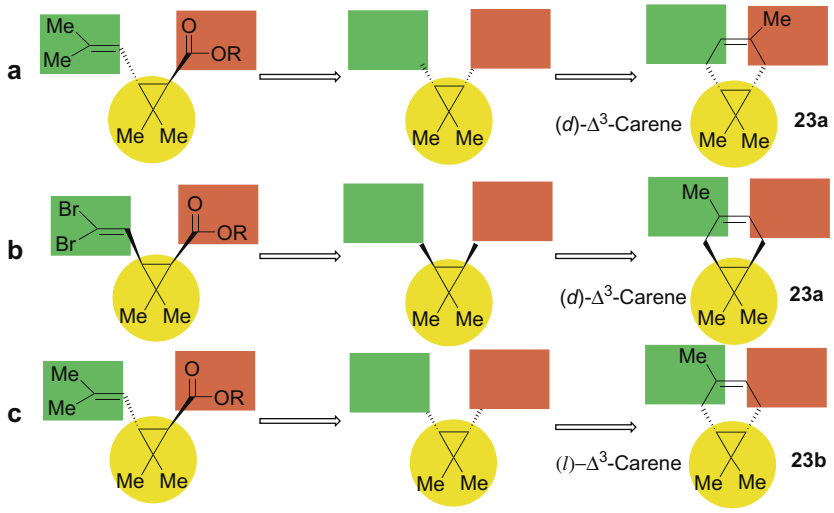
Scheme 9. Reagents and conditions: (i) Aq KOH, MeCN, 25 °C, 23 h; (ii) HCl, 100 °C, 6 h; (iii) (a) $SOCl_2$, 80 °C, 4 h (b) $SOCl_2$, NClS, *hv*, 60 °C, 5 h (iv) $Me_2C{=}CH_2$, Zn; (v) (a) 2.4 equiv aq NaOH, 0 °C, 22 h, 95 °C, 3 h (b) H_3O^+; (vi) (a) SO_2, H_2O, MeCN (b) (*S*)-phenylethylamine ' NR_3' (c) crystallization from EtOH–H_2O (vii) aq $NaHCO_3$, 20 °C; (viii) (a) aq NaOH, 20 °C (b) 100 °C, then H_3O^+.

Scheme 10 details some key intermediates precursors of hemicaronaldehyde **A**. All those precursors possess the carboxy group present on the target structure **A**. **A** has been generated from compounds whose structure already possesses the cyclopropane ring (**B**–**I**). The aldehyde present in **A** has been generated by functional group manipulations from functional groups which possess the same oxidation level and therefore imply a hysohipsic process such as the acetal **B** or related cyclic compounds **C**. The isomeric hemicaronic aldehyde **D** requires epimerization alpha to the formyl group to be transformed to **A**, whereas oxidation leading to the cleavage of a C,C bond is involved in the transformation of compounds possessing the structure **E** or **F** to **A**. Oxidation of the hydroxyl or the latent hydroxyl group is also needed to transform **G** or **H** to **A**. Finally hemicaronates have been produced by selective reduction of compound **I** possessing on the carbon adjacent to the cyclopropane bearing already a carboxylate, a carboxylic acid, an alkyl carboxylate, a thioester or an acid chloride.

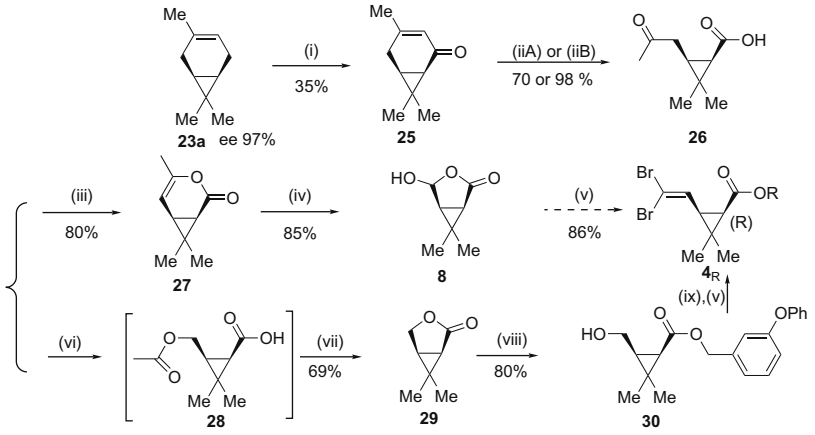


Scheme 10.

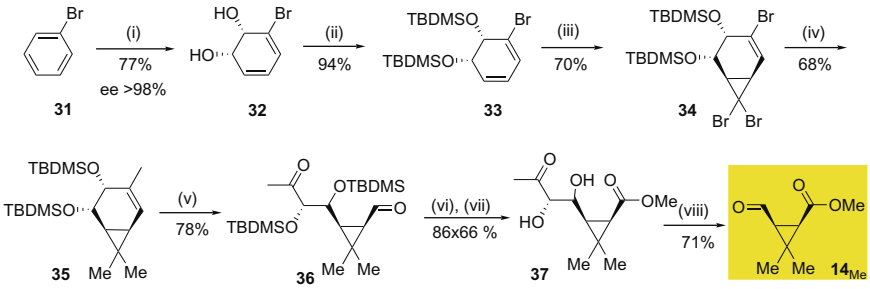
We will briefly disclose some selected syntheses of deltamethrinic acid which involve such or related intermediates and use diastereoselective transformation starting from (i) a scalemic natural product such as (*d*)-Δ^3-carene **23a** (Scheme 12) or L-(*S*)-*t*-leucinol **44** (Scheme 15) or an enantioselective step from a prochiral compound such as bromobenzene **31** using a microorganism (Scheme 13) or a man-made transition metal-catalyst surrounded



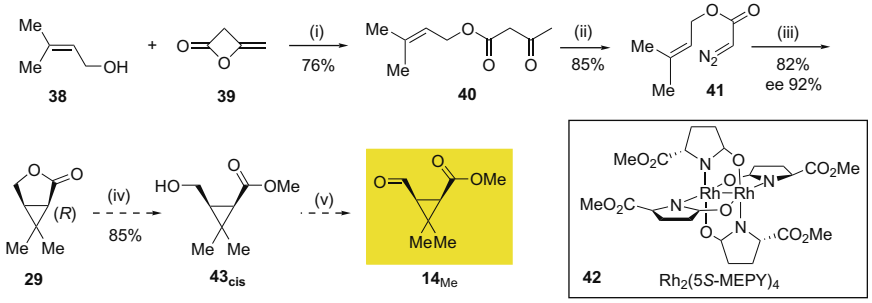
Scheme 11.



Scheme 12. Reagents and conditions: (i) O_2, $Co(acac)_2$; (iiA) (a) $KMnO_4$, AcOH–H_2O, 25 °C, 1 h (b) SO_2, 0–5 °C; (iiB) (a) O_3, AcOEt, 0–2 °C (b) Me_2S, 0–5 °C; (iii) Amberlyst-15, Ac_2O, 30 °C, 3 h; (iv) (a) O_3, MeOH, 0–5 °C, 2.5 h (b) Me_2S, 5 °C (c) aq oxalic acid, 30 °C, 3 h; (v) CBr_4, PPh_3, CH_2Cl_2; (vi) (a) *m*-CPBA, CH_2Cl_2, 25 °C, 72 h, away from light; (vii) HCl, MeOH–H_2O, 25 °C, 18 h; (viii) (a) NaOH, EtOH–H_2O (b) 3-phenoxybenzyl bromide, NEt_3, EtOH, reflux, 3 h; (ix) CrO_3, pyr., CH_2Cl_2, 25 °C, 2 h.



Scheme 13. Reagents and conditions: (i) *Pseudomonas putida*, O_2, 24 h; (ii) *t*-$BuMe_2SiCl$, NEt_3, THF–HMPA; (iii) $CHBr_3$, aq NaOH, $[PhCH_2NEt_3]^+Cl^-$, benzene, 5–18 °C, 16 h; (iv) $Me_2Cu(CN)Li_2$, MeI, THF–Et_2O, −78 °C to 0 °C, 0.5 h; (v) O_3, CH_2Cl_2, −78 °C, 0.1 h then Me_2S (excess), −78 °C to 18 °C, 16 h; (vi) (a) $NaClO_2$, NaH_2PO_4, 2-methyl–butene, *t*-BuOH–THF–H_2O, 18 °C, 3 h (b) CH_2N_2 (excess), Et_2O–CH_2Cl_2, 18 °C, 2 h; (vii) TBAF·H_2O, THF, 18 °C, 3 h; (viii) $Pb(OAc)_4$, $CaCO_3$, CH_2Cl_2, 0 °C, 0.75 h.



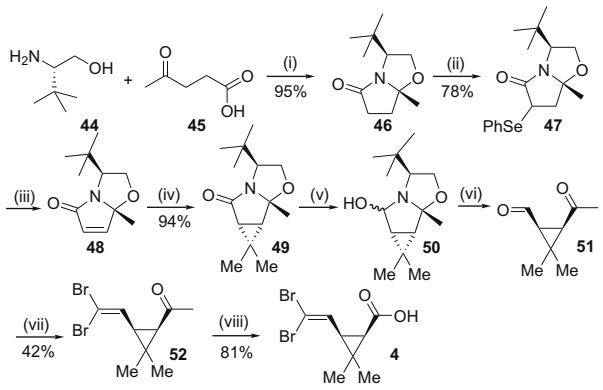
Scheme 14. Reagents and conditions: (i) Diketene, NaOAc, 0 °C, 1.5–2 h then 75–80 °C, 1 h; (ii) (a) *p*-toluenesulfonyl azide, NEt_3, AcCN, 20 °C, 2 h (b) 1 N NaOH, 20 °C, 0.75 h; (iii) Rh_2(5*S*-MEPY)$_4$ **42**, CH_2Cl_2, 12 h, 25 °C, ee 92%; (iv) (a) 3 equiv KOH, MeOH, 1.5 h (b) 1 N HCl (c) CH_2N_2; (v) $HCrO_3Cl$–pyr., 20 °C, 1 h.

by scalemic ligands such as **42** in the transformation disclosed in Scheme 14.

2.1.2.3.2. From carenes: diastereoselective syntheses starting from the chiral pool. Thus deltamethrinic acid **4** has been generated from (*d*)-Δ^3-carene **23a**, a scalemic natural monoterpene which is so cheap that it costs less than the usual solvents used for organic synthesis. (*d*)-Δ^3-Carene is present in the essential oil of Indian turpentine, Scandinavian turpentine, pine needle, galangal and *Pinus sylvestris*, commercially available and Δ^3-carenes **23** not only possess the *gem*-dimethyl cyclopropane ring present in pyrethroic acids but a C,C double bond precursor of the carboxylic acid moiety and of the vinylic side chain after proper functional group manipulations. We disclose in Scheme 11 the different strategies used to produce vinyl cyclopropane carboxylic acids from Δ^3-carenes **23**. The requirements are (i) to achieve the cleavage at the proper stage of its C,C double bond, (ii) to avoid, at all the stages, generation of an achiral intermediate, (iii) to select the location of the carboxy and vinyl groups to get, at the end of the synthesis the required stereochemistry. The strategy disclosed in Scheme 11, entry b is the only one which allows the synthesis of deltamethrinic acid **4**.

Several routes allow the synthesis of vinyl cyclopropane carboxylic acids from carenes **23** but many of them suffer from poor overall yields due to the large number of steps required and in many cases poor yield in individual steps.

The two methods described in Scheme 12 suffer from the poor yield of car-3-en-5-one **25** (<20%) resulting from the transition metal catalyzed allylic oxidation of carene **23a**. But it is not an important handicap since all the other steps are good yielding and the poor yielding step is located at a very early stage of the syntheses.



Scheme 15. Reagents and conditions: (i) Toluene; (ii) (a) LDA, THF, −78 °C (b) PhSeBr, −78 °C, 4 h; (iii) H_2O_2; (iv) diphenylsulfonium isopropylide, de >99%; (v) Red-Al, THF, 25 °C; (vi) $Bu_4N–H_3PO_4$, $CH_2Cl_2–H_2O$ (1–1), 96 h, 25 °C; (vii) CBr_4, PPh_3, CH_2Cl_2, 25 °C, 0.15 h; (viii) NaOH, Br_2, −10 °C, 4 h then reflux 1 h.

In fact these methods are used for the industrial syntheses of deltamethrin and even have been preferred by the Roussel–Uclaf company to the method they previously used and which involves α-metallosulfones (Schemes 1b and 3). Anyhow the poor yielding route (<20% yield) has not only been improved to 35% yield by (i) using cobalt acetyl acetonate[32b] or cobalt stearate[33] as catalysts (ii) performing the reaction at little conversion and (iii) reacting the crude mixture containing the very unstable hydroperoxide with water at room temperature[33] to allow the easy separation of the desired product **25** from the unreacted carene **23a** which is then recycled.

The synthesis of deltamethrinic acid **4** or its benzylic ester has been achieved according two different routes (Scheme 12, step iii or vi) which involve cleavage of the C,C double bond of the enone **25** using potassium permanganate[32a] or better ozone[32b] which leads to the ketoacid **26**. Sequential acid catalyzed cyclization of **26** to the enolacetate **27**. Its ozonolysis allows the synthesis of biocartol **8**. Alternatively the Bayer–Villiger reaction on **26** followed by acid catalyzed cyclization of the intermediate **28** furnishes (1*R*,5*S*)-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one **29** an excellent precursor of deltamethrinic acid **4** and related esters (Scheme 12).[32a,b]

2.1.2.3.3. Synthesis from bromobenzene using a microbial enantioselective step. Another ingenious approach to deltamethrinic acid **4** uses a much less elaborated bromobenzene **31** as starting material (Scheme 13).[34] It takes advantage of:

(i) The presence of the bromine atom on the aromatic ring which favors (a) the regioselective microbial catalyzed enantioselective dihydroxylation of **31** (b) the regioselective cyclopropanation of the C,C double bond of **33** away from the one bearing the bromine atom (c) the formation of highly nucleophilic trialkyl substituted C,C double bond by substitution of the bromine atom in **34** using the high order methylcuprate. This dramatically increases the reactivity of the C,C double bond towards ozone leading to **36**.

(ii) Efficient dimethylation of the two geminal bromine atoms present **34** effecting at the same time the substitution of the bromine atom by a methyl group at the vinyl carbon.

(iii) The extremely high directing effect of the two bulky TBDMSO groups present on **33** which favors the cyclopropanation with dibromocarbene on the other face leading, almost exclusively, to the stereoisomer **34**.

(iv) The efficient lead tetraacetate cleavage of the β-diol present on **37** leading to the aldehyde functional group present on $\mathbf{14_{Me}}$.

2.1.2.3.4. Enantioselective synthesis involving the transition-metal catalyzed cyclopropanation by decomposition of diazo-compound. The synthesis of $\mathbf{14_{Me}}$ described in Scheme 14 offers the advantage of being highly specific producing the *cis*-stereoisomer with very high enantioselectivity.[35] The *cis*-geometry on the cyclopropane ring comes from the intramolecular cyclopropanation of the trisubstituted C,C double bond present on **41** which results from the rhodium catalyzed decomposition of the built-in diazoacetate. It delivers the bicyclic [3.1.0] carbon framework present in **29** which possesses the appropriate functionalities to generate $\mathbf{14_{Me}}$ efficiently. The chiraly liganded rhodium catalyst **42** used in catalytic amounts offers also the advantage to favor the facial stereocontrol leading to the desired $\mathbf{14_{Me}}$ with extremely high enantioselectivity.

This method also offers the advantage of being extremely short and using incredibly simple and commercially available starting materials **38** and **39** (Scheme 14).

2.1.2.3.5. Asymmetric cyclopropanation of a scalemic α, β-unsaturated cyclic lactam. The construction of the cyclopropane ring with the two *cis*-related appendages present in deltamethrinic acid **4**, has been achieved on the scalemic cyclic structure **48** possessing the α,β-unsaturated carboxyl functionality able to efficiently add in a 1,4-mode the isopropylidene moiety delivered by isopropylidene diphenylsulfurane (Scheme 15).[36]

In this specific case, asymmetric induction is extremely high since the isopropylidene moiety is delivered, as expected, on **48** from the face opposite to the one on which bears the methyl and the *tert*-butyl groups. Surprisingly however no such stereocontrol is operative when 2-diazopropane, which is also able to transfer the isopropylidene moiety, is instead used.[36] Other salient features of this method are disclosed below:

(i) Easy synthesis of the α,β-unsaturated carbonyl motif which combines the efficient elaboration of the five membered framework by condensation of L-(*S*)-*t*-leucinol **44** with 4-oxo-butenoic acid **45** and the introduction of the unsaturation by present selenoxide elimination reaction leading to **48**.

(ii) Efficient transformation of **49**, bearing the bicyclic lactame and the hemiaminal functional groups to **51** possessing the *gem*-dimethyl cyclopropane framework bearing a formyl and an acetyl groups in *cis*-position on the two others vicinal carbons using a two step process involving DIBAL-H and acid catalyzed hydrolysis.

(iii) Regioselective olefination of the formyl group of **51** leading to the dibromovinyl group present in **52**, followed by the efficient transformation of the acetyl group to the carboxyl group present in **4** using the haloform degradation reaction.

Note that in such synthesis the strategy used to build the two side chain present in **4** is the reverse to that usually used which implies the construction of the dibromovinyl moiety at the latest stage of the synthesis.

2.1.2.3.6. Enantioselective synthesis of deltamethrinic acid from Namur

2.1.2.3.6.1. Introduction We have been active in this field over the past 34 years and have disclosed racemic and scalemic syntheses of the most active pyrethric and pyrethroic acids. We have been in contact with the companies which have actively discovered and synthesized the compounds which possess the most salient insecticidal properties and patented them such as Roussel–Uclaf company (France) [then Hoescht (Germany), now Bayer crop science (Germany)], ICI company (UK) [then Zeneca (UK), now Syngenta (UK–Switzerland)], Ciba-Geigy (Switzerland, now Syngenta), Bayer (Germany) and Sumitomo (Japan). We have actively collaborated and patented results with Roussel–Uclaf and ICI and have appreciated the constant interest of the colleagues and leaders of the Sumitomo Company.

We have been deeply depressed to observe the dismantling of the European chemical industry which consequently left many chemists unemployed. We were please to observe competition growing between chemical companies to use the cheapest methods to produce deltamethrin **1c** for selling it.

We have been interested in disclosing new synthetic strategies and routes to vinyl cyclopropane carboxylic acids especially deltamethrinic acid **4**. We have carried out retrosynthetic analyses of chrysanthemic acid in (i) Roussel–Uclaf Company in the 70' using the MASSO software created by Dr. P. Moreau and (ii) ICI Company in the early 1990 using LAHSA, created by Professor E. J. Corey and his team and implemented by a community of chemical companies. We have been astonished by the huge number of synthetic methods generated by those computerized systems for such family of terpenes possessing at much 10-carbon atoms on which a large variety of functionality including the cyclopropane ring is concentrated. We have been also surprised by the degree of chemical knowledge and perspicacity required to compare the propositions and to select those which fit the best to the objectives.

We have developed our research in different directions. We will describe only those which involve as the starting material α,β-unsaturated carbonyl compounds **K**, **L** and **M** (Scheme 16) or dimethyldimedone **N** which is in fact an isomer of chrysanthemic acid. All the methods will involve at one stage or another synthesis the hemicaronic acid or one of its esters **A** possessing the *cis*-geometry on the cyclopropane ring. The formation of the cyclopropane ring involves in the three first cases (Scheme 16, entries a–c) the introduction of an isopropylidene moiety producing the 'c–b' and 'c–d' bonds. In the latter case (Scheme 16, entry d) the synthesis of the cyclopropane ring requires the formation of the 'b–d' bond by an intramolecular process.

The production of a bicyclic [3.1.0] compound from **M** and **N**, will ensure the *cis*-geometry required for **A** due to steric reasons (Scheme 16, entries c and d). The cyclopropanation however requires the proper alignment of the corresponding orbitals.

Cyclopropanation of **K** is expected to produce the *cis*-stereoisomer **A**, under kinetic control, using starting enoates possessing the *cis*-geometry between the carboxy group and the precursor of the formyl group. This will in turn require not only a stereoselective synthesis of **K** but also to use a reagent able to stereoselectively produce a *cis*-cyclopropane derivative (Scheme 16 entry a). This is no longer the case for the strategy disclosed in Scheme 16, entry b since the relative geometry of the appendages on the cyclopropane ring is not affected by the outcome of cyclopropanation reaction but has to be fixed later.

The synthesis of scalemic deltamethrinic acid **4** and the hemicaronate **A** involves an asymmetric induction at the time the cyclopropane ring is generated (Scheme 16, entries a–c) using a chiral center on the 'carbon-e' of **K**, **L** or **M**. In the case of **N** (Scheme 16, entry d) the situation is different since the formation of the cyclopropane ring will produce a symmetrical [3.1.0] bicyclohexanone which will require at one stage desymmetrization of a prochiral intermediate.

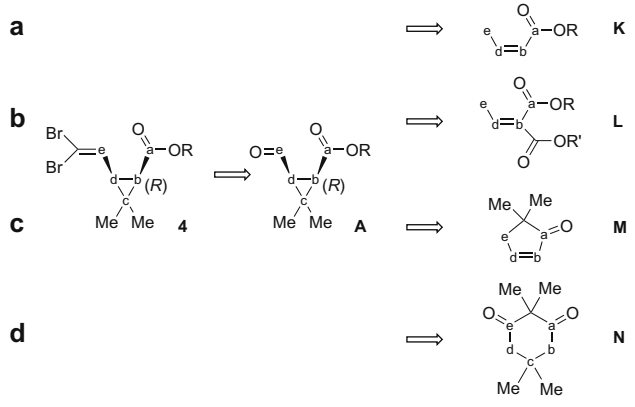
Dimethyldimedone **N** has been also transformed to the related prochiral γ,δ-unsaturated ketone **O** and the chiral homoallylalcohol **P** which also proved to be valuable precursors of deltamethrinic acid as well as of scalemic chrysanthemic acids (Scheme 17).

2.1.2.3.6.2. Syntheses involving cyclopropanation of scalemic α,β-unsaturated esters using α-heterosubstituted organometallics. The cyclopropanation reaction of α,β-unsaturated carboxyl compounds plays an important role for the syntheses of deltamethrinic acid and esters that we have published.

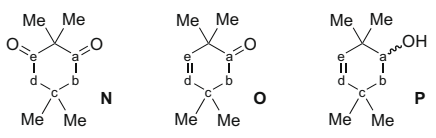
We have used isopropylidene diphenylsulfurane, isopropylidene triphenylphosphorane, 2-metallo-2-phenylsulfonylpropane and 2-metallo-2-nitropropane to deliver the isopropylidene moiety needed for building the cyclopropane ring of pyrethric and pyrethroic esters but they are not interchangeable to do so. When we started this work Corey had already described the behavior of isopropylidene diphenylsulfurane towards dimethyl fumarate, dimethyl maleate (**37**) and methyl 5-methyl-2,3,4,5-hexadienoate[19] and had performed the synthesis of methyl (*d,l*)-*trans*-chrysanthemate.[19] Grieco had also published that isopropylidene triphenylphosphorane allows the cyclopropanation of some α,β-unsaturated esters.[38]

(i) The family of α-heterosubstituted organometallics disclosed above is usually synthesized by metallation of the corresponding carbon acid. They are all thermally stable for reasonably long period of time except isopropylidene diphenylsulfurane. It has been previously prepared at temperatures lower than −50 °C from the corresponding sulfonium tetrafluoroborate, LDA and dichloromethane in DME[37,40a] or phenyllithium.[39,40a] We have found that although potassium *tert*-butoxide (*t*-BuOK) easily metallates the isopropyldiphenylsulfurane at −78 °C, the resulting ylide almost instantaneously decomposes at the same temperature. Cyclopropanation has been however successfully achieved by adding, at −78 °C, potassium *tert*-butoxide to a mixture of isopropyldiphenylsulfonium tetrafluoroborate and the electrophilic olefin.[40a] Better results have been obtained on sonication (see Scheme 18). On the other side isopropylidene triphenylphosphorane is produced from isopropyltriphenylphosphonium iodide and butyllithium at −30 °C and is stable for very long time at room temperature.

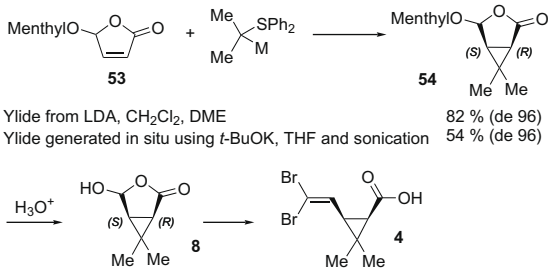
(ii) Isopropylidene diphenylsulfurane as well as isopropylidene triphenylphosphorane produce the corresponding cyclopropane derivatives from α,β-unsaturated esters and alkylidenemalonates[13m] and although both ylides add across the C,C double bond of five membered cyclic compounds such as cyclopentenones and butenolides, only the isopropylidene diphenylsulfurane allows their cyclopropanation and leads to a [3.1.0]-bicyclic compound. For example the scalemic γ-menthyloxy-butenolide **53** reacts with isopropylidene diphenylsulfurane to produce 4-(L)-menthyl-biocartol **54** in very good yield and facial stereocontrol. The latter has been easily transformed to deltamethrinic acid **4** (Scheme 18).[40]



Scheme 16.



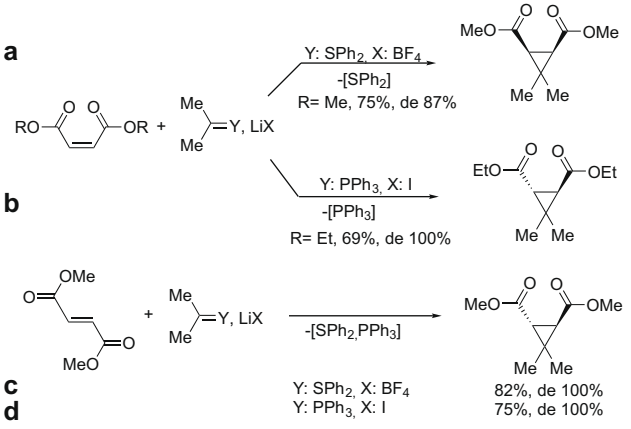
Scheme 17.



Scheme 18.

(iii) The reaction of isopropylidene diphenylsulfurane is stereospecific and for example leads mainly to dialkyl caronate possessing (a) the *trans*-stereochemistry from dialkyl fumarates (b) the *cis*-stereochemistry from dialkyl maleates.[37,39]

(iv) In contrast isopropylidene triphenylphosphorane reacts highly stereoselectively with each of the two stereoisomeric electrophilic olefins to exclusively produce dialkyl *trans*-caronates (Scheme 19).



Scheme 19.

(v) Asymmetric induction is very poor from isopropylidene diphenylsulfurane or the related phosphorane and α,β-unsaturated esters derived from scalemic alcohols (ee <20%). This is probably due to the fact that the inductor is far from the reactive site.[41]

(vi) Reasonably good asymmetric induction has been however observed from isopropylidene triphenylphosphorane and di-(*l*)-menthyl fumarate (THF, −78 to +20 °C, 85%, (*S,S*) de: 74%, Scheme 20, entry a).[20b] Even better results have been obtained using instead di-(*l*)-phenylmenthyl fumarate (THF, −78 to +20 °C, 80%, (*S,S*) de: 82%, Scheme 20, entry b). This is probably due to the presence of one of the two menthyloxy groups closer to the site of attack of the ylide (Scheme 20).

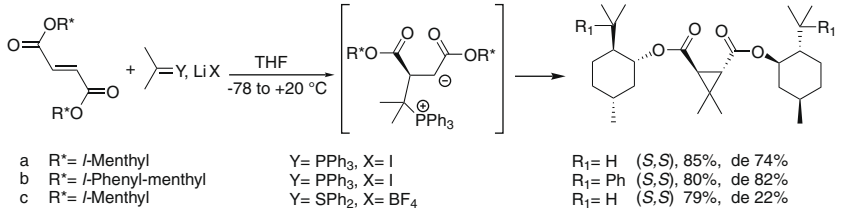
(vii) Surprisingly the diastereoselection is poorer when isopropylidene diphenylsulfurane is instead used (THF, −78 to +20 °C, 79%, (*S,S*) de 22%, Scheme 20, entry c).[20b,40]

This difference of diastereoselectivity is not general, since as it will be disclosed later isopropylidene diphenylsulfurane often allows the construction of the cyclopropane ring from γ-alkoxy-α,β-unsaturated esters with an even higher diastereocontrol than its phosphorus analogue.

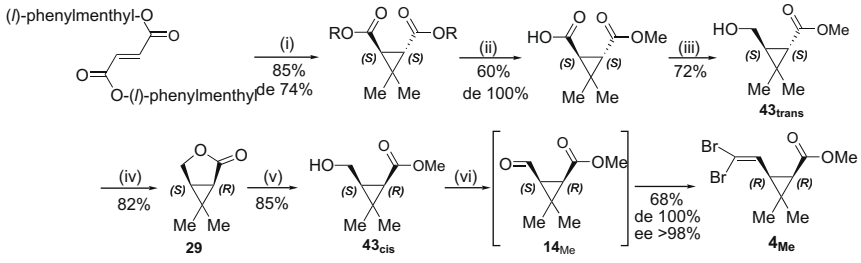
It would have been particularly elegant to use dimenthylmaleate as starting material for the synthesis of deltamethrinates, but because the diastereoselectivity of cyclopropanation is poor whatever the ylide used,[40] we have achieved it from di-(*l*)-phenylmenthyl fumarate and isopropylidene triphenylphosphorane (Scheme 21).

This in turn requires the base promoted isomerization of the methyl cyclopropane carboxylate **43*trans*** bearing a hydroxymethylene moiety on the adjacent carbon to its *cis*-stereoisomer **43*cis***, which possesses the *cis*-geometry between the carboxy and the hydroxymethylene (Scheme 21). The easy cyclization of **43trans** to the bicyclic lactone **29** is the driving force of this *trans*- to *cis*-contrathermodynamic process.

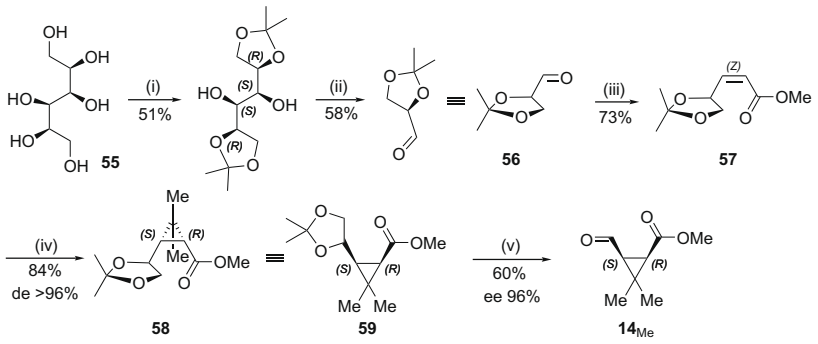
As already stressed the best asymmetric induction in producing the cyclopropane ring came from α,β-unsaturated esters bearing a chiral center at the γ-position. This center (as for example in **57**, Scheme 22) should be destroyed at a later stage to produce the diagonal carbon present on the hemicaronate aldehyde **14Me** as well as on the methyl deltamethrinate **4Me**. It should also induce



Scheme 20.



Scheme 21. Reagents and conditions: R = (*l*)-Phenylmenthyl. Reagents and conditions: (i) (a) 1.2 equiv $Me_2C{=}PPh_3$, THF, −78 °C to 20 °C, 0.5 h, de 86% (b) one crystallization from ethanol, de 100% (ii) (a) MeOLi, MeOH, 75 °C, 4 h (b) H_2O, 75 °C, 3 h, (c) BH_3–SMe_2,THF, 20 °C, 0.5 h; (iv) (a) *t*-BuOK, benzene, 80 °C, 1 h (b) H_2SO_4 cc., 20 °C, 0.2 h; (v) (a) 3 equiv KOH, MeOH, 1.5 h (b) 1 N HCl (c) CH_2N_2, Et_2O, 20 °C, 0.2 h; (vi) (a) $HCrO_3Cl$–pyr., 20 °C, 1 h (b) CBr_4, PPh_3, CH_2Cl_2, 25 °C, 0.15 h.



Scheme 22. Reagents and conditions: (i) 2,2-Dimethoxypropane, $SnCl_2$, DME, 1.5 h, reflux; (ii) $Pb(OAc)_4$, THF, 0 °C, 0.2 h; (iii) 2.5 equiv $Ph_3P{=}CHCO_2Me$, MeOH, 0 °C, 3 h; (iv) $Ph_2S{=}CMe_2$, DME, −78 °C, 0.2 h to −50 °C, 0.7 h to 20 °C, 0.3 h de 96%; (v) (a) aq $HClO_4$, THF, 20 °C, 6 h (b) $NaIO_4$, MeOH, phosphate buffer pH 7.2, 20 °C, 1 h.

the required (*S*)-stereochemistry on the cyclopropane carbon adjacent to the carboxy group and precursor of the formyl group in **14_{Me}**.

We have for that purpose adapted the approach described by Mulzer[42] for the synthesis of methyl (1*R*)-*trans*-chrysanthemate (1*R*)-**$2a_{Me}$** to the synthesis of methyl deltamethrinate **4_{Me}**. Accordingly we have found that the only matching pair of reagents is isopropylidene diphenylsulfurane and the *Z*-enoate **57**, easily prepared from D-mannitol **55** (Scheme 22).[43] It is interesting to note that isopropylidene diphenylsulfurane approaches **57** by its *Re*-face producing the methyl cyclopropane carrboxylate **58** bearing the two *cis*-appendages whereas isopropylidene triphenylphosphorane, which belongs to the same family of reagents, reacts by the same *Re*-face but produces the methyl *trans*-cyclopropane carboxylate instead.[43] This propensity of isopropylidene triphenylphosphorane to produce *trans*-cyclopropane derivatives from C,C disubstituted double bonds bearing two *cis*-substituents has been already pointed out above.

The salient features of the approach to methyl deltamethrinate **4_{Me}**, described in Scheme 22, are without doubt:

(i) Convergence of the synthesis.

(ii) Easy access to the *Z*-enoate **57** with very high stereocontrol. This has been achieved by reacting the acetonide of D-glyceraldehyde **56** with carbomethoxymethylene triphenylphosphorane ($Ph_3P{=}CHCO_2Me$).[43] Interestingly the synthesis of the *E*-enoate of **57**, precursor of methyl (1*R*)-*trans*-chrysanthemate (1*R*)-**$2a_{Me}$** can be achieved from the same aldehyde **56** by using instead the sodium salt of *O*,*O*-diethylcarboxyalkyl phosphonates in DME.[43b]

(iii) Extremely high stereocontrolled cyclopropanation the *Z*-enoate **57** which is influenced by both the stereochemistry of its C,C double bond and of its γ-carbon which leads to **58** in high yield and high ee.

(iv) Easy access to methyl hemicaronate **14_{Me}** by deprotection of the acetonide functional group present on **58** and subsequent cleavage of the resulting diol.

This approach to vinyl cyclopropane carboxylates has to be compared to that described in Scheme 1 which uses instead alkyl γ-oxo-butenoate. Therefore the acetonide moiety on *Z*-enoate **57** plays formally the role of a 'masked' formyl group.

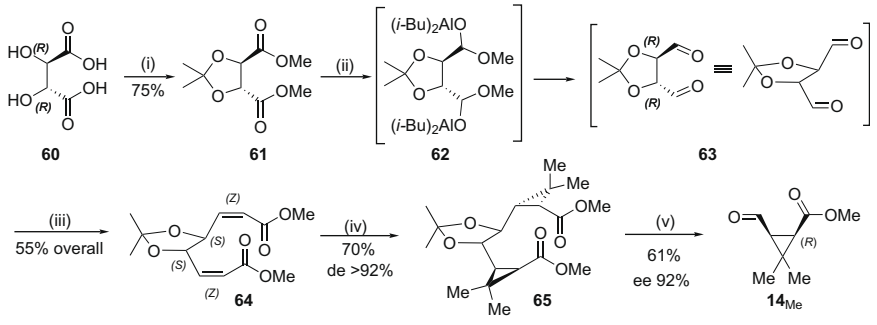
An even more efficient method uses the same strategy but starts from the readily available (*R*,*R*)-tartaric acid **60** (Scheme 23).[43] It shares with the approach described in Scheme 22 the same valuable characteristics but produces an added value due to:

(i) The efficient synthesis of *Z*,*Z*-(di)enoate **64**, which possesses the correct stereochemistry at the two carbon atoms part of its acetonide moiety, to allow the synthesis of deltamethrinic acid. This has been achieved in a single pot from **61** using sequentially DIBAL-H and carbomethoxymethylene triphenylphosphorane.[43]

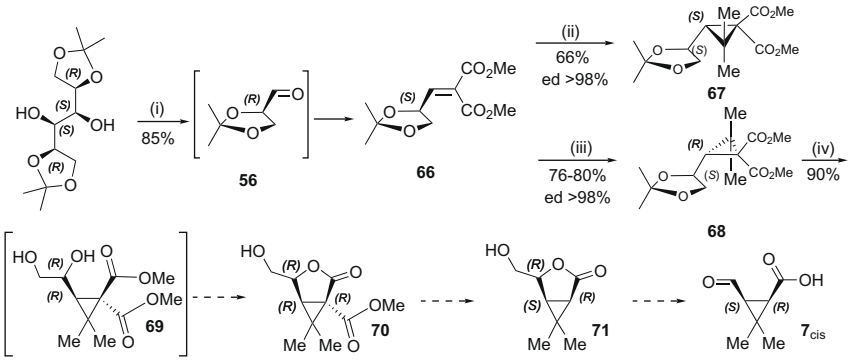
(ii) The extremely high stereocontrol observed after the two stepwise additions of isopropylidene diphenylsulfurane to the *Z*,*Z*-(di)enoate **64** leading finally to **65** very efficiently and with extremely high stereocontrol.

(iii) The highly 'atom economy' process which produces **14_{Me}** from **65** with no lost of any carbon atoms in the 'deprotection step' (compare Scheme 23 to Scheme 22) and the fact that formally **14_{Me}** is produced in 200% yield from **65**.

2.1.2.3.6.3. Syntheses involving cyclopropanation of scalemic α,β-unsaturated alkylidene malonates using α-heterosubstituted organometallics. The last synthesis of that series involves dimethyl alkylidene malonate **66** which is produced in high yield, in two steps but in a single pot from diacetonide of D-mannitol (Scheme 24).



Scheme 23. Reagents and conditions: (i) $Me_2C(OMe)_2$, TsOH, MeOH, reflux, 14 h; (ii) DIBAL-H, toluene, −78 °C, 2 h; (iii) 2.5 equiv $Ph_3P{=}CHCO_2Me$, MeOH, −78 °C to 20 °C, 1 h; (iv) 2.5 equiv $Ph_2S{=}C(Me)_2$, DME, −78 °C, 0.2 h then −78 °C to −50 °C, 0.7 h then −50 °C to 20 °C, 0.3 h, de >92%; (v) (a) aq $HClO_4$, THF, 20 °C, 6 h (b) $NaIO_4$, MeOH, phosphate buffer pH 7.2, 20 °C, 1 h, ee 92%.



Scheme 24. Reagents and conditions: (i) (a) $Pb(OAc)_4$, THF, 0 °C, 0.2 h (b) dimethyl malonate (c) Ac_2O, reflux, 24 h; (ii) (a) $PhSO_2C(Me)_2Li$, THFHMPA, 0 °C (b) DMSO, 80 °C, 64 h; (iii) $Me_2C{=}SPh_2$, $LiBF_4$, DME, −78 °C, 2 h then 20 °C, 1 h or $Me_2C{=}PPh_3$, LiI, THF, 0 °C, 1 h then 20 °C, 24 h; (iv) aq HCl.

As already pointed out, cyclopropanation of the scalemic alkylidene malonate **66** only involves facial stereocontrol.[27,44] The control of the stereochemistry at the carbon bearing the carbomethoxy group will be now achieved at the decarboxylation stage (compare this approach to that described in Scheme 22). We have found that isopropylidene diphenylsulfurane and isopropylidene triphenylphosphorane react both almost exclusively by the same *Re*-face of the dimethyl alkylidene malonate **66** producing the malonate **68** possessing the *S*-stereochemistry on the cyclopropane ring identical to that present in deltamethrinates $\mathbf{4_{Me}}$ (Scheme 24). Therefore those ylides react by the same face with alkylidene malonate **66** whose structure is disclosed in Scheme 24 and the *Z*-enoate **57** whose structure is disclosed in Scheme 22.

This is in sharp contrast with the reaction of isopropylidene triphenylphosphorane with the related *E*-enoate of **57** which takes place instead from its *Si*-face,[42] and that of 2-lithio-2-phenylsulfonylpropane which also adds to **66** almost exclusively by the *Si*-face (Scheme 24)[13,27,44] allowing the synthesis of *trans*-chrysanthemic acid **2a** instead.[13,27,42,44]

We planned to achieve the synthesis of deltamethrinic acid **4** from **68** expecting that (i) the diol present on **69**, resulting from the acid catalyzed deacetalization of the acetonide moiety of **68**, would spontaneously cyclize to produce the lactone ring present on **70**, fixing at that stage the *cis*-stereochemistry on the cyclopropane ring, required for deltamethrinic acid **4** production, (ii) the carbomethoxy lactone **70** would decarboxylate readily to produce **71**.

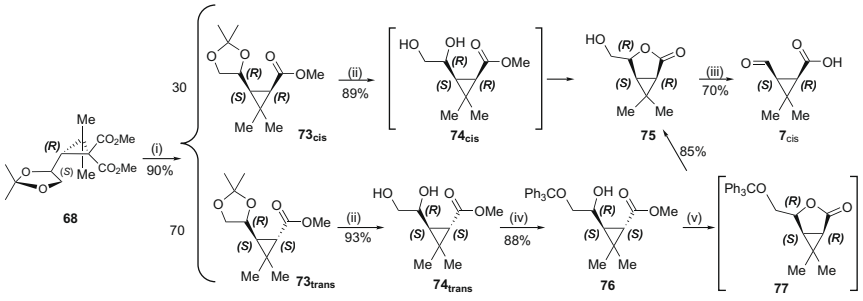
But our experimental results proved to be different from our expectations. For example, all our efforts to produce **71** from **70** proved to be unsuccessful whatever ionic or radical promoted decarboxylation is used. This is probably related to the bicyclic nature of **70** whose, for example, decarboxylation in basic media involves the formation of a transcient bridged enolate incompatible with the Bredt's rule and requires to use drastic conditions incompatible with the stability of the cyclopropane ring.[13,27,44]

The synthesis of deltamethrinic acid **4** has been nevertheless effectively achieved by inverting the two steps described above (Scheme 25). Unfortunately, the first step which implies the tandem demethylation-decarboxylation is not stereoselective and delivers a 30/70 mixture of monoesters **73** in which the unwanted *trans*-stereoisomer $\mathbf{73}_{\boldsymbol{trans}}$ prevails (Scheme 25). Thus whereas acid catalyzed deprotection of the acetonide moiety present in $\mathbf{73}_{\boldsymbol{cis}}$ provides directly the desired bicyclic [3.1.0]lactone **75** by cyclization of the intermediate diol $\mathbf{74}_{\boldsymbol{cis}}$ its *trans*-stereoisomer $\mathbf{73}_{\boldsymbol{trans}}$ delivers instead the diol $\mathbf{74}_{\boldsymbol{trans}}$. This, as expected, does not cyclize to the bicyclic [3.1.0]lactone **75** since it requires first epimerization at the carbon atom bearing the carboxyl group. This proved to be unsuccessful using potassium *tert*-butoxide (Compare to Scheme 21).

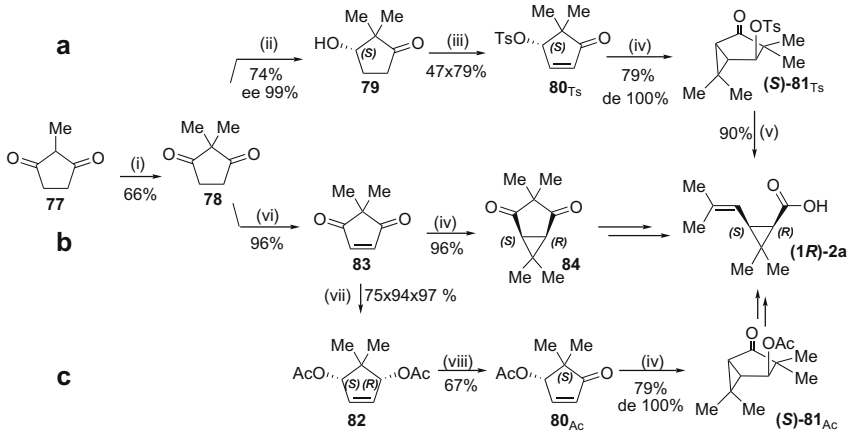
We have however, been successful when the reaction is carried out on the trityl derivative **76**. It delivers **75** after base promoted epimerization on the cyclopropane ring followed by acidic treatment which allows lactonization as well as detritylation reactions.

Transformation of **75** to hemicaronic acid $\mathbf{7}_{\boldsymbol{cis}}$ has been performed by periodate cleavage of the diol resulting from base catalyzed lactone ring opening (Scheme 25).[13,27,44]

2.1.2.3.6.4. Syntheses involving cyclopropanation of scalemic α, β-unsaturated ketones using α-heterosubstituted organometallics. Isopropylidene diphenylsulfurane also reacts with the γ-tosyloxy-cyclopentenone $\mathbf{80_{Ts}}$ whose structure is depicted in Scheme 26 entry a. The ylide is delivered to $\mathbf{80_{Ts}}$ from the face opposite to that bearing the tosyloxy group, generating the bicyclic derivative (*S*)-$\mathbf{81_{Ts}}$ in very high yield.[45] Reaction of (*S*)-$\mathbf{81_{Ts}}$ with the Gassman reagent ((*S*)-$\mathbf{81_{Ts}}$/*t*-BuOK/H_2O: 1/7.6/2.3)[46a,47] in THF or DMSO allows at room temperature the Grob type fragmentation reaction[46b,47] to take place to deliver (1*R*)-*cis*-chrysanthemic acid (1*R*)-**2b** in very high yield and extremely high enantiomeric excess.[47] The reagent used for that purpose differs from the one we describe in our original approach which uses potassium hydroxide in DMSO instead to promote the Grob-type fragmentation reaction leading to *cis*-



Scheme 25. Reagents and conditions: (i) Me_4NOAc, HMPA, 95 °C, 4 h; (ii) 10% HCl, MeOH, 20 °C, 0.3 h; (iii) (a) KOH, H_2O, 20 °C, 0.5 h then adjusted to pH 7 with CO_2 (b) $NaIO_4$, H_2O, 0 °C, 0.5 h (c) HCl; (iv) Ph_3C–DMAP, CH_2Cl_2, reflux, 16 h; (v) (a) *t*-BuOK, THF, 20 °C, 2 h (b) 10% HCl, MeOH, 20 °C, 1 h.



Scheme 26. Reagents and conditions: (i) K_2CO_3, MeI, acetone, reflux, 4 h; (ii) *Saccharomyces cerevisiae*, H_2O, glucose, 48 h; (iii) (a) LDA, THF, PhSeCl, −78 °C (b) H_2O_2, CH_2Cl_2, 20 °C, 0.3 h (c) TsCl, DMAP, CH_2Cl_2, 20 °C, 24 h (iv) $Me_2C{=}SPh_2$, $LiBF_4$, DME, −78 °C, 1 h then 20 °C, 1 h (v) (a) *t*-BuOK–H_2O, THF, 20 °C, 2 h; (b) H_3O^+ (vi) 2.2 equiv $CuBr_2$, MeOH, reflux, 2 h; (vii) (a) 1 equiv $NaBH_4$–1 equiv $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C, 0.03 h (b) 1 equiv $NaBH_4$–1 equiv $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 2 h (c) 2.2 equiv Ac_2O, 2.2 equiv pyr., 0.22 equiv DMAP, CH_2Cl_2, 20 °C, 12 h (b); (viii) (a) PLE + PLAP, 0.1 M phosphate buffer, MeOH, pH 7.0, 20 °C, 43 h (b) 1.3 equiv PDC, molecular sieves 4A, CH_2Cl_2, 20 °C, 4 h.

chrysanthemic acid (70 °C for 4 h)[49] which, we and others, have been unable to reproduce.[47]

The method, disclosed in Scheme 26 entry a, offers the advantages of an easy access to the scalemic γ-tosyloxy-cyclopentanone **80$_{Ts}$** which is readily achieved by performing the microbial reduction of the prochiral β-diketone **78**. Transformation of **81** to deltamethrinic acid **4** requires a few more steps which we have parallel to that described in Scheme 7, entry a.

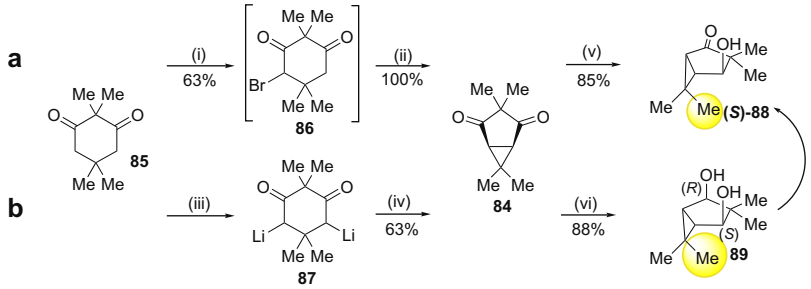
Another synthesis of deltamethrinic acid **4** uses the monodeacetylation of the prochiral (1*R*,3*S*)-2,2-dimethylcyclopent-4-ene-1,3-diyl diacetate **82** by a mixture of *Pig liver esterase* (PLE) and *Pig Liver Acetone Powder* (PLAP), 0.1 M Phosphate buffer, MeOH, pH 7.0, 20 °C, 43 h[45b] and oxidation of the resulting scalemic monoalcohol to deliver **80$_{Ac}$**. The latter, on reaction with isopropylidene diphenylsulfurane, produces (*S*)-**81$_{Ac}$** which is easily transformed to the analogue tosylate (*S*)-**81$_{Ts}$** (Scheme 26, entry c).

Isopropylidene diphenylsulfurane also reacts with the unsaturated diketone **83** to generate the bicyclic diketone **84** almost quantitatively (Scheme 26b). The latter has been transformed as disclosed below to deltamethrinic acid **4**.

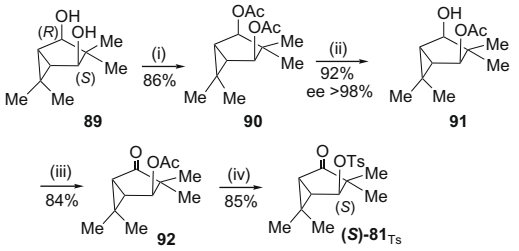
2.1.2.3.6.5. Syntheses of chrysanthemic acids using dimethyl dimedone. The prochiral diketone **84**, whose synthesis from the cyclopentanedione **83** is disclosed in Scheme 26, entry b, has been also synthesized from dimethyldimedone **85** in two steps involving its mono-bromination[48,49a] to **86** and subsequent treatment with potassium *tert*-butoxide acting as the base (Scheme 27, entry a).[49] Alternatively, **84** has been synthesized in a single pot from **85** using sequentially lithium diisopropylamide (LDA) and cupric chloride to oxidize the dilithio intermediate **87** (Scheme 27, entry b).[50]

The synthesis of (1*R*)-*cis*-chrysanthemic acid (1*R*)-**2b** requires enantioselective mono-reduction of the bicyclic diketone **84** and tosylation of the resulting β-ketoalcohol (*S*)-**88** to produce the bicyclic β-tosyloxy-ketone (*S*)-**81$_{Ts}$** (Schemes 26 and 27). Four diastereoisomers are susceptible to be formed in that process. We have found that only the *exo*-alcohol **88** is susceptible to be activated to a sulfonate such as **81$_{Ts}$** on which the Grob type fragmentation proceeds.[46b] The reducing agent should therefore react not only on one of the two carbonyl groups (Pro *S*) of the prochiral diketone **84** but also from its *endo*-face which is the most hindered one.

Most of the reducing agents (such as $NaBH_4$, $LiAlH_4$, Li–NH_3) tested,[49a] react mainly from the *exo*-face of the β-diketone **84** as for example sodium borohydride ($NaBH_4$) when the reaction is carried out in methanol at low temperature (−78 °C, **88$_{exo}$**/**88$_{endo}$** 0/100). Performing the reduction under similar conditions but in the presence of 1 equiv of cerium trichloride (the Luche's reagent)[51] allows however the reverse stereocontrol (Scheme 27, entry a; **88$_{exo}$**/**88$_{endo}$** 98/2).[49a] Furthermore the di-*exo*-diol **89** is produced in very good yield and almost complete stereocontrol when twice the amount of sodium borohydride and cerium trichloride is instead used (Scheme 27, entry b).[49c] The latter has been transformed to the scalemic bicyclic ketotosylate (*S*)-**81$_{Ts}$** precursor of (1*R*)-*cis*-chrysanthemic acid (1*R*)-**2b** on sequential (i) acetylation, (ii) enzymic deacetylation, (iii) oxidation and (iv) tosylation (Scheme 28)[47,49c] followed by treatment of the resulting scalemic



Scheme 27. Reagents and conditions: (i) 1 equiv Br_2, CCl_4, 0 °C, 2 h; (ii) 1 equiv *t*-BuOK, THF, −78 °C to 20 °C; (iii) 2 equiv LDA, −78 °C; (iv) $CuCl_2$; (v) 1 equiv $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C, 0.2 h; (vi) 2 equiv $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C to 20 °C, 16 h.



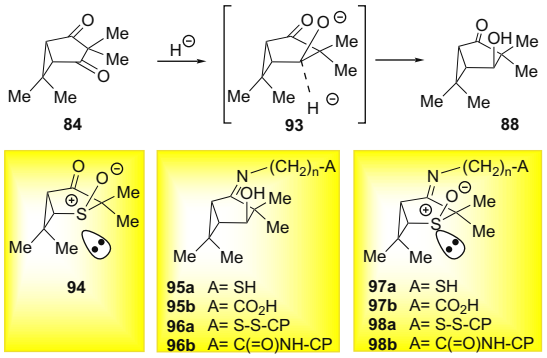
Scheme 28. Reagents and conditions: (i) Ac_2O, pyr., DMAP, CH_2Cl_2, 20 °C, 2 h; (ii) PLE, pH 6.9–7, 32 °C, 7 d; (iii) CrO_3–pyr, CH_2Cl_2, 20 °C, 2 h (iv) (a) K_2CO_3, MeOH (b) *p*-$MePhSO_2Cl$, NEt_3, CH_2Cl_2, 20 °C, 2 h.

bicyclic β-ketotosylate **81$_{Ts}$** with the Gassman reagent as disclosed above (Scheme 26).[47]

This very high stereocontrolled reduction of **84** to *exo*-β-ketoalcohol **88** and the di*exo*-β-β-diol **89** has been accounted to the propensity of the cerium salt to complex to the oxygen of their carbonyl groups. It activates it and hinder one of the least hindered face favouring thus the attack of the hydride by the other face. The presence of the *endo*-methyl group on **84** and **88** favors the complexation from the *exo*-face and the attack of the hydride by the required *endo*-face. This proposal is supported by the observation that the desmethyl **84** missing the *endo*-methyl group is reduced by both faces.[49b]

Different methods have been tested to produce scalemic bicyclic alcohol (*S*)-**88** or its tosylate (*S*)-**81$_{Ts}$** from the β-diketone **84**. Among them the enantioselective reduction is the most obvious. We have developed a strategy using antibodies directed towards the transition state **93** of the hydride reduction of **84** (Scheme 29).[52] The β-ketosulfoxide **94** was chosen as the transition state analogue since it mimics **93** by the presence on the sulfur of the lone pair, mimicking the income of the hydride and of negatively charged oxygen, mimicking the oxygen of the alcoholate.

In order to collect information to secure efficient antibody production and effective recognition by the antibody of the unusually small molecule **94**, we have, in a preliminary work, generated antibodies to recognize scalemic **88.** For that purpose, we have prepared scalemic haptens whose structures are close to **88** but which possess a functionalized arm to attach them to a carrier protein. Therefore we have synthesized compounds derived from **88** as their *O*-alkyloxime **95a** and **95b** (Scheme 29) possessing a chain of variable length and bearing at their terminus either a thianyl or a carboxyl group to link the haptens to the thianyl or the amino group of the carrier protein respectively. Alternatively we have synthesized conjugates in which the alkyl or aryl side chain bear a thiol group at their terminus attached to the cyclopropane ring at the place of the *endo*-methyl group. For practical reasons, we



Scheme 29.

have focused our energy on the former strategy which is by far easiest and involves the synthesis of the oximes **95a** and **95b** from the common (*S*)-**88**, which have been attached to proteins (CP, carrier protein) such as Bovine Serum Albumine (BSA), Ovalbumin (OVA) or better Keyhole Limlet Hemocyanin (KLH)[52,53] leading to **96a** and **96b**. Antibodies have been harvested from mice (IgY technology),[52a] as well as from hens (IgG technology) which offers the enormous advantages of no bleeding and access to large quantities of antibodies by easy extraction of the yolk of the eggs.[52b] Antibodies from different origins proved to possess similar behavior. They recognize **95a** and **95b** or related compounds possessing alkyl chains of similar size but are extremely selective. They only recognize scalemic *O*-alkyloximes which possess the complete bicyclic skeleton with the correct stereochemistry even those missing the thiol or carboxylic acid functionalities on the side chains which has to be of the same size as the one present on **95a** and **95b**. Recognition of (*S*)-**88** was only observed when the *O*-alkyl group on the oxime is the smallest, that is, a methylene group.

We have synthesized in scalemic form hapten **98b** and tried to produce, using the same technique, related antibodies. Surprisingly, we have been unable[52b] to isolate from the medium antibodies which recognize either **98b** or (*S*)-**88**.

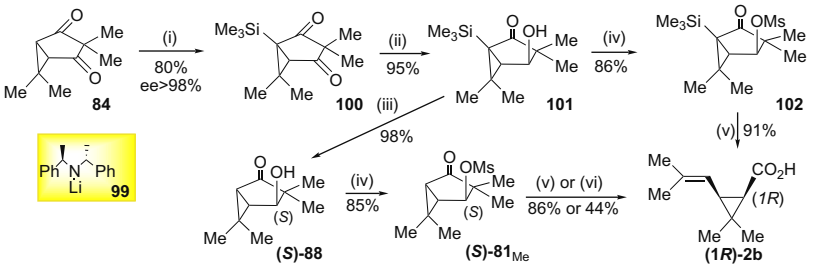
Successful approaches involve:

(i) Desymmetrization of the β-diketone **84** which has been also achieved[47] by enantioselective silylation using scalemic lithium (*R,R*)-bis-(1-phenyl-ethyl)-amide **99** in the presence of lithium chloride (1.2 equiv) and trimethylsilyl chloride (10 equiv −78 °C to 20 °C, 5 h, Scheme 30), using the Simpkins' method.[54] The resulting scalemic β-trimethylsilyl-diketone **100**, obtained with extremely good ee has been first reduced, by the Luche reagent, with complete regio- and stereocontrol to **101**.

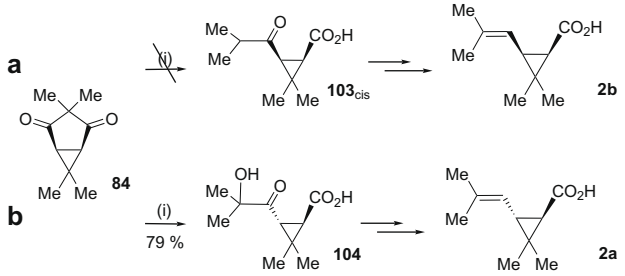
Compound **101** has been in turn transformed to (*S*)-**88**, the known precursor of (1*R*)-*cis*-chrysanthemic acid (1*R*)-**2b** by desilylation by tetrabutyl ammonium fluoride (Scheme 30)[47] or more conveniently, since it saves one reaction step, transformed to the mesylate **102** then to (1*R*)-*cis*-chrysanthemic acid (1*R*)-**2b** by the Gassman reagent.[47] In the latter reaction the hydroxyl ion sequentially performs the tandem desilylation–fragmentation reactions. Notice that this two steps process is by far best achieved when it is carried out in DMSO rather than in THF (Scheme 30).[47]

We expected that treatment of the β-diketone **84** with hydroxide derived reagents would have easily produced the *cis*-cyclopropane carboxylic acid **103$_{cis}$** after acid treatment (Scheme 31, entry a) but that was not the case.[55] β-Diketone **84** fragmentation requires heating in aq DMSO and if not very careful instead produces **104**, resulting from a series of reactions in cascade which involve in the same pot an exceptional succession of individual steps such as (i) 1,3-diketone fragmentation (step a), (ii) enolates isomerization (steps b and c) which lead to *cis–trans* isomerization on the cyclopropane ring and last but not least (iii) an unusually high propensity of the *trans*-isopropylidene enolate to be oxidized by the oxygen dissolved in the DMSO (steps d and e).[55] We have been able to avoid the formation of the hydroxylketone **104** by performing the reaction under similar conditions with potassium hydroxide which apparently dramatically lowers the propensity of the latest formed enolate to be oxidized by air but all attempts to preserve the *cis*-stereochemistry present on **84** were unsuccessful since we instead obtained the *trans*-β-ketocyclopropyl ester **103$_{trans}$**.[55]

Oxidation of the enol lactone **105**, readily available by photochemical rearrangement of **84**[48] (Scheme 32), with *m*-CPBA (2 equiv, dioxane/H_2O: 4/1, 20 °C, 3 h) directly affords the δ-hydroxy-γ-keto-carboxylic acid **106** in good yield (74%) and with complete control of the *cis*-stereochemistry. Transformation of **106** to methyl *cis*-chrysanthemate **2b$_{Me}$** relies on the cycloreductive fragmentation of the thionocarbonate function present on **107** using



Scheme 30. Reagents and conditions: (i) 1.2 equiv lithium (*R*,*R*)-bis-(1-phenyl-ethyl)-amide **99**, 1.2 LiCl, 10 equiv Me_3SiCl, THF, −78 to 20 °C, 5 h; (ii) (a) 1 equiv $CeCl_3{\cdot}7H_2O$, MeOH (b) 1 equiv $NaBH_4$, MeOH, −78 °C, 5 h; (iii) 1.1 equiv $Bu_4NF{\cdot}3H_2O$, THF, 0–20 °C, 60 h; (iv) 1.1 equiv MsCl, 1.5 NEt_3, CH_2Cl_2, −20 °C, 0.75 h; (v) (a) *t*-BuOK–H_2O (7.6/2.3 equiv), DMSO, 20 °C, 0.5 h (b) H_3O^+; (vi) *t*-BuOK–H_2O (7.6/2.3 equiv) THF, 20 °C, 0.75 h (b) H_3O^+.



Scheme 31. Reagents and conditions: (a) 6 equiv NaOH, O_2, DMSO/H_2O (4/1), 70 °C, 14 h (b) H_3O^+.

the Corey–Winter method using dimethyl-2-phenyl-[1,3,2] diazaphospholidine. The transformation of **106** to **107** has been achieved by esterification followed by reduction of the β-hydroxyketone moiety present on **106** to the corresponding diol using boron hydride–dimethyl sulfide complex (Scheme 32) followed by reaction with thionocarbonyldiimidazole.

We have tried, but unsuccessfully,[55] to adapt the approaches described in Scheme 31 and 32 to the synthesis of scalemic methyl (1*R*)-*cis*-chrysanthemate (1*R*)-**2b$_{Me}$**.

In the first case (Scheme 31) we have tried to perform[55] the fragmentation of the β-diketone **84** with a scalemic alcoholate or using an achiral alcohol in the presence of a chiral catalyst, mimicking the method which successfully worked on the related bicyclic anhydride **12** (Scheme 3). In the second case (Scheme 32) we have tried to promote an enantioselective photo-induced Norrish type I reaction[56] in the presence of a chiral Lewis acid. We expected that it would complex one of the two enantiotopic carbonyl groups of **84**, discriminating therefore their susceptibility towards light and favoring thus the formation of scalemic **105**.

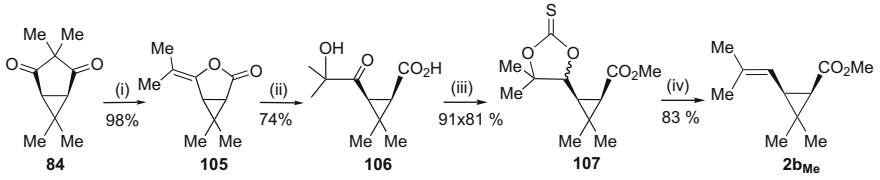
2.1.2.3.6.6. Syntheses involving β,γ-unsaturated-cyclohexanone or -cyclohexanol

2.1.2.3.6.6.1. Involving the intermediate synthesis of epibromonium ion. Other approaches imply the prochiral β,γ-unsaturated ketone **109** which has been conveniently generated from ketone **85** (Scheme 33)[57] using as a key step the Bamford-Stevens reaction.[58]

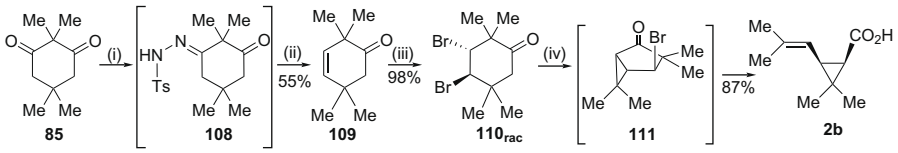
Regiocontrol of the reaction of tosylhydrazone with **85** is not perfect. For that purpose the reaction is best performed at room temperature even if it requires seven days to do so. The next step which produces the olefin present on **109** has been carried out on the crude hydrazone/dihydrazone mixture. From that point the transformation of **109** to **2b** is highly efficient and short. Bromination takes place as a titration and potassium hydroxide in aqueous DMSO produce after acid hydrolysis *rac-cis*-chrysanthemic acid **2b** (Scheme 33).[57]

It is interesting to notice that potassium hydroxide in aqueous DMSO is able to perform the tandem cyclization reaction leading to **111** and the Grob fragmentation producing the potassium chrysanthemate. It is also interesting to notice that this reagent, which is very efficient to perform the fragmentation reaction with bromine as the leaving group, is unable to perform the same reaction on **81$_{Ts}$** which bears a tosylate at the same place with the same stereochemistry. We believe[47] that the hydroxide ion reacts on the sulfur of the tosylate rather than on the carbonyl group of **81$_{Ts}$** and that competing retroaldol, *cis*/*trans* epimerization and polymerization instead take place.

We have even been able to produce the bicyclic *exo*-β-bromoketone **111**, in high yield by reacting the racemic dibromoketone **110**



Scheme 32. Reagents and conditions: (i) *hv*, benzene, 20 °C, 9 h; (ii) *m*-CPBA, dioxane–H_2O, 20 °C, 3 h; (iii) (a) CH_2N_2, Et_2O, 0 °C (b) $BH_3{\cdot}Me_2S$, toluene, 0 °C, 0.5 h (c) S=C(imid.)$_2$, toluene, reflux, 14 h (d) 1,3-dimethyl-2-phenyl-[1.3.2]diazaphospholidine, 40 °C, 8 h.



Scheme 33. Reagents and conditions: (i) 1.1 equiv $TsNHNH_2$, anhydrous EtOH, 20 °C, 7 d; (ii) 5 equiv $HOCH_2CH_2ONa$, ethyleneglycol, 180 °C, 0.5 h; (iii) 1 equiv Br_2, 0.1 equiv $AcNH_2$, CCl_4, 0 °C; (iv) (a) 6 equiv KOH, DMSO–H_2O (4/1), 70 °C, 2 h (b) aq HCl.

with lithium diisopropylamide[57] or potassium *tert*-butoxide,[57] (1 equiv LDA, THF, −78 °C, 1 h, 86% yield or 2 equiv *t*-BuOK, 23 °C, 2 h, 94% yield) and have shown that on reaction with a suitable base **111** is transformed after acid hydrolysis to *rac*-*cis*-chrysanthemic acid **2b** using KOH in DMSO (6 equiv KOH, DMSO–H_2O (4–1), 70 °C, 0.7 h, 87%) or the Gassman reagent (7.6 equiv *t*-BuOK, 2.3 H_2O, DMSO, 20 °C, 0.5 h, 53% or 7.6 equiv *t*-BuOK, 2.3 H_2O, THF, 20 °C, 0.5 h, 94%).

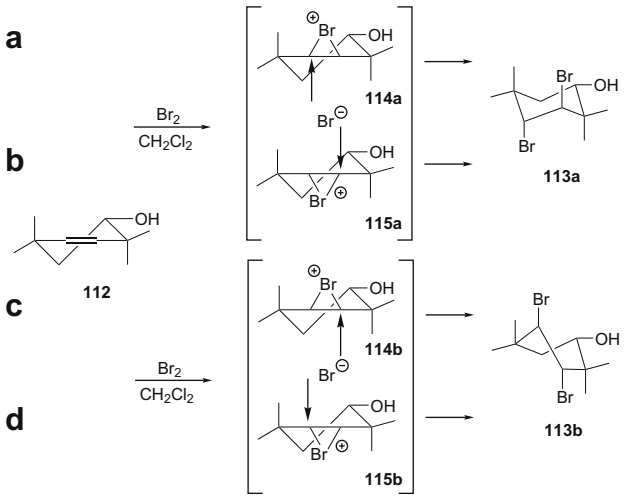
The enantioselective version of the transformation reported above implies a slight modification of the synthetic scheme disclosed in Scheme 33 which involves:[59]

(i) Enantioselective reduction of 2,2,5,5-tetramethyl-cyclohex-3-enone **109** using (−)-*B*-chlorodiisopinocampheylborane[60] and quenching the mixture with diethanolamine to provide (1*S*)-2,2,5,5-tetramethyl-cyclohex-3-enol (*S*)-**112** in 85 % yield, with very high stereocontrol (ee > 97%, Scheme 34).

(ii) Dibromination of the resulting homoallyl alcohol (*S*)-**112** using elemental bromine which proved to be highly stereoselective and leads to (3*R*),(4*R*)-dibromo-2,2,5,5-tetramethyl-cyclohexan-1(*S*)-ol **113a** in high yield and with very high stereocontrol if the reaction is carried at low temperature (−78 °C, 95% yield; de 97%, Scheme 34).

(iii) Oxidation of the **113a** with pyridinium dichromate which finally produces the scalemic dibromocyclohexanone (*R*,*R*)-**110** with enantioselectivity higher than 98%.

(iv) Preliminary results lead us to suspect that (i) the attack of bromine occurs from the two faces of the unsaturated alcohol (*S*)-**112** in which the hydroxyl group lies in equatorial position, (ii) that ring opening of the resulting a 60/40 mixture of the epibromonium ions **114**/**115**, is stereoselective and produces **113a** form either **114a** and **115a** so the chair transition states are being preferred to the boat ones which would have lead to the diastereoisomer **113b** (Scheme 35).



Scheme 35.

The strategies used to transform the scalemic homoallyl alcohol (*S*)-**112** to (1*R*)-*cis*-chrysanthemic acid (1*R*)-**2b** disclosed in Scheme 36 involves the intermediate formation of scalemic dibromide **113**, scalemic mixture of the two isomeric bromohydrins **116** and **117** or the scalemic epoxyde **116**. They require:

(i) Stereocontrolled oxidation of its C,C double bond directed by the hydroxyl group and involving (a) '*anti*-addition' of (α) dibromine (Scheme 36, entry a) leading to the β,γ-dibromo cyclohexanol **113** or (β) hypobromous acid leading to regioisomeric bromohydrins **116** and **117** (Scheme 36, entries b and c) or (b) '*syn* addition' for the production of the epoxyde **118** (Scheme 36, entry d). Alternatively the synthesis of bromohydrins **116** and **117** has been achieved from **118** by epoxyde ring opening (Scheme 36, entry d).

(ii) Oxidation of original carbinol moiety of **113**, **116**, **117** and **118** to the corresponding compounds **110**, **119**, **120** and **121,** all possessing a carbonyl group. As expected oxidation, of **116** or **117** to **119** or **120** was not easy due to the presence of a second alcohol functional group.

(iii) Cyclization taking advantage of the base promoted enolization on the methylene group alpha to the carbonyl carbon of **110**, **119**, **120** and **121**. This requires at first the activation of the hydroxyl group present in **119** and **120** and is expected to be particularly difficult in the case of **121** due the improper alignment and the strain which should result from the ring opening of epoxyde in the bicyclic structure.

(iv) Fragmentation reaction implies that the hydroxide ion acts as a nucleophile on the carbonyl group of **110** and **120** and requires to be successful on **119** as well as on the product resulting from the ring opening of the epoxyde **121** after activation of the remaining hydroxyl groups.

We have therefore adapted accordingly the synthetic routes to scalemic (1*R*)-*cis*-chrysanthemic acid (1*R*)-**2b** from scalemic homoallyl alcohol (*S*)-**112** disclosed in Scheme 36.

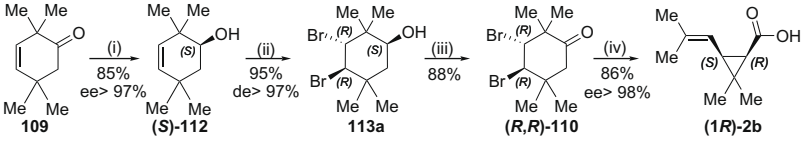
We have been able to control the stereochemistry of addition of the bromine and the hydroxide moieties to the scalemic homoallyl alcohol (*S*)-**112**[61] or its acetate **122**[59,61] but have been unable to control the regiochemistry of the reaction of N-bromosuccinimide (NBS) in acetone which produces a mixture of the two regioisomers of bromohydrins **123** and **124** (**123**/**124** ratio: 65/35) (**123** ee: 70%, **124** ee: 83%) (Scheme 37).

We have however used this mixture of regioisomers to produce (1*R*)-*cis*-chrysanthemic acid **(1*R*)-2b** in few steps.[59] This transformation which is disclosed in Scheme 38 involves:

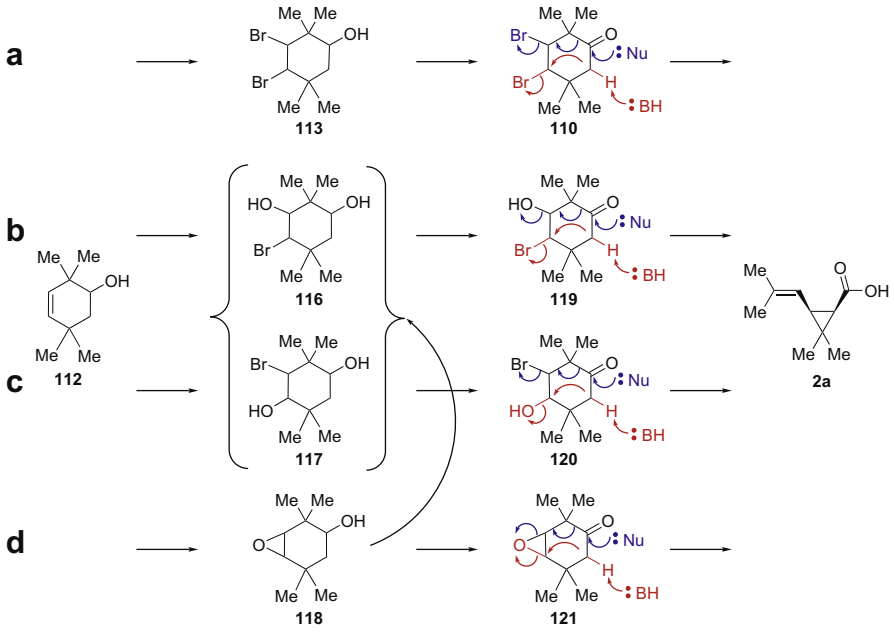
(i) Transformation of the mixture of bromohydrins **123** and **124** to the mixture of their mesylates **127** and **128**.

(ii) Smooth deprotection of the acetate moieties of the latter and oxidation of the resulting alcohols to the mixture of the corresponding ketones **131** and **132**.

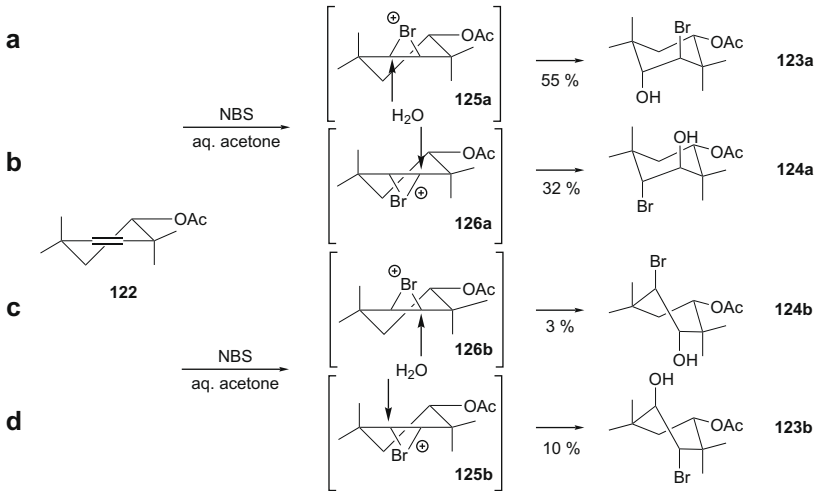
(iii) Treatment of the mixture of **131** and **132** with the Gassman reagent[46a] to effect consecutively (a) the intermediate formation of cyclopropane ring leading to the mixture of (*S*)-**111** and (*S*)-$\mathbf{81_{Ms}}$ and the Grob type fragmentation[46b] leading after acid hydrolysis to the desired compound (1*R*)-**2b** in modest yield (64%) and ee (76%).



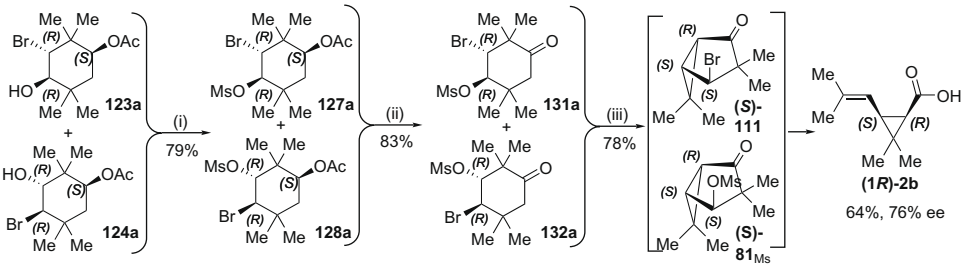
Scheme 34. Reagents and conditions: (i) (a) 1.05 equiv (−)-Ipc_2BCl, neat, 25 °C, 48 h (b) 2.2 equiv diethanolamine, Et_2O, 25 °C (ii) 1 equiv Br_2, 0.3 h, CH_2Cl_2, −95 °C; (iii) PDC, CH_2Cl_2, 20 °C, 0.3 h; (iv) (a) *t*-BuOK/H_2O: 7.6/2.3, THF, 20 °C, 0.5 h (b) aq HCl.



Scheme 36.



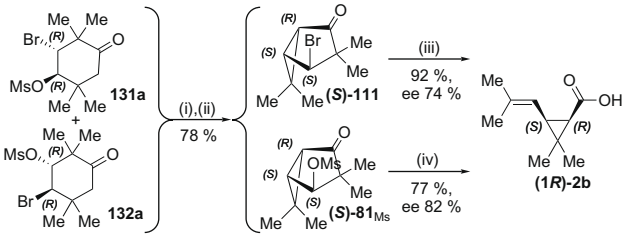
Scheme 37.



Scheme 38. Reagents and conditions: (i) 2 equiv MsCl, 2 equiv NEt_3, 0.2 equiv DMAP, CH_2Cl_2, −10 to 20 °C, 5.5 h; (ii) (a) K_2CO_3, THF–MeOH, 20 °C, 5.5 h (b) 1.4 equiv PDC, M.S. 4A, CH_2Cl_2, 0–20 °C, 4 h; (iii) (a) 7.6 equiv *t*-BuOK, 2.3 equiv H_2O, THF, 20 °C, 2.5 h (b) aq HCl.

Alternatively, using potassium hexamethyldisilazide (KHMDS) we have been able to produce the mixture of the bicyclic bromide (*S*)-**111** and mesylate (*S*)-**81$_{Ms}$** which have been easily separated by chromatography on silica gel and have been then subjected separately to the fragmentation reaction using the Gassman reagent. Apparently best yields have been obtained in THF from (*S*)-**111** and in DMSO for (*S*)-**81$_{Ms}$** (Scheme 39).

2.1.2.3.6.6.2. Involving the intermediate synthesis of epoxydes. The synthesis of bromohydrins can be achieved via epoxyde ring opening from **121**. Stereoselective epoxidation of the scalemic homoallyl alcohol (*S*)-**112**[61] was not so easy. Reaction of *m*-CPBA proved to be completely unselective[62,64a] and leads to a 1/1 mixture of the two 3,4-oxido-2,2,5,5-tetramethyl-cyclohex-1(*S*)-enols **118a** and **118b** in excellent yield (81 %, Scheme 40) resembling the approach



Scheme 39. Reagents and conditions: (i) 1.2 equiv KHMDS, THF, 0 °C, 0.5 h; (ii) separation using silica gel and ether pentane as eluant; (iii) (a) 7.6 equiv *t*-BuOK, 2.3 equiv H_2O, THF, 20 °C, 0.3 h (b) H_3O^+; (iv) (a) 7.6 equiv *t*-BuOK, 2.3 equiv H_2O, DMSO, 20 °C, 0.4 h (b) H_3O^+.

involving NBS which produces the corresponding bromonium ions **125** and **126** and which takes place without stereocontrol (Scheme 37). Several reagents have been tested but proved poor yielding and/or did not allow good stereocontrol.[62] Even the Sharpless method that uses *t*-butyl hydroperoxide and vanadium bis-acetonyl acetonide[64b] was not efficient due to the competing formation of the epoxy-ketone **121**.[62,64b] We finally found that the synthesis of **118a** can be achieved in good yield (88 %) and very high diastereoselection (**118a**/**118b**: 98/2) using another Sharpless method[64b] involving molybdenum hexacarbonyl as catalyst (Scheme 40).

Epoxyde ring opening in **121a** is not regioselective and produces a 43/57 mixture of the diastereoisomers **131a**/**132b** from which, using the same set of reactions as described in Scheme 38 and Scheme 39, *cis*-chrysanthemic acid **2a** is produced.

If (*S*)-**111** and (*R*)-**81$_{Ms}$** which are pseudo-enantiomers are not separated, *cis*-chrysanthemic acid **2a** is generated in good yield but with extremely low enantiomeric excess. Separation of (*S*)-**111** and (*R*)-**81$_{Ms}$** mixture is very easy due, as already disclosed in a related case (Scheme 39), to the higher polarity on silica gel of the sulfonate (*R*)-**81$_{Ms}$** compared to that of the bromide (*S*)-**111**. On reaction with the Gassman reagent, (*S*)-**111** leads[46a,47] to (1*R*)-*cis*-chrysanthemic acid (1*R*)-**2b** whereas (*R*)-**81$_{Ms}$** produces[62] its enantiomer the (1*S*)-*cis*-chrysanthemic acid (1*S*)-**2b** (Scheme 40). Those have been transformed[62] to deltamethrin **1c** and *S*-bioallethrin, respectively, as already mentioned in Scheme 7.

Another even more challenging transformation of the scalemic homoallyl alcohol (*S*)-**112** to (1*R*)-*cis*-chrysanthemic acid (1*R*)-**2b** has been successfully achieved and is described in Scheme 41.[63]

It takes advantage to the observation that the epoxyde ring of scalemic epoxy-alcohol **118a** can generate, under suitable conditions, regio- and stereo-selectively the bromohydrin **116b** and, after regioselective oxidation, the corresponding ketone **119b**.

Challenging chemoselective transformation of **119b** to the bicyclic β-ketomesylate (*S*)-**81$_{Ms}$** has been successfully performed and allow using the methods and reagents already described to achieve the synthesis of (1*S*)-*cis*-chrysanthemic acid (1*S*)-**2b**.

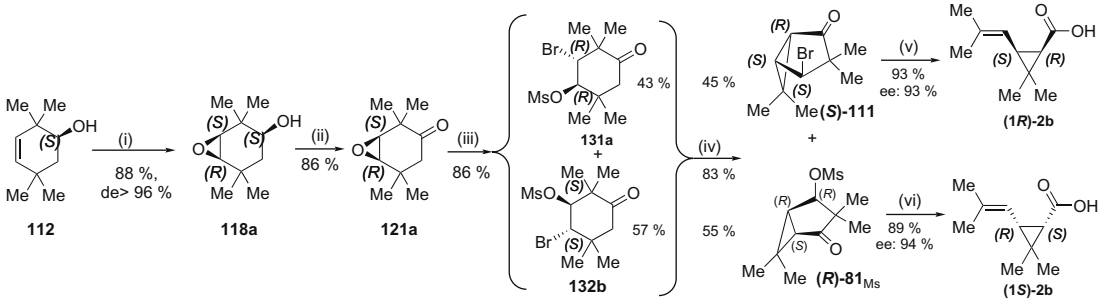
This published synthetic route to (1*S*)-*cis*-chrysanthemic acid (1*S*)-**2b** can be used for the synthesis of (1*R*)-*cis*-chrysanthemic acid (1*R*)-**2b** starting from (1*R*)-2,2,5,5-tetramethyl-cyclohex-3-enol (1*R*)-**112** which should be achieved by enantioselective reduction of 2,2,5,5-tetramethyl-cyclohex-3-enone **109** using instead (+)-*B*-chlorodiisopinocampheylborane.[60]

Successful transformation involves:

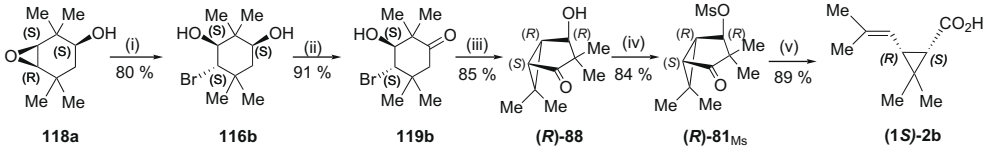
(i) Regioselective epoxide ring opening of **118a** to **116b** has been successfully achieved using the titanium isopropoxide and bromine couple which is expected to produce $BrTi(OiPr)_3$.[65a] It proved to be, among the various reagents tested, the only one which delivers **116b** in extremely good yield and with high regiocontrol. For example, titanium tetrabromide[65b,c] mainly provides the bromohydrin **117a** possessing the unwanted regiochemistry ($TiBr_4$, 0–20 °C, 5 h, **116b + 117a** in 87% yield, **116b**/**117a**: 32/68, Scheme 42, entry a).

(ii) Chemoselective oxidation of the alcohol whose hydroxyl group is the farthest to the halogen atom in **116b** to the ketone present in **119b** without oxidation of the other alcohol (Scheme 41 and 42, entry b). Jones' reagent proved to be the only one among the oxidants we tested to allow it.

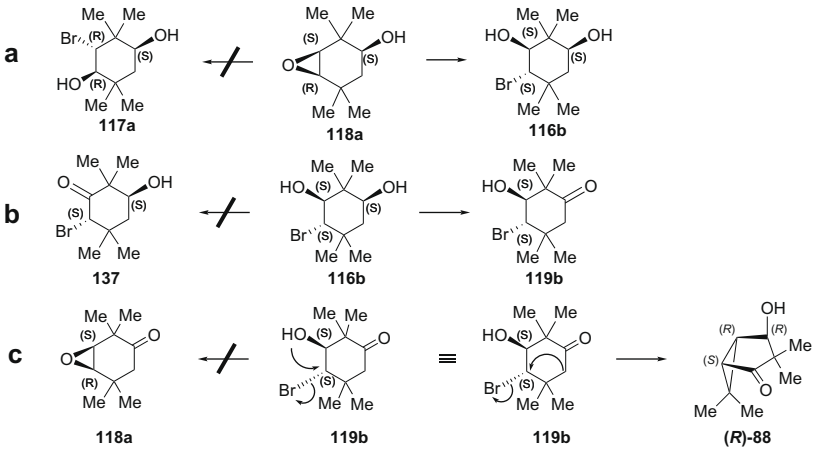
(iii) Selective cyclization of **119b** to (*R*)-**88** possessing the cyclopropane ring. For that purpose the 1,3-carbocyclization leading to the epoxide has to successfully compete with the 1,3-*O*-cycloalkylation generating the epoxide ring present in **118a** (Scheme 42, entry c). This transformation is not a simple task since mono-metallation is expected to occur under kinetically controlled conditions at the hydroxyl hydrogen rather than alpha to the carbonyl



Scheme 40. Reagents and conditions: (i) 1.5 equiv *t*-BuOOH, 0.015 equiv $Mo(CO)_6$, C_6H_6, 80 °C, 2 h; (ii) PDC, CH_2Cl_2, 20 °C, 0.33 h; (iii) (a) 0.5 equiv $TiBr_4$, CH_2Cl_2, 20 °C, 2 h (b) 1.2 equiv MsCl, 1.5 equiv NEt_3, CH_2Cl_2, −10 to 0 °C, 5 h; (iv) 1.2 equiv KHMDS, THF, 0 °C, 1 h; (v) (a) 7.6 equiv *t*-BuOK, 2.3 equiv H_2O, THF, 20 °C, 0.6 h (b) aq HCl; (vi) (a) 7.6 equiv *t*-BuOK, 2.3 equiv H_2O, DMSO, 20 °C, 0.6 h (b) aq HCl.



Scheme 41. Reagents and conditions: (i) $(Ti(OiPr)_4/Br_2$, CH_2Cl_2, 0–20 °C, 5 h; (ii) 0.66 equiv H_2CrO_4, acetone, 0 °C, 0.75 h; (iii) 2 equiv LiTMP, reverse addition, −25 °C, 1 h; (iv) 1.1 equiv MsCl, CH_2Cl_2; (vi) 7.6 equiv *t*-BuOK, 2.3 equiv H_2O, DMSO, 20 °C, 0.5 h; (vii) aq HCl.



Scheme 42.

group of **119b** suggesting that the unwanted epoxide **118a** will be produced at the expanse of (*R*)-**88** (Scheme 42, entry c). We have found that carbocyclization can be exclusively achieved using a stoichiometric amount (2 equiv) of a strong base at the express condition that the base is always present in excess. This has been successfully achieved by adding **119b** to LiTMP and not the reverse. Poorer results have been observed with lithium diisopropyl amide (LDA) and especially with lithium hexamethyl disilazide (LiHMDS). Use of lithium base is crucial for cyclopropanation since the epoxide **118a** is formed in very high yield when KHMDS is used under similar conditions.

2.1.2.3.6.7. Involving α,α'-dibromo-dimethyl dimedone. We have finally devised a new route to (1*R*)-*cis*-chrysantemic acid (1*R*)-**2b** then to deltamethrinic acid **4** which is disclosed in Scheme 43, entry b.[61b] It involves the α,α′-dibromination of the β-diketone **85** followed by enantioselective metallation/cyclization reaction of the α,α′-dibromo-cyclohexadione **133** which produce scalemic bicyclic β-diketone (*S*,*S*)-**134**.

This approach has to be compared to that schematized in Scheme 43a, already commented in Scheme 30, which involves the formation of the prochiral bicyclic β-diketone **84** which is then metallated to produce scalemic **100**. It offers the advantage over the latter to produce the α,α′-dibromo-cyclohexadione **133** the precursor of (*S*,*S*)-**134** in much better yield (93%) that the one involving its monobromination which leads to **86** (63% yield), the direct precursor of **84** (see Scheme 27, entry a).

The metallation of **133** provides a chiral enolate which by cyclization is expected to produce (*S*,*S*)-**134** or/and its enantiomer (*R*,*R*)-**134** depending on the nature of the chiral base used.

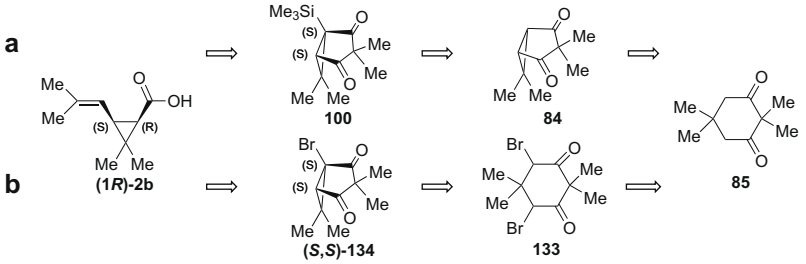
A rapid preliminary screening performed with a series of achiral and chiral bases has shown than lithium amides are not appropriate for cyclopropane ring formation since Br/Li exchange leading finally to the α-bromo-diketone **86** (see for example Scheme 27) competes with the H/Li exchange expected to produce the three membered cycle by intamolecular carbocyclization.

Potassium bases such as, for example, potassium hexamethyldisilazide (KHMDS) even at low temperature (−78 °C) efficiently metallate **133t** (H/K Exchange).[61b] Methanolysis of the resulting mixture at this temperature does not allow the carbocyclization reaction, expected to lead to **134**, to take place. It instead produces the *cis*-α,α′-dibromo-cyclohexadione **133c** almost quantitatively and with very high stereocontrol.[61b]

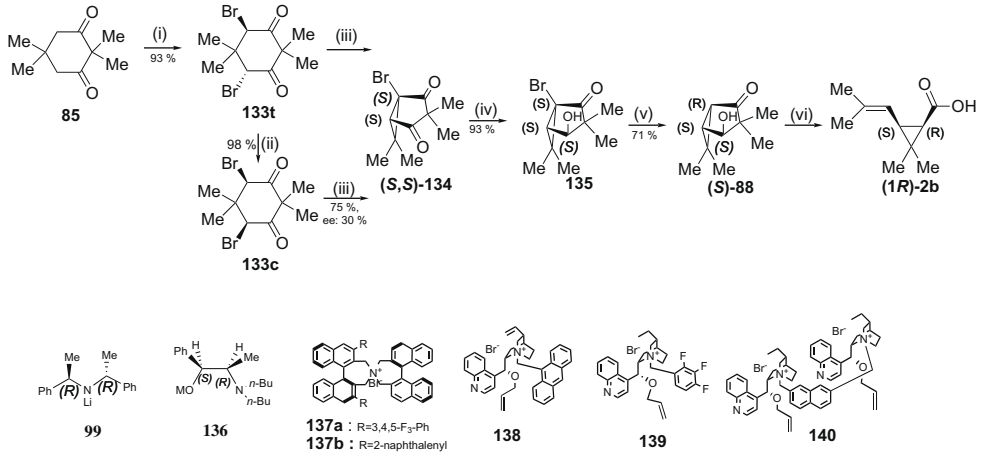
The desired carbocyclization, leading to **134** has been achieved from that stage by rising the temperature at around 0–15 °C (Scheme 44). Alternatively the synthesis of **134** has been also achieved in 92% yield, by direct metallation of **133** by KHMDS or KOH at room temperature (1.3 equiv solid KOH, THF, 20 °C, 4 h). Chiral bases such as **99** or **136** did not achieve the desired transformation of **133** to **134** but this was successfully performed by sodium hydroxide (50% aqueous) in the presence of a chiral ammonium salts acting as phase transfer catalysts (**137**–**140**, Scheme 44). Unfortunately however the enantioselectivity is usually very poor in all the cases except when using the BINAP derived catalyst **137a** which leads to the (*S*,*S*)-**134** unfortunately in modest enantiomeric excess.

Transformation of the β-bromo-diketone **134** to the β-bromoketone **135** possessing the hydroxyl group in *exo*-position has been successfully carried out using sodium borohydride–cerium trichloride mixture according to the protocol used to transform **84** to **88** (Scheme 27).

The Br/H exchange at bridgehead of **135** was not, as we expected, as easy as for straight chain β-bromo-ketones and the presence of the aldol moiety adds to the difficulties. Tributyltin hydride however reduces **135** to (*S*)-**88** very efficiently (1.1 equiv Bu_3SnH, 0.1 equiv AIBN, benzene, reflux, 5 h, 71% yield) and achieves the formal synthesis of (1*R*)-*cis*-chrysanthemic acid (1*R*)-**2b** (Scheme 44).



Scheme 43.



Scheme 44. Reagents and conditions: (i) 2 M equiv Br_2, CCl_4, 0 °C, 1 h; (ii) (a) 1.1 equiv KHMDS, THF, −78 °C, 2 h (b) methanolic HCl, −78 °C; (iii) 0.01 equiv **139a**, 50% aq KOH, toluene, 0 °C, 6 h; (iv) 1 M equiv $NaBH_4$, 1 M equiv $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C, 0.3 h; (iv) 1.1 equiv Bu_3SnH, 0.1 equiv AIBN, benzene, reflux, 4 h.

In conclusion we have described several methods which allow the enantioselective synthesis of deltamethrinic acid part of a commercially valuable insecticide whose market is about 1.5 billion dollars/year. We took this opportunity to disclose some efficient synthetic reactions. The last notion can only be related to an economical aspect.[66] It implies to take into account regio- and stereochemical problems, atom economy, the rejection of as little waste as possible by recycling for example the unwanted chemicals, and use of safe and reproducible processes.[66]

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