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Review

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Pyrethroid insecticides. Chapter II: Synthesis of rethrolones

Alain Krief

University of Namur, and International Organization for Chemical Sciences in Development (IOCD), 61 Rue de Bruxelles, B-5000 (Namur), Belgium
Email: alain.krief@unamur.be

To the memory of the late Dr Gérard Nominé and late Dr Gofu Suzukamo, Research Directors of Roussel Uclaf (France) and Sumitomo (Japan) Companies, for sharing their enthusiasm for organic chemistry

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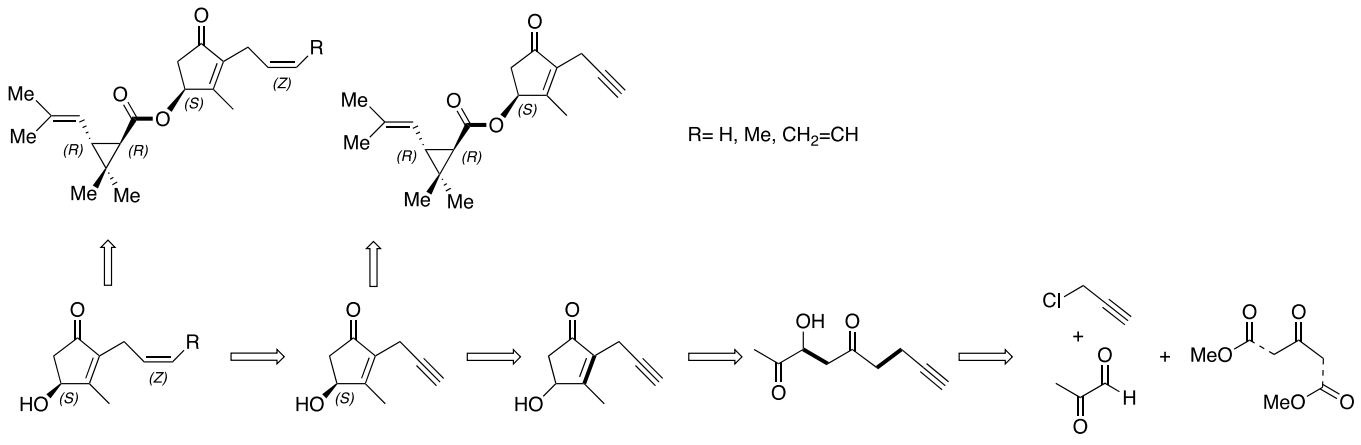
Abstract

The various syntheses of rethrolones, γ-hydroxycyclopent-2-enones possessing an unsaturated side chain at C-2, are precursors of natural pyrethrins as well as unnatural analogues possessing at C-2 a less elaborated propenyl or propynyl side chain, are discussed and compared. They usually involve a decarboxylative aldol reaction involving methylglyoxal, followed by a regioselective intramolecular aldolization-crotonization reaction. Racemic compounds have been resolved, especially by lipases, and the unwanted enantiomer recycled, often *in situ*, by epimerization. Prallethrolone possessing the propynyl side chain at C-2 on the cyclopentenone is a key intermediate to access all the other rethrolones.



Keywords: Aldol reactions, decarboxylative aldol, intramolecular aldol, alkyne-Z-alkene reduction, alcohol resolution with lipase

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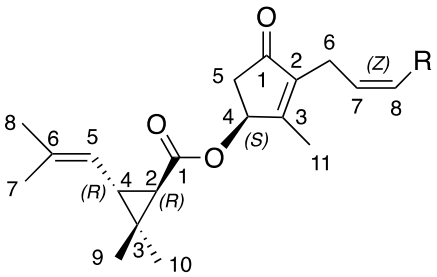
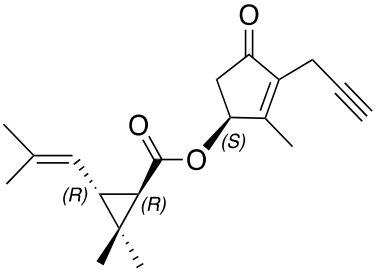
1. Introduction

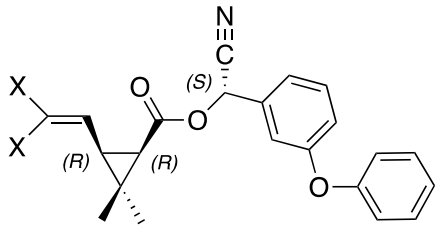
As was pointed out in the first chapter,[1] pyrethrins (natural) and pyrethroid (synthetic/non-natural) insecticides **1** can be divided into two classes: (i) those that are degraded readily (half-life of several days) and are used as household insecticides, such as **1a**, **1b**, **1c**, **1d**, **1d'** (Figure 1) and (ii) those that keep their insecticidal properties much longer (half-life of several weeks) and are widely used in agriculture, such as **1e**, **1f** (Figure 1).



1a Pyrethrin I, R= $CH=CH_2$
1b Cinerin I, R= Me
1c Jasmolin I, R= Et
1d Allethrin, R= H



1d' Prallethrin



1e Cypermethrin, X= Cl
1f Deltamethrin, X= Br

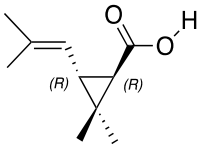
Figure 1. Structures of some of the most bioactive natural and synthetic pyrethrins and pyrethroids. Note that due to CIP priority rules, the (1*R*,3*R*) nomenclature refers to the *trans*-pyrethrin and *trans*-allethrin stereoisomers but to the *cis*-cypermethrin and *cis*-deltamethrin stereoisomers.

In fact, the former series involves: (i) the natural products **1a**-**1c** that have less economic value but have been of great academic and industrial interest, being at the source of the innovation and the basis of all the work carried out in the field; and (ii) some unnatural compounds such as allethrin (**1d**) and especially enantiopure (*S*)-bioallethrin (*S*)-**1d**, and prallethrin **1d'**, especially enantiopure (*S*)-prallethrin (*S*)-**1d',** that are commercially valuable for use in a domestic context. The amount of insecticide needed is far more important for agricultural use than when for domestic purposes; however, cost/kg brought by the latter is much greater /by far the more important.

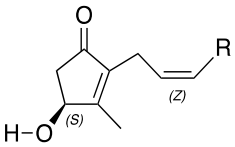
Although both series belong to the family of cyclopropanoic esters, the constituents of the "domestic" series possess the same vinylcyclopropanecarboxylic moiety (*gem*-dimethylvinylcyclopropanecarboxy group) but differ in the nature of their alkoxy moieties **3a**-**3d** and **3d'** (Figure 2); the compounds of the "agricultural" series possess different vinylcyclopropanecarboxylic moieties (*gem*-dichloro- or *gem*-dibromo-vinyl-cyclopropanecarboxy groups), but all possess the same alkoxy moiety related to 3-phenoxymandelonitrile **3e**.

The alkoxy-groups of both behave differently, since whereas **3a**-**3d** and **3d'** are quite stable especially in basic media, **3e**, a cyanohydrin is in equilibrium with the corresponding aldehyde and hydrogen cyanide. They however share some striking similarity. Their oxygen atom is attached to a (*S*)-configurated carbon center that is either allylic (**3a**-**3d, 3d'**) or benzylic (**3e**).

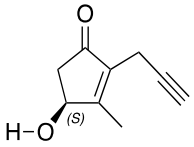
The strategies used for the synthesis of each of the two series are different but often involve parallel approaches. This is particularly true for the synthesis of enantiopure alcohols and cyanohydrins, with separation of the racemates, especially using lipases, and recycling of the unwanted enantiomers or diastereoisomers, especially by epimerization.



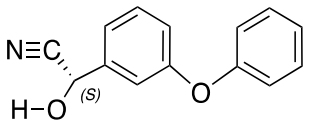
2a
Chrysanthemic acid



3a Pyrethrolone, R= vinyl
3b Cinerolone, R= methyl
3c Jasmololone, R= ethyl
3d Allethrolone, R= H,



3d' Prallethrolone



3e 3-Phenoxy mandelonitrile

Figure 2. Structures of the acid and alcohols and cyanohydrin components of some natural and synthetic pyrethrins and pyrethroids.

This chapter deals with the synthesis of racemic as well as enantiopure cyclopentenolones **3a**, **3b**, **3c**, **3d** and **3d'** (Figure 2). We shall present an account of the syntheses of 3-phenoxymandelonitrile **3e** in the next chapter. The reaction of the alcohols with the vinylcyclopropanecarboxylic acids or their activated analogs such as (i) their acid chlorides with the related alcoholates, or (ii) their metal carboxylates and the corresponding sulfonates or the related chlorides, will be related in a subsequent chapter.

2. Generalities Concerning Rethrolones as Partners in Pyrethrin and Pyrethroid Synthesis

The representative alcohols of this series[1] are the enantiopure pyrethrolone **3a**, precursor of natural pyrethrin I **1a**, the related allethrolone **3d** that lacks the terminal vinyl group and is the precursor of the commercial allethrin **1d** as a racemate, or (*S*)-bioallethrin that exclusively involves its (S)-enantiomer, and prallethrolone **3d'**,

precursor of prallethrin **1d'**. Racemic prallethrolone **3d'** proved also to be an excellent precursor of (i) related allethrolone **3d**, jasmololone **3c**, cinerolone **3b** pyrethrolone **3a**, (ii) enantiopure (*S*)-allethrolone (*S*)-**3d** as well as (*S*)-prallethrolone (*S*)-**3d'**, (*S*)-jasmololone (*S*)-**3c**, (*S*)-cinerolone (*S*)-**3b**, and (*S*)-pyrethrolone (*S*)-**3a** as will be discussed below.

All those rethrolones possess in common a pentacyclic conjugated enone moiety substituted at C-3 by a methyl group and at C-4 by a hydroxyl group. They all possess a chiral carbon at C-4, the (S)-enantiomer being the precursor of the related most biologically active insecticides.[1] Those rethrolones however differ by the side chain attached at C-2. Those are allylic (**3a**-**3d**) or propargylic (**3d'**) in nature and in case of the natural products (**3a**-**3c**) all possess a Z-disubstituted C=C double bond.

Natural rethrolones possess two asymmetric centers one at the carbon bearing the hydroxyl group that is (*S*)-configurated and that of the side chain that as already mentioned is (*Z*)-configurated. Unfortunately however, the correct stereochemistry at both sites was not properly determined until quite lately.[1] Thus many of the early reported syntheses of racemic compounds proved to be incorrect since they bear the *E*-instead of the required Z-olefinic moiety. In many instances, the strategy used to build their skeletons could be applied to produce the natural diastereoisomer and therefore we have included some of these to offer a wider overview. Allethrolone **3d** and prallethrolone **3d'** have attracted the most attention due to their economic value arising from the absence of stereochemistry on their side chains that simplifies their syntheses, and the discovery that the biological activity of their allethrin **1d** and prallethrin **1d'** esters is closely related to that of the natural products **1a**-**1c** (Figure 1). Furthermore, prallethrin **1d',** especially its (*S*)-**1d'** enantiomer, has proved to be a valuable precursor of **1a**-**1c**.

3. Synthetic Strategies in the Synthesis of Rethrolones

The strategies used for the synthesis of the requested rethrolones are outlined in retrosynthetic convention in Scheme 1. Except in the case of entry f, they involve the formation of the five-membered ring by carbocyclization, either at an early, or in the last, stage of the synthesis.

The strategies in Scheme 1 have been organized in 8 subsections, in which the rethrolones **3** are synthesized by:

5.1. Carbocyclization involving an aldolization-crotonization reaction of 3-hydroxy-2,5-diketones (Scheme 1, entry a), forming the Cf=Cb double bond;

5.2. Isomerization of iso-rethrolones **7** (Scheme 1, entry b), forming the Cf–Cb single bond;

5.3. Synthesis of the rethrolones **3** by carbocyclisation of 1,4-ketoaldehydes (Scheme 1, entry c); forming the Cc–Cd bond;

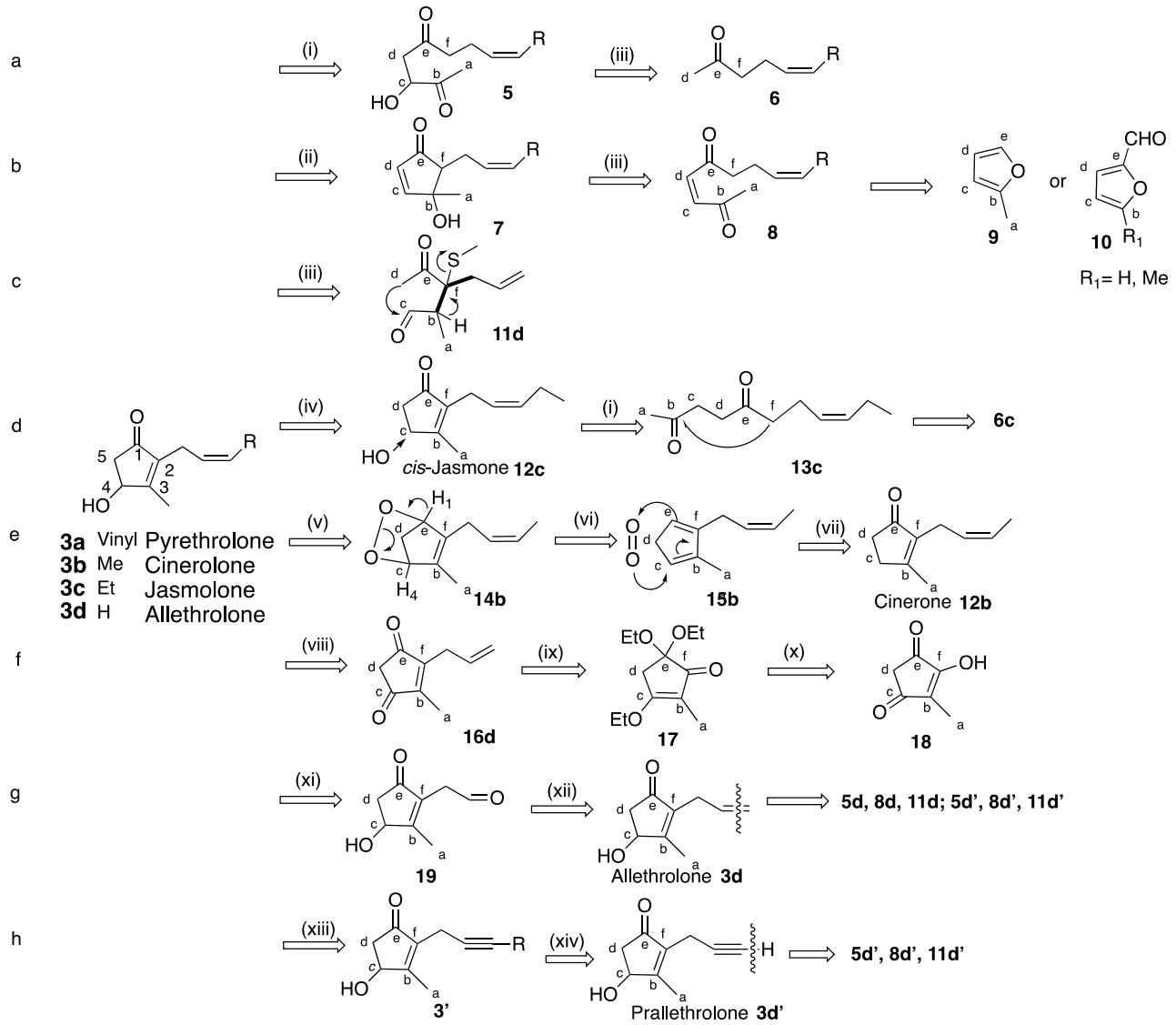
5.4. Oxidation at Cc of preformed rethrones **3"** (Scheme 1, entry d);

5.5. Oxidation at Cc and Ce positions of a cyclic diene **15** produced from rethrone **3"** (Scheme 1, entry e);

5.6. Regioselective reduction of cyclopentene-2,4-diones **16** bearing the required appendages at Cb and Cf (Scheme 1, entry f);

5.7. Stereoselective synthesis of their side chain from allethrolone **3d** by degradation and rebuilding its allylic side chain (Scheme 1, entry g);

5.8. Stereoselective synthesis of their side chain from prallethrolone **3d'** by sequential metalation, vinylation and hydrogenation of its side chain (Scheme 1, entry h).



Scheme 1. Synthetic strategies applied to rethrolones (i) Aldol condensation-crotonization (ii) isomerization (iii) aldol condensation/olefin synthesis (iv) Selective allylic oxidation (v) Peroxide cleavage (vi) 2+4 Cycloaddition of singlet oxygen (vii) (a) 1,2 Hydride reduction of enone (b) Acid catalyzed dehydration of sec-allyl alcohol (viii) Ketone carbonyl group regioselective reduction by metals of α,β-enedione (ix) (a) Organometallic addition to carbonyl compounds (b) Acid catalyzed hydrolysis of acetals to carbonyl compound and allylic hydroxy-substituted vinyl ether to α,β unsaturated ketone (x) ketone acetalization / vinyl ether from ketone to (xi) Wittig olefination reaction (xii) (a) Ozonolysis of olefin or oxidation of olefin to diol / diol cleavage (xiii) Dihydrogenation of alkyne (xiv) (a) terminal alkyne metallation (b) alkynyl metal alkylation (R= Me, Et) or vinylation reaction (R= vinyl).

These strategies will not apply as it is usually the case to a single compound but to a family of compounds, the rethrolones **3**, that only differ from each other by the nature of the side-chain attached at C-2 on the cyclopentane ring as discussed above. Each individual retrosynthetic scheme involves different type of starting materials and a series of different retrosynthetic steps (see caption to Scheme 1) that are quoted on each retrosynthetic arrow displayed in Scheme 1.

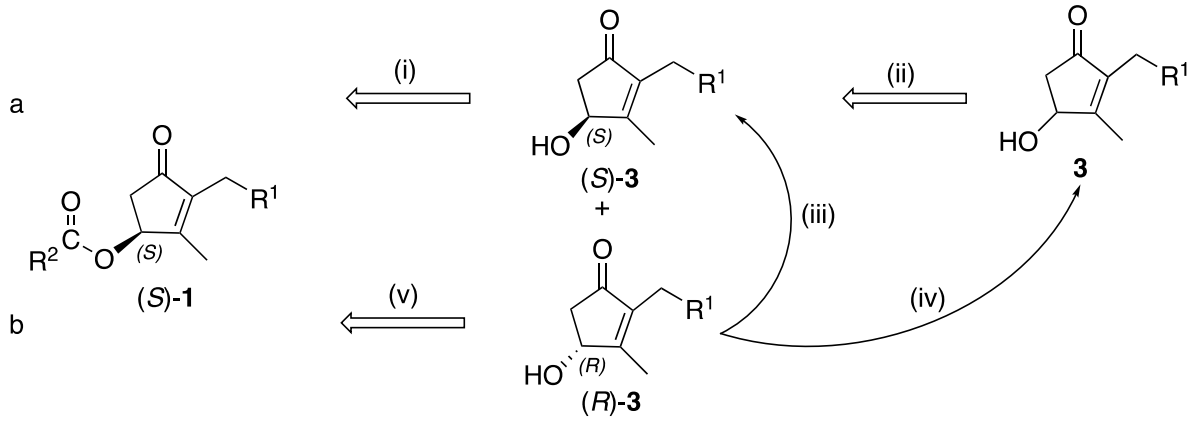
These retrosyntheses that are expected to apply to the different compounds listed (**3a**-**3d** and **3d'**) possess three common features that require: (i) access to the required (S)-stereoisomer at C-4; (ii) the control at an early

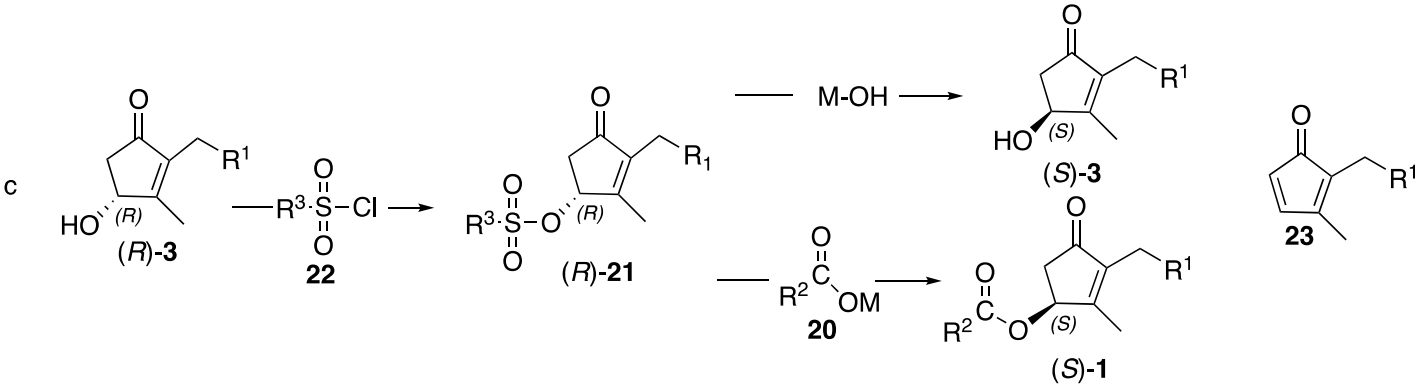
or last stage of the stereochemistry of the side chain attached to C2 on the cyclopentane ring if needed; and (iii) the construction of the five-membered cyclic ketone that allows at an early or late stage to introduce the side chains at C-2 and C-3, the hydroxyl group at C-4 and the unsaturation between Cb and Cf. Formation of the five-membered ring is also required for the synthesis of rethrones **12** from which rethrolones **3** could derive (Scheme 1 entries d and e). We will discuss in the first paragraph the problems encountered in each of those three topics and the solutions that have been proposed. We will then discuss in Sections 5.1 to 5.8 the synthesis of rethrolones according to the organization shown in Scheme 1.

4. Solutions to Generic Problems involved in the Synthesis of Rethrolones

4.1. Strategies to access enantiopure pyrethroids derived from (*S*)-rethrolones

Up to now, all the syntheses of rethrolones produce a racemate since the enantioselective syntheses published are far from efficient (Section 7). For that purpose, the desired (*S*) enantiomer is separated from the racemic mixture by resolution of the racemate either by crystallization of a related diastereoisomer or by kinetic resolution employing a lipase (Scheme 2, entry a).





Scheme 2. Overview of the synthetic strategies to access enantiopure rethrolones from racemic mixtures.

In both cases, the yield in the (*S*)-enantiomer (*S*)-**3** cannot exceed 50 % unless the (*R*)-enantiomer (*R*)-**3** after separation is recycled by net inversion of the configuration at the C-4 center (Scheme 2, (iii)). This has been effectively achieved by sequential activation of the hydroxyl group of (*R*)-**3**, for example as a sulfonate (*R*)-**21**, its further substitution with for instance an hydroxide or a carboxylate **20** including chrysanthemate or permethrinate (Scheme 2, entry c). Furthermore, each of the steps must be carried out with extreme care to avoid a competing elimination reaction to take place leading to the highly energetic "antiaromatic"

cyclopentadienone **23** (Scheme 2). Another approach involves the racemization of the residues from the resolution and repeating the resolution (Scheme 2, (iv)).

Specific results will be reported in Section 6.2**.**

4.2. Strategies to control of the *Z*-stereochemistry of the C-2 side chain of rethrolones and rethrones

The alcohols **3a**, **3b**, **3c** related to the natural pyrethrins possess side chain at C-2 of four- (**3b**) or five- (**3a**,**3c**) carbons that include at least one C=C double bond with the *Z*-stereochemistry. In the case of pyrethrolone **3a**, the C=C double bond is part of a 1,3-diene that brings an even higher degree of complexity for its synthesis.

Two different approaches have been used to synthesize them that either require the generation of the *Z*-C=C double bond early in the synthesis,[2] before the cyclization leading to the cyclopentenolone is achieved (Scheme 1, entries a-c), or at a late stage[3] (Scheme 1, entries g or h) from prallethrolone **3d'** or allethrolone **3d** as precursors. In each case two different strategies have been used (Scheme 3) that either involve the stereoselective *cis*-dihydrogenation of a built-in C≡C triple bond[2-5,77] (Scheme 3, Routes i) or an olefination reaction that brings together two sp^2 carbons to create the C=C double bond with the *Z*-stereochemistry either using a Wittig[2,6-11] (Scheme 3, Route ii) or a metathesis[12-15] (Scheme 3, Route iii) reaction.

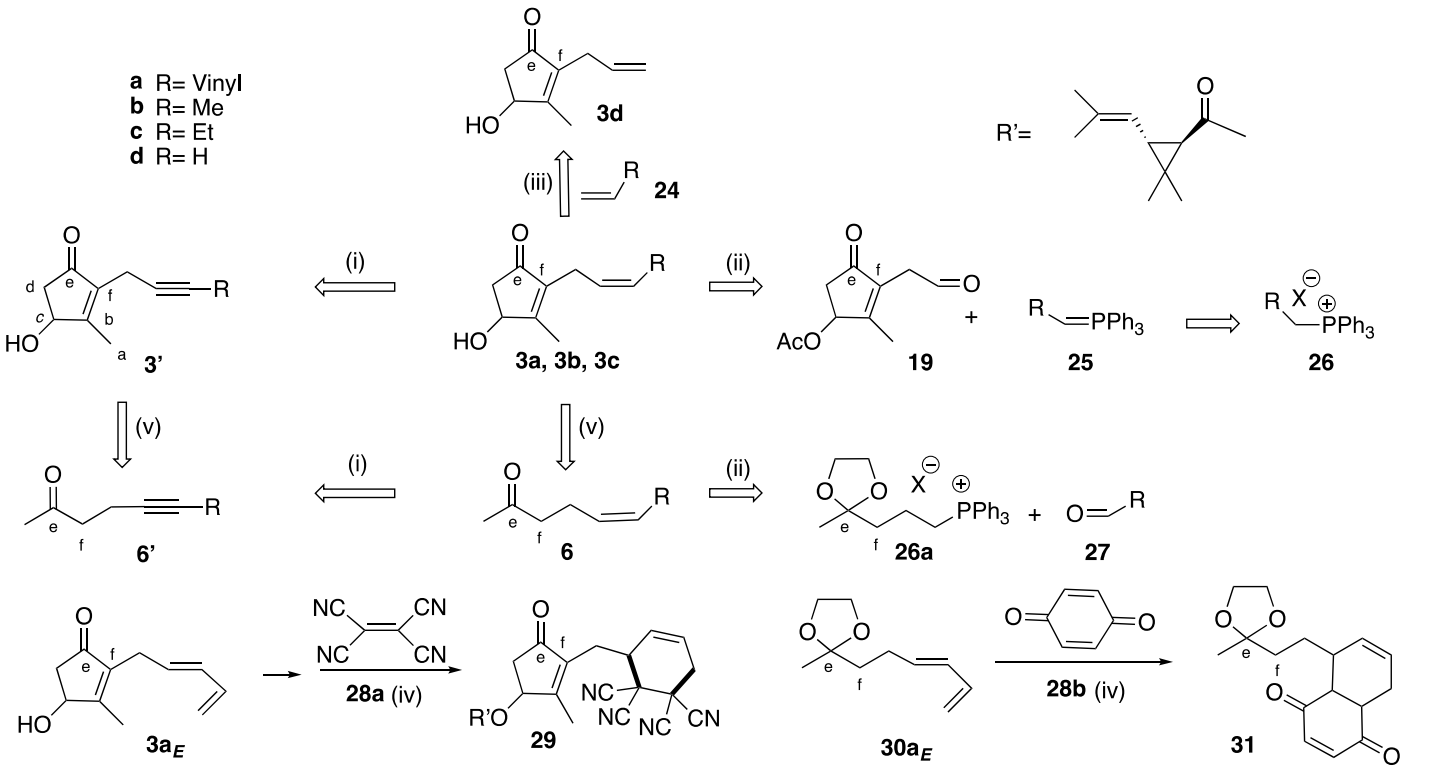
Each type of approach employs a different strategy for the construction of the carbon framework of the side chain. In the case of the Wittig reaction (Scheme 3, routes ii), it requires the presence of a formyl group on one side and a partner phosphonium salt on the other (Scheme 3, routes ii), and a terminal C=C double bond in case of a metathesis reaction (Scheme 3, routes iii). The approach involving a C≡C triple bond to build the side chain takes advantage of the easy metalation of terminal acetylenes and their efficient alkylation (for **3b**, **3c, 6b', 6c'**) or vinylation (for **6a'**) of the related organometallics (Scheme 3, routes i).

Each strategy possesses its advantages and its problems that will be commented upon here and discussed in more detail when specific examples will be considered.

Finally, the strategy developed to remove the unwanted stereoisomer that use the Diels-Alder reaction is shown in Scheme 3, route iv.

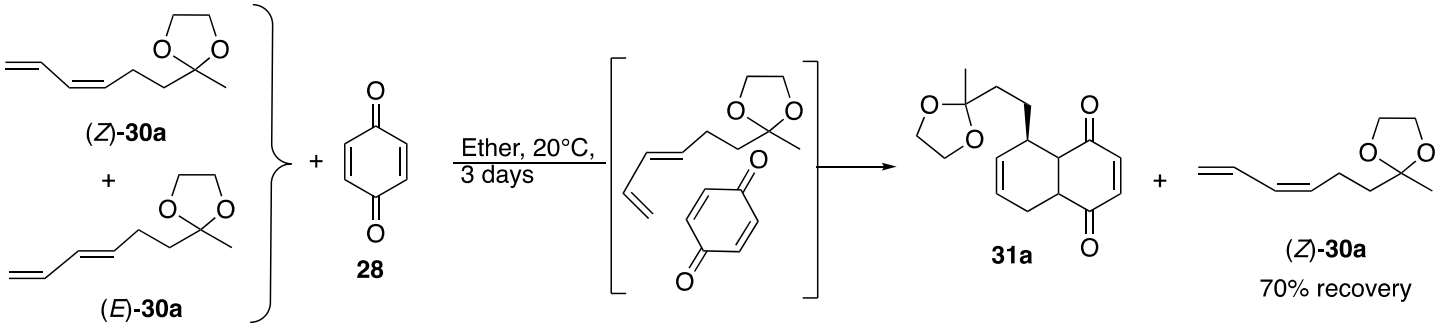
Monohydrogenation of a triple bond is not an easy task.[2-5] Reduction by metals usually leads to the formation of a C=C double bond with the *E*-stereochemistry,[16] and catalytic hydrogenation, although producing the Z-stereoisomer, is often contaminated by products resulting from over-hydrogenation. The use of Lindlar's[2-4,77] poisoned palladium catalyst to avoid over-reduction of the *Z*-unsaturated intermediate proved very efficient especially for the reduction of ynones **6'** or alkylated prallethrolone derivatives **3'** (Scheme 3, Routes i).[2,3,77] This reaction does not however apply to the reduction of the 1-en-3-yne **144**,[3] precursor of pyrethrolone **3a**, for which zinc/HCl in isopropanol[5] has proved to be the reagent of choice[3,77] (See below, Scheme 53, entry d) in a reaction that occurs stereoselectively.

The Wittig reaction is highly regioselective but does not usually proceed stereoselectively.[6] Nevertheless the "salt free" version, discovered by Schlosser[9] then revisited by Corey,[10,11] allows reasonable stereocontrol favoring the synthesis of the *Z*-stereoisomer of β-dialkyl substituted olefins (de: 88%).[2,7-11] This stereocontrol is effectively achieved by performing the metalation of the phosphonium salts with a base and in a medium in which the resulting salt (*viz.* sodium chloride, in benzene)[9] is insoluble and can be separated by filtration or using a solvent that sequesters the cation *in situ* (e.g. DMSO, dimsyl sodium or butyllithium in HMPA).[10,11] There is strong evidence that this very high stereocontrol involves the decomposition of a cis-oxaphosphetane resulting from the cycloaddition between the alkylidene phosphoranes **25** and the aldehyde **19**.[2] This control is particularly poor when it involves the allylic phosphonium salt **25a** (R= vinyl, Scheme 3) precursor of pyrethrolone **3a**, even when salt-free conditions are used.[2]



Scheme 3. Overview of strategies used to generate rethrolones possessing *Z*-side chains (a,b,c,d are related to the specific structures disclosed in this and other schemes. In the same family, ' refers to the acetylenic compounds and " to the saturated derivatives).

In fact, it is particularly difficult to isolate the pure *Z*-stereoisomer of **3b** or **3c** from a stereoisomeric mixture especially on a large scale. In the case of **3a**, the unwanted *E*-isomer **3a*E*** has been removed[2,8] from the medium by selective reaction with an electrophilic dienophile to specifically produce the Diels Alder adduct **29** or **31** (Scheme 3, routes iv), leaving untouched the **3a** *Z*-diastereoisomer that is unable, for steric reasons, to attain the *S*-cis conformation requested for the carbocyclization to occur.[17] The specific case of **30** is shown in Scheme 4.[2]



Scheme 4. Diels-Alder cycloaddition reaction allowing to remove undesired *E*-diene from their *Z*+*E*-mixture.

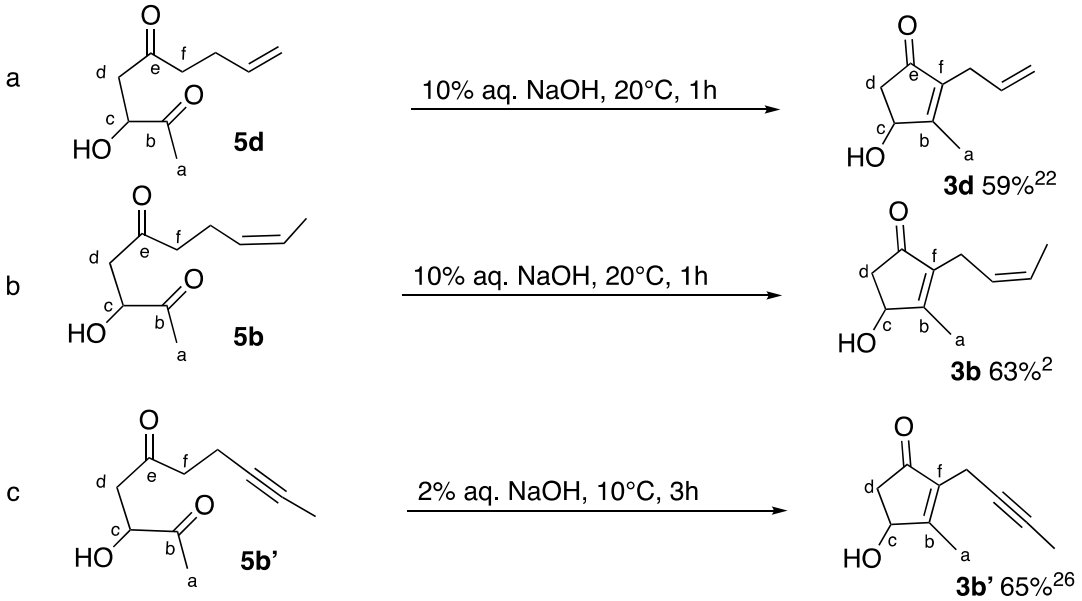
The cross-metathesis reaction would have been particularly attractive if it could have produced from the commercially available (S)-allethrolone **3d**, all the other enantiopure rethrolones **3a**, **3b** and **3c**. However,

although important progress has been achieved to favor the selective formation of the *Z*-stereoisomer, the less stable of the two, by selecting the adequate catalyst the sterocntrol is far from perfect.[13-15] Since the content of the patent did not provide a stereochemical information, and with regard to the knowledge available in the field, it seems highly improbable that the authors of the patent have achieved highly diastereoselective syntheses (Scheme 3 route iii; See below - Scheme 52).[12]

4.3. Strategy and practice involved in intramolecular aldol-reactions leading to rethrolones and rethrones

As already pointed out, all the syntheses of rethrolones **3** and **3'** related to the retrosynthetic Scheme 1, except the one shown in entry f, require at one or another stage the formation of the five-membered ring by carbocyclisation through an aldol reaction[18-20] that allows the formation of either the C_f–C_b bond (Scheme 1, entry a, route (i); entry b, route (iii)) or the C_c–C_d bond (Scheme 1, entry c, route (iii)). Those aldol reactions have also been used in the syntheses of natural pyrethrins shown in Scheme 1, entries g and f, that use the unnatural allethrin (Scheme 1, entry g) or prallethrin (Scheme 1, entry h) as starting materials. The aldol reaction has been also involved in the synthesis of rethrones **12**, especially jasmone **12c**, that have been used as precursors of rethrolones **3** (Scheme 1, entries d and e) as well as for the synthesis of earlier precursors of rethrolones such as the one allowing the synthesis of **5** from the methyl ketones **6** (Scheme 1, entries a, route (iii)).

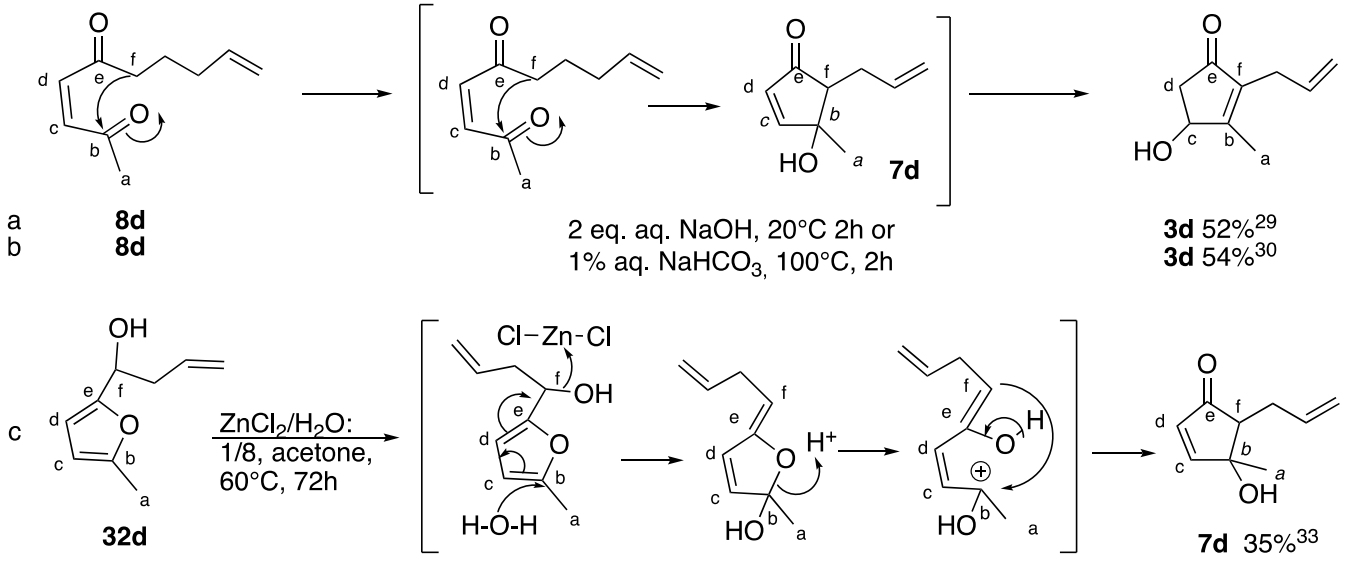
Most of the transformations described in this review use the aldol reaction and lead to to β-hydroxycarbonyl compound either under base or acid catalysis. They use the propensity of this reaction to revert, to equilibrate or to eliminate water to produce α,β-unsaturated carbonyl compounds through the crotonization reaction. The nature of the products as it will be reported depends upon the structure of the partners, the nature of the catalyst, the pH at which the reaction is carried out and the concentration of reactants. Although the use of metal hydroxides on the mixture of two carbonyl compounds often leads to an intractable mixture of compounds, separate formation of the enolate and its further reaction with the partner carbonyl compound can minimize the mixture and even allow the synthesis, at will, of one of the two diastereomers or even of a single enantiomer.[19]



Scheme 5. Aldolization-crotonization reactions leading to cyclopentenolones from 2-hydroxy-1,4-diketones.[2,22,26]

We especially report in this chapter the transformations of 3-hydroxy-2,5-ketoalkenes **5d** and **5b** (Scheme 5, entries a, b)[2,21-26] or -alkynes **5b'** (Scheme 5, entry c)[27] to the related cyclopentenones **3** especially those involved in the synthesis of pyrethrins **1a**-**1c** and pyrethroids **1d**,**1d'** or their precursors such as **5b'** precursor of **3b'** and finally to cinerolone **3b** (Scheme 5, entry b).[26] Those transformations involve the cascade aldol reaction followed by subsequent elimination of water (crotonization).

This process is also involved in the transformation of the related enedione **8** to rethrolones **3** and **3'** [28,29,30,31] that implies a different mechanism in which the aldol reaction is followed by a rearrangement (Scheme 6, entries a,b).[30,32,33] A related case disclosed in Scheme 6, entry c, involves an acid catalyzed furan ring opening followed *in situ* by an acid catalyzed aldol reaction.[33-36]

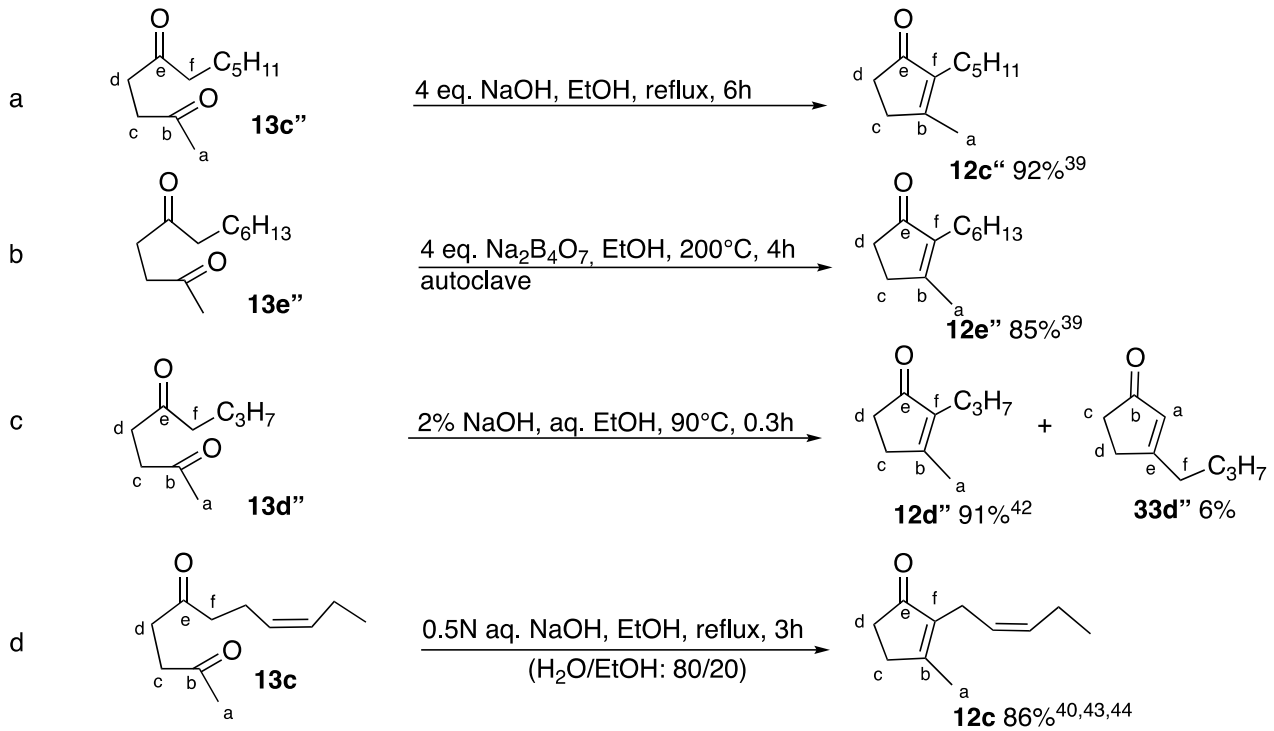


Scheme 6.[29,30,33] Regioselective aldolization of 1,4-enediones in basic and acidic media.

We have also included some information on the synthesis of related 1,4-diketones **13** lacking the hydroxyl group at C-3 of the precursor of rethrones[37-44] **12**, especially *cis*-jasmone **12c**,[40,42-44] a constituent of jasmine oil, an intermediate in the biosynthesis of pyrethrolone **3a** and jasmololone **3c**, and a potential precursor in the synthesis of the latter on oxidation at C-4 (Scheme 1, entry d). A similar process that involves sequential aldol and elimination reaction takes place on the related saturated 1,4-diketones **13**" (Scheme 7, entries a,b,c) and proved particularly valuable for determining the mechanism of those reactions.[37-39,41]

The carbocyclisation reaction of 5-oxo-methyl ketones has been originally described on saturated derivatives by Blaise[37] and extended later by Hunsdiecker.[38-40] It accepts wide structural variation (Schemes 5-7) but requires, as shown by Blaise,[37] Hunsdiecker[39] and LaForge,[22] the presence of one methylene at the C-6 carbon α to the carbonyl group (Cf-carbon).

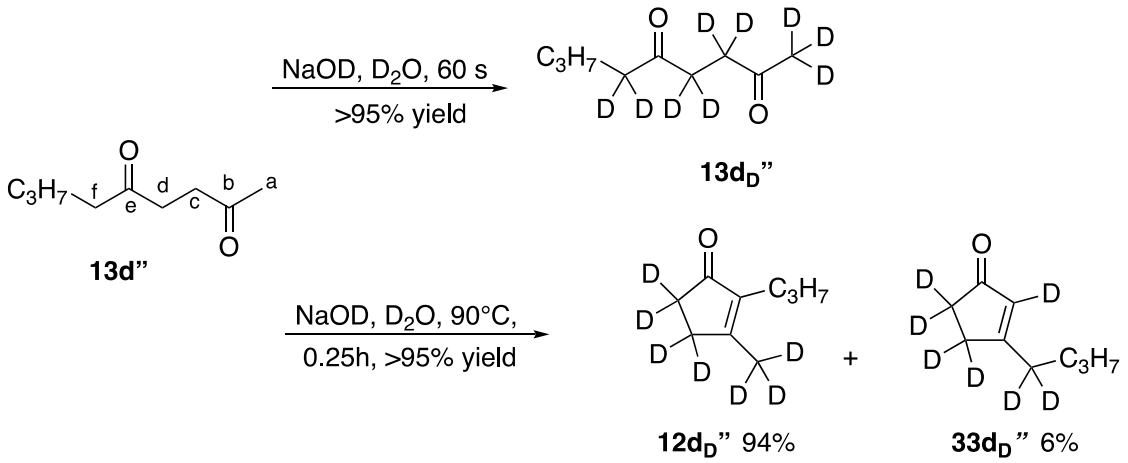
The reaction can be brought about with various bases such as sodium-, potassium-, or barium hydroxides but sodium hydroxide has been found to be the reagent of choice, better for example than potassium hydroxide.[23] The reaction is best carried out in water[23,39] or in a hydro-alcoholic solvent, at high dilution to avoid competing polymerization and in the presence of hydroquinone to avoid air oxidation. It usually takes place at low temperature (5-10°C) but has been also carried out at reflux of the solvent for a short period (1-2 h) (Schemes 5-7). It has also been achieved with piperidine[23] or borax[39] but in the latter cases requires a high temperature (200 °C) in an autoclave to proceed (Scheme 7, entry b).[39]



Scheme 7. Base promoted regioselective aldolization-crotonization of 1,4-diketones. [39,40,42-44]

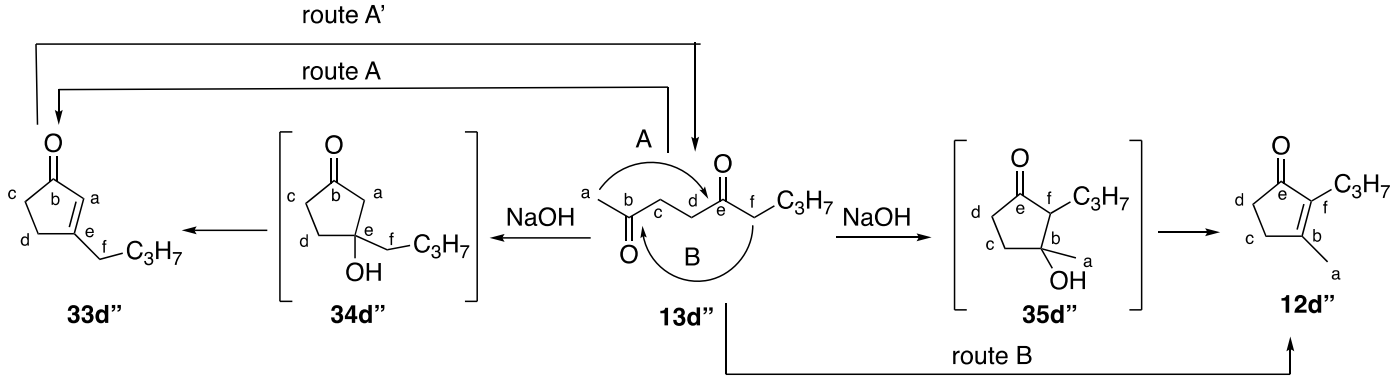
The reactions are highly regioselective since a single stereoisomer is usually formed (Schemes 5-7) and in only one case, the regioisomeric cyclopentenone **33d"** has been isolated, in trace amount beside the cyclopentenone **12d"** obtained in almost quantitative yield (Scheme 7, entry c).[41]

However, as expected, metalation of the diketone **13d"** with bases proved to take place at all enolisable carbons leading to the formation of the fully deuterated nona-2,5-dione **13d$_D$"** on reaction of **13d"** with sodium deuteride in deuterated water for even less than a minute (Scheme 8, entry a).[41] Performing the reaction for a little longer leads to deuterated cyclopentenones **12d$_D$"** and **33d$_D$"** in almost quantitative yields (0.25h, Scheme 8, entry b).[41] Those results clearly show that enolization is as expected reversible and cannot be construed as the product-determining step in the transformation of **13d"** to **12d"** and **33d"**.[41]



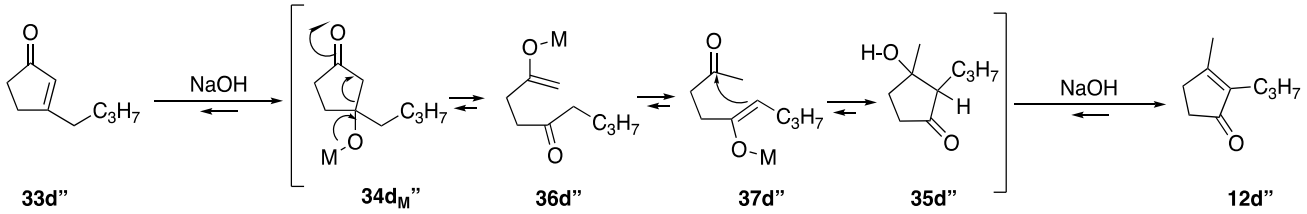
Scheme 8. Base-promoted regioselective aldolization-crotonization of nona-2,5-dione in deuterated medium.[41]

Failure to obtain substantial amounts of **33d"**, in base catalyzed reaction of **13d"** and related enones from 1,4-diketones **5** and **13** as well (Scheme 5, Scheme 7), could be explained by either of two hypotheses:[41] (i) The tetrasubstituted enone **12d"** is thermodynamically more stable than **33d"** and under the above reaction conditions, the tri-substituted products **33d"** first formed (kinetic product, Scheme 9, route A) reverts to **12d"** (thermodynamic control, then routes A' and B) or (ii) The reaction is kinetically controlled : the tetra-substituted enone **12d"** being formed (Scheme 9, route B) to the exclusion, at least to a large extent, of the tri-substituted enone **33d**.[41]



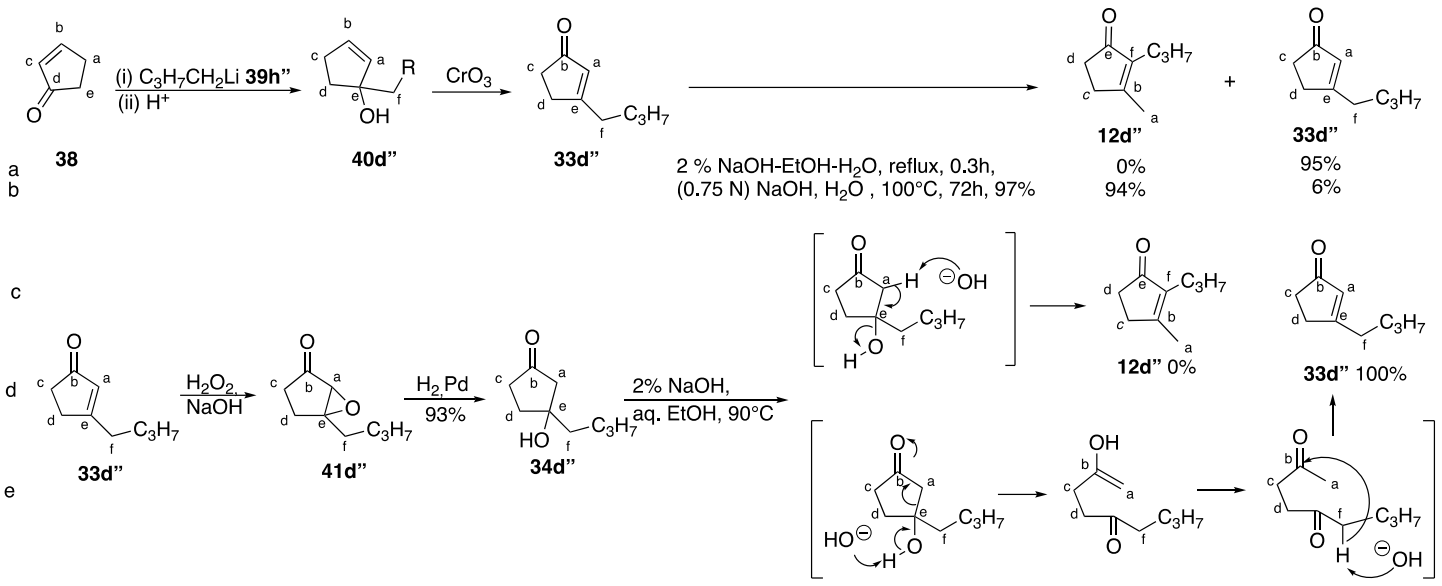
Scheme 9. Postulated intermediates in the base-promoted regioselective aldolization-crotonization of nona-2,5-dione.[41]

If the transformation of **13d"** to **12d"** occurred under thermodynamic control, then the trisubstituted enone **33d"** and is potential precursor **34d"** (Scheme 9), if independently synthesized, was expected to revert to **12d"** under the experimental conditions that allow its synthesis from **13d"** (2 % NaOH-EtOH-H_2O, reflux, 0.3h) as shown in Scheme 10.



Scheme 10. Kinetically versus thermodynamically controlled aldolization-crotonization of nona-2,5-dione. [41,42]

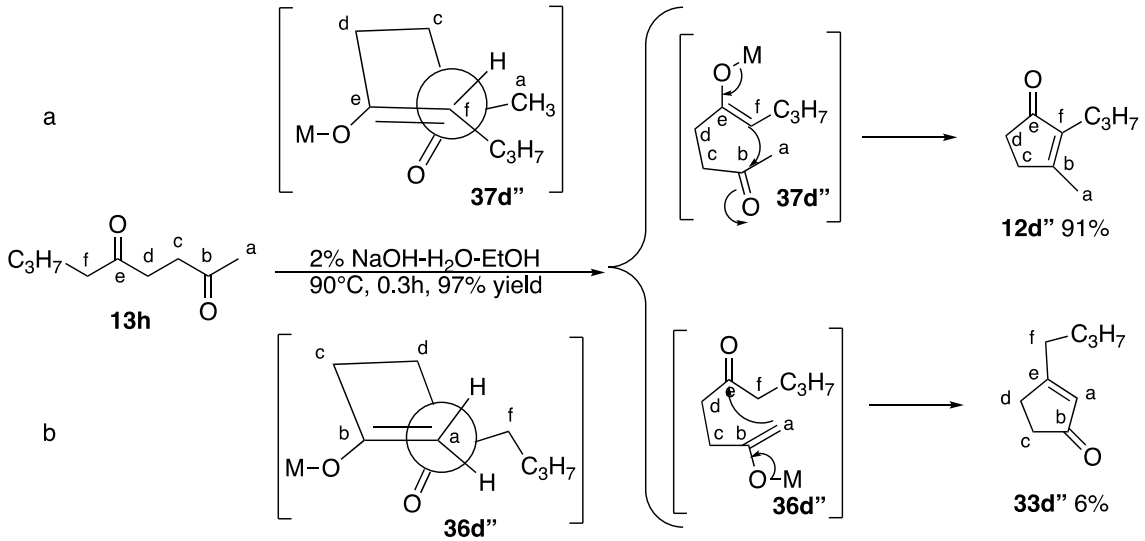
Accordingly, the mono-substituted cyclopentenone **33d"** has been synthesized[42] from cyclopentenone **38** in two steps that involve its reaction with n-butyllithium **39d** and chromium trioxide oxidation of the resulting allyl alcohol **40d"** that takes place through an allylic rearrangement (Scheme 11, entry a). 3-Hydroxy-3-butyl-cyclopentanone **34d"** that could have been an intermediate in the transformation of **33d"** to **12d"**, has been synthesized by epoxidation of **33d"** by hydrogen peroxide followed by a regioselective reduction of the resulting epoxide **41d"** (Scheme 11, entry d).



Scheme 11. Regioselective synthesis of cyclopentenones resulting from kinetic or thermodynamic control. [42]

It was found[42] that the cyclopentenone **33d"** bearing a butyl substituent at C-3 (C_e) does not lead to its isomer **12"** possessing two alkyl substituents on the cycle (a propyl at C-2 (C_f) and a methyl at C-3 (C_b)) on reaction with 2% sodium hydroxide in aqueous ethanol at 90°C for more than 1 h. Instead, the starting material is recovered almost quantitatively (Scheme 11, entry a)[41] under the conditions that allow the almost quantitative conversion of 2,5-dioxononane **13d"** to **12d"** (Scheme 7, entry c).[41,42] It was also found[42] that the 3-hydroxy-3-butylcyclopentanone **34d"** on reaction with 2% sodium hydroxide in aqueous ethanol at 90°C for more than 1 h does not lead to the tetracyclic cyclopentenone **12d"** but instead produces the disubstituted cyclopentenone **33d"** that results from water elimination (Scheme 11, entry d).[41]

Thus, **33d"** is not an intermediate in the transformation of **13d"** to **12d"** discussed above that is obviously taking place under kinetic control at the level of the aldol step.[41] The selectivity observed therefore reflects the difference in energy between the transition states for cyclization of enolate **37d"** generating **12d"** that is expected to be approximately 2.0 kcal/mol. more stable than that for **36d"** leading to **33d"** (Scheme 12).

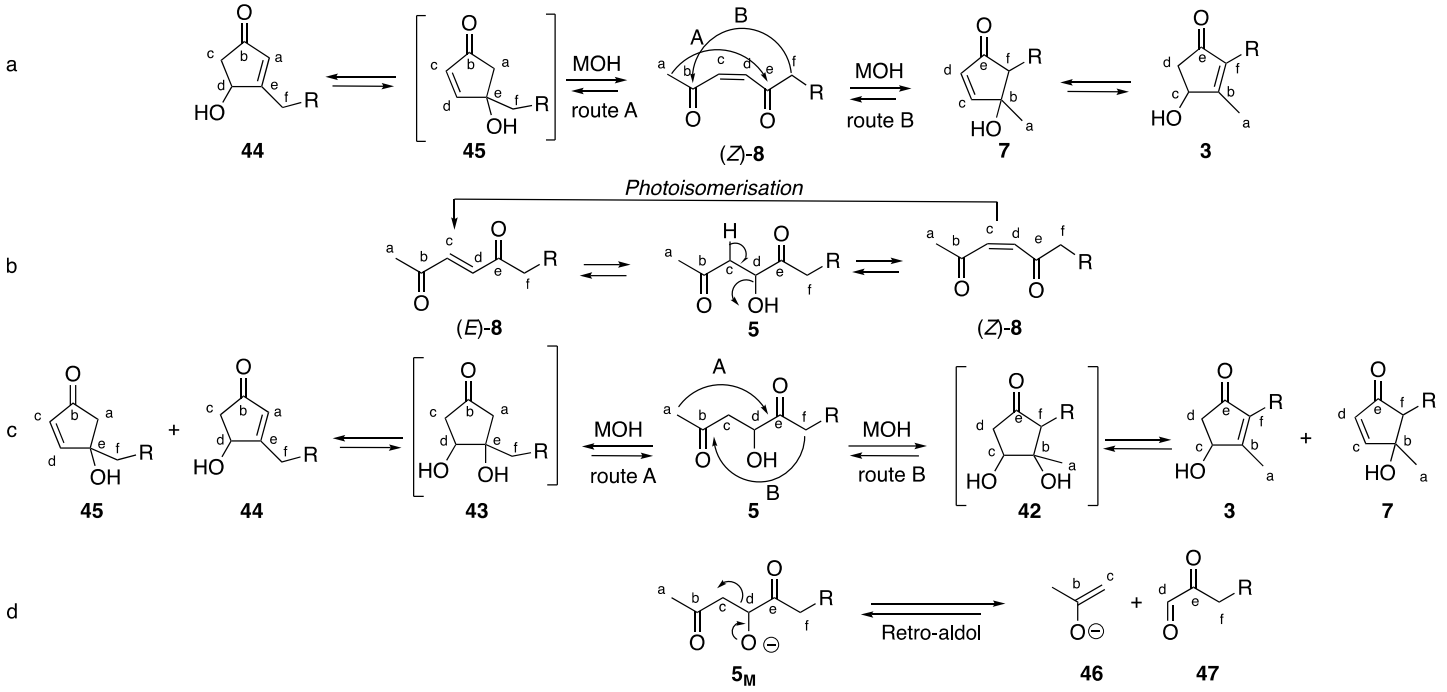


Scheme 12. Modelling the transition states of reactions involving kinetic or thermodynamic control. [41]

The same authors later carried out the reaction of the monosubstituted cyclopentenone **33d"** with sodium hydroxide under slightly modified conditions without ethanol as a co-solvent and take place for a much longer time at a similar temperature (0.75 N NaOH, H_2O, 100°C, 72h, 97%) and found that those conditions very effectively allow the isomerization of the monosubstituted cyclopentenone **33d"** to the disubstituted cyclopentenone **12d"**.[42] The strategy reported in Scheme 11 allows the short synthesis of 2-propyl-3-methylcyclopent-2-en-1-one in 26 % yield from cyclopentenone **38** (Scheme 11, entry b) and has been successfully applied to the synthesis of *cis*-jasmone as we shall show in due course (see below: Scheme 41, entry a).[42]

The synoptic presentation in Scheme 9 for the reaction of the hydroxide ion with the 1,4-diketone **13d"** has been extended to the case of hydroxy-1,4-diketones **5** (Scheme 13). Although several concurrent and/or subsequent reactions are disclosed in Scheme 13, it does not mean that they really compete and that all the products, the structures of which are disclosed there are formed or could be isolated, but only that they could be conceptually formed. Some of the intermediates such as of iso-rethrolones **7** in route from **5** to **3** have been isolated,[30] others such as hydroxy-cyclopentenone **45** or dihydroxycyclopentanones **42** and **43** have been postulated but never isolated.[30]

Thus, the presence of a hydroxyl group on the 1,4-diketone **5** could involve a β elimination of water leading to the unsaturated diketones **8** (Scheme 1, entry b) that can further react through an aldol reaction susceptible to generate the cyclopentenones **7** or **45** first or the more stable isomers **3** and **44** (Scheme 1, entry a) possessing a more substituted C=C double bond or even initiate the retroaldol reaction indicated in Scheme 13, entry d.

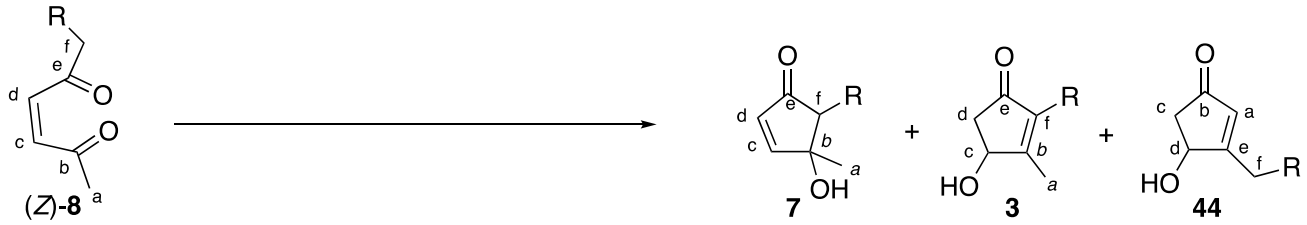


Scheme 13. Interconnected intermediates in aldol-retro-aldol reactions leading to cyclopentenolones.

In fact, reaction of the β-hydroxy-diketone **5** with hydroxide ion, leads to the dialkyl-substituted cyclopentenones **3** as the only isolable compound (Scheme 5, Scheme 13, entry b).[28-31] Its formation apparently follows the pathway already disclosed for the nona-2,5-dione **13h"** under similar conditions (Scheme 7, Scheme 13, entry c). However, the exclusive formation of **3** suggests that the postulated intermediate **42**, exclusively

loses the hydroxyl group from C_b to produce the more stable C=C double bond, or alternatively that the first formed iso-rethrolone **7** rearranges to **3** in this basic medium (as in Scheme 13, entry a).

The transformation of **5** to **8** (Scheme 13, entry b) has not been noticed in basic media but it instantaneously occurs on reaction with acetic anhydride under conditions expected to generate the corresponding acetate.[22]
It has been found that the unsaturated 1,4-diketones **8**, synthesized independently from 2-methylfuran derivatives by different routes (as will be discussed later in this chapter - see Section 5.2), when subjected to acidic or basic media, cyclizes through aldol reactions with the exclusive requirement that it carries the *Z*-stereochemistry (Schemes 6, 14).[30,33] It is interesting to note that it provides different products under the different conditions listed in Scheme 14.[30,33,45]



			7	3	44
a	R= C_3H_7	1% aq. Na_2CO_3, 100°C, 2h	0%[30]	59%	—
b	R= C_3H_7	1% aq. Na_2CO_3, 100°C, < 2h	75%[30]	—	—
c	R= C_3H_7	Amberlite 120B, H_2O, 0.5h	67%[30]	—	—
d	R= $C_{10}H_{21}$	0.1N aq. NaOH, dioxane, 100°C, 1h,	0%[45]	40%	20%
e	R= $C_{10}H_{21}$	0.1N aq. NaOH, dioxane, 20°C, 2h	0%[45]	18%	43%

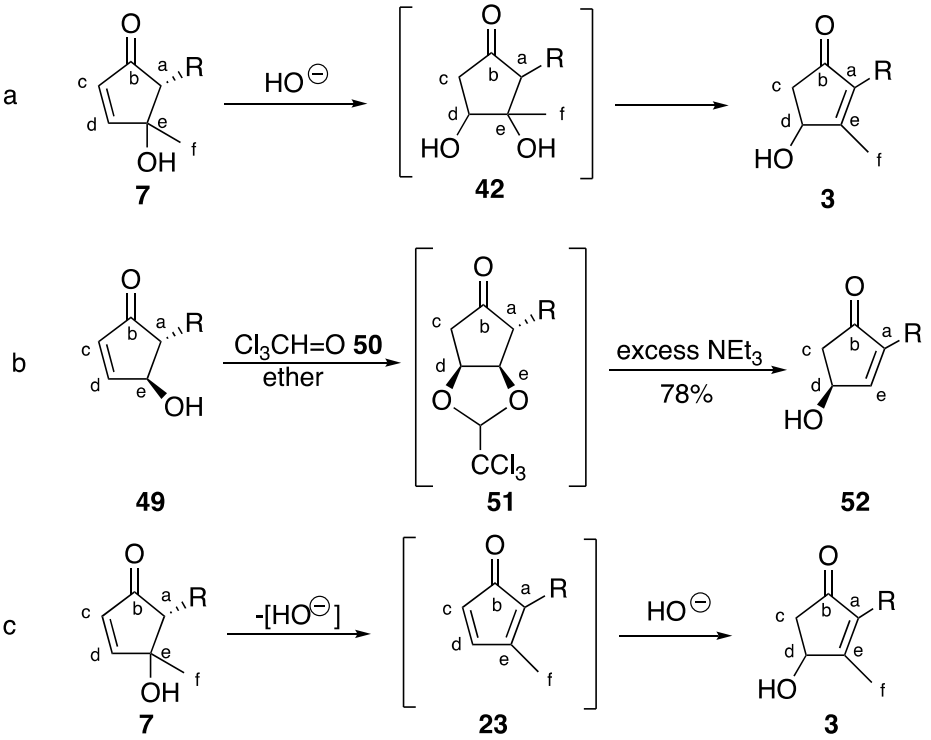
Scheme 14. Role of conditions on the outcome of the carbocyclisation of (*Z*)-1,4-enediones. [30,45]

Thus, 1,4-enediones (*Z*)-**8** are smoothly cyclized to the hydroxycyclopentenones (iso-rethrolones) **7** in:
(i) acidic media such as aqueous zinc dichloride,[33,34] or with Amberlite 120[30] (Scheme 14, entry c);
(ii) basic media such as aqueous sodium carbonate at 100 °C but for a short period (1 h) (Scheme 14, entry b),[30] since reacting for a longer time leads to the rearranged dialkyl-substituted hydroxy-cyclopentenones **3** (Scheme 14, entry a).[30,45] *iso*-Rethrolones **7** have been also obtained in dilute aqueous sodium hydroxide.[29] Isomerization of unsubstituted hydroxycyclopentenones (*iso*-rethrolones) **7** to the dialkyl-substituted hydroxy-cyclopentenones (rethrolones) **3** has been achieved with a large number of reagents under neutral (water, 180 °C, autoclave, 6 h),[35] acid (Amberlite 120B;[30] $ZnCl_2$-H_2O, 100 °C, 1 5h; [33,35] $MgCl_2$-H_2O, 100 °C, pH 7, 50 h[35]) and basic conditions ($NaHCO_3$, H_2O, 100 °C, 1 h;[34] Na_2CO_3, H_2O, 100 °C, 1 h;[30] Al_2O_3, benzene, reflux[32,33]).

It has been found that reacting the ene-1,4-diones **8*Z*** with dilute (0.1 N) aqueous sodium hydroxide at room temperature produces a mixture of the mono-alkyl-substituted hydroxycyclopentenones **44** (the kinetic product) and its isomeric dialkyl-substituted hydroxy-cyclopentenones **3** (the thermodynamic product) that results from intramolecular aldolization reaction of the ene-1,4-diones **8*Z*** respectively from their methyl (C_a) and methylene group (C_f).[29] Performing the reaction with a more concentrated sodium hydroxide solution (0.2 N instead of 0.1 N) leads to the exclusive formation of the hydroxycyclopentenones **3**. [29]

Similar observations have been made when the Z-ene-1,4-diones **8*Z*** are reacted at room temperature with 0.1 N aqueous solution of sodium hydroxide in the presence of a dipolar aprotic solvent such as 1,4-dioxane. They provide, alongside the hydroxycyclopentenones **3**, the isomeric hydroxycyclopentenones **44 (**43% yield, Scheme 14, entry e),[45] the amount being, as expected, much reduced when the reaction is carried out at higher temperature (20% yield, Scheme 14, entry d).[45]

The transformation of **7** (iso-rethrolones) to **3** (rethrolones) (Scheme 15, entry a) merits further comment since it is expected to take place through the intermediate formation of the diol **42** involving a formal water addition at C_c,C_d followed by water elimination at C_a,C_e (Scheme 13, entry c). In such case the departing group (OH) is sufficiently poor that enolate equilibration is considerably more rapid than elimination.[46] Therefore, the transition state for dehydration reflects the thermodynamic considerations which favor the formation of the more substituted double bond in (**3** from **42**).[46]



Scheme 15. Directed isomerization of cyclopentenolones.[46]

The alternative elimination-addition process that would instead produce the highly energetic and anti-aromatic cyclopentadienones **23** intermediate is not likely to occur (Scheme 15, entry c).

The process is not general, since for example it does not apply to **49**, missing the methyl substituent at Ce (Scheme15 entry b). This has been ascribed[46] to steric hindrance that hampers the intermolecular hydration of **49** that proceeds reliably only on the stereoisomer possessing the *cis*-relationship between the hydroxyl groups at C_e and the side chain at C_a (that leaves one face of the cyclopentenone entirely unhindered).[46] This problem which is not apparently observed in the iso-rethrolone series **7**,[46] has been successfully solved by making the hydration effectively intramolecular on reaction of chloral **50** in the presence of triethylamine. It leads to the acetal intermediate **51** which then collapses to produce **52** the more stable of the two allyl alcohols **49**/**52** (Scheme 15, entry b).[46]

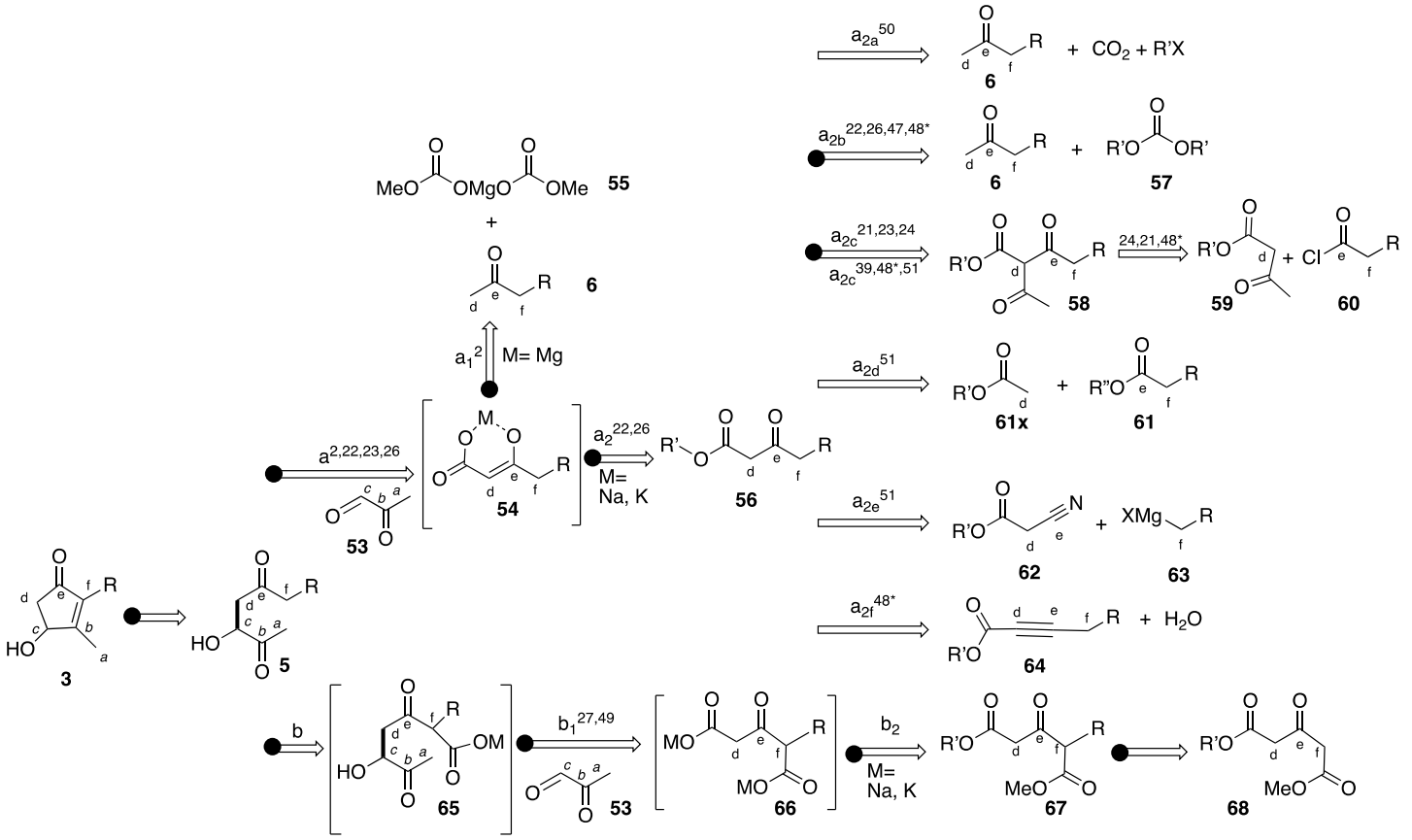
Finally, the aldol reaction has been also used to produce rethrolone **3** by forming the C_c–C_d bond (Scheme 1, entry c; Section 5.3) and for the synthesis of rethrones such as jasmone, the precursor of rethrolones by oxidation (Scheme 1, entry d; Section 5.4). Specific results will be reported in each of those sections.

5. Synthesis of Rethrolones

5.1. Synthesis of rethrolones by carbocyclisation of 1,4-diketones

5.1.1 Generalities. This approach to rethrolones **3** involves the carbocyclisation of 1,4-diketones **5**, implying the formation of the C_b=C_f double bond (Scheme 1, entry a) and was the first to be described. In many instances it has been used for the synthesis of regio- or stereoisomers because of misleading structural determinations that remained unknown until around 1949 when it was discovered that the properties of the synthetic products did not match those of the natural ones. Researchers took this opportunity to check if any of those unnatural alcohols when esterified by chrysanthemic acid would have been better insecticides that the natural products and that proved to be the case of allethrin and (*S*)-bio allethrin among others.

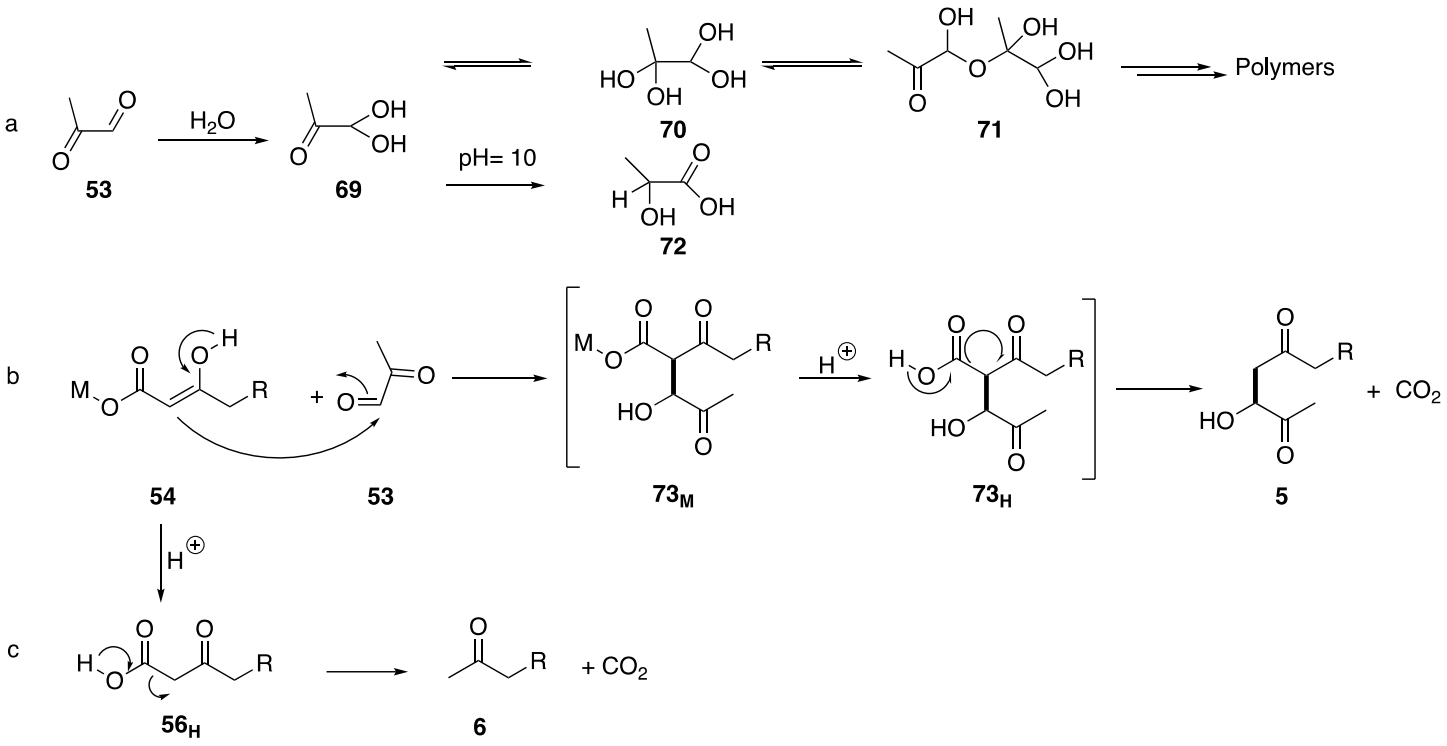
We have gathered in Scheme 16 the different strategies that have been used within this approach to prepare the precursors **5** of rethrolones **3** (including **3'**).



Scheme 16. Detailed synthetic strategies to produce cyclopentenolones.[2,21-24,26,27,39,47-,51]

All of them involve at the final stage the cyclization of 3-hydroxy-2,5-diketones **5** that we have already extensively discussed in the previous section (Section 4.3, Scheme 13). They are best achieved by carrying out the reaction with sodium hydroxide (1 or 2%) in very dilute aqueous solution, at around 10 °C for 1 to 3 h.[26] This procedure brings about the cyclization that should take place at high dilution, to decrease the chance for bimolecular side reactions.[26] It is an improvement on related procedures from the same authors that uses higher temperatures and higher concentration of base.[22] The authors pointed out that "although other alkaline cyclizing agents such as potassium hydroxide, barium hydroxide and piperidine can be used, sodium hydroxide gives good yields and was generally employed". The reaction is sensitive to oxidation and is often carried out under nitrogen in the presence of hydroquinone as an anti-oxidant.[22]

The synthesis of 3-hydroxy-2,5-diketones **5** usually involves the reaction of the β-oxocarboxylates **54** or of the β-oxodicarboxylates **66** with pyruvaldehyde (methylglyoxal) **53** (Scheme 16, entries a,b). Those reactions are expected to take place in two consecutive steps that involve at first an aldol reaction followed by a decarboxylation as shown in Scheme 17, entry b. In the case of the β-oxocarboxylates **54** (Scheme 16, route a) each step (i) the synthesis of the adduct $\mathbf{73_M}$ from the enolate **54** and pyruvaldehyde **53** and (ii) the transformation of the latter to **5**, requires slightly different conditions to be ideally achieved that make the overall process difficult to perform and to reproduce. The same features apply to the related transformation of dimethyl acetonedicarboxylate (dimethyl 3-oxoglutarate) **66** (Scheme 16, route b) that moreover requires two subsequent decarboxylation reactions to produce the same β hydroxy-diketone **5,** but nevertheless it proved particularly efficient for the synthesis of allethrolone **3d**[49] and prallethrolone **3d'**[27] as will be discussed below (Sub-section 5.1.2.4.; Schemes 24, 25).



Scheme 17. Aldol reaction between β-ketoacids and pyruvaldehyde (methylglyoxal).

The success of the reaction that produces **5** from **54** and **53** has been found to depend upon the pH of the medium. It affects the reactivity of each of the two partners as well as that of the intermediates shown in Scheme 17. [57] It was advised[22] not to use too alkaline or too acidic solutions but rather to carry out the reaction in water at room temperature at pH 8[22,23,26] under what may be considered "biological" conditions.[23,57]

Effectively, under basic conditions pyruvaldehyde **53** tends to polymerize or dismutate to lactic acid **72** (Scheme 17, entry a). [22,58] In a too acidic media the starting metal β-ketocarboxylates **54** (or their enolates) tend to be protonated leading to the corresponding acids $\mathbf{56_H}$**.** These are prone to decarboxylate to the methyl ketones **6** (Scheme 17, entry c)[22] instead of reacting with **53** (Scheme 17, entry b), lowering dramatically in the two cases the yield of the desired 3-hydroxy-2,5-diketones **5**.

Even so, the situation is complex since the successful synthesis of **5** from the postulated intermediates $\mathbf{73_M}$ requires its protonation followed by decarboxylation of the resulting acids $\mathbf{73_H}$. This transformation at the same time releases carbon dioxide that changes the pH of the medium (as carbonic acid or as metal carbonates) and

tends to change in turn the course of the reaction and the production of the 3-hydroxy-2,5-diketones **5** (Scheme 17, entry b).

For these reasons, different procedures, in some case contradictory, have been recommended.[2,22,23,26,57] It was for example suggested, in order to circumvent polymerization of pyruvaldehyde **53**, to use the freshly prepared reagent resulting from oxidation of acetone by selenium dioxide,[25] or generated by adjustment of the pH of the aqueous solution (35% w/v containing sulfuric acid) of the commercially available product used in excess (10%, method A),[2,22] or to use its protected form as its bisulfite combination[22] or its diethyl or diisopropyl acetals that are expected to be decomposed in acidic media just before reacting (Scheme 21).[26] These procedures however do not bring dramatic improvements (yields around 59-65% except for the bisulfite combination: 19%).

The variations have also been performed on the β-ketocarboxylates **54.** They have been synthesized *in situ* by (i) saponification of the corresponding alkyl β-ketocarboxylates $\mathbf{56_R}$ using sodium or potassium hydroxide in water at room temperature "for a few days" according to "the cold saponification protocol" (Scheme 16, route a_2, Schemes 17,[25] 21,[47,54] 23,[24] 24,[22,34] 25,[27]) or by (ii) titration using potassium hydroxide of the corresponding acids $\mathbf{56_H}$ obtained by acidification of the magnesium ketocarboxylates $\mathbf{54_{Mg}}$ (Schemes 16, route a_1, 18, 19)[2] or sodium or potassium β-ketocarboxylates $\mathbf{54_{Na}}$ or $\mathbf{54_k}$ (Schemes 16, route a_2, 20).[22,26,52,53]

The reaction between **54** and **53** has been carried out at *p*H 4.9-8 by Laforge[22] who noticed that "the decarboxylation proceeds spontaneously under the conditions of the reaction, the final product being the hydroxy-diketone". It was also reported[57] that the decarboxylation occurs when condensing aldehydes with β-oxocarboxylic acids within the *p*H range 3-11 and that in a more alkaline solution (*p*H 13) the carboxyl group does not split off as a competing reaction during the condensation process.[57] It has been also noticed that decarboxylation of $\mathbf{87_H}$ is accelerated by heating to 50 °C. Accordingly, the yields of allethrolone **5a** generated under closely related conditions can vary dramatically depending upon the experimentalist (30%[2]-58%[22]).

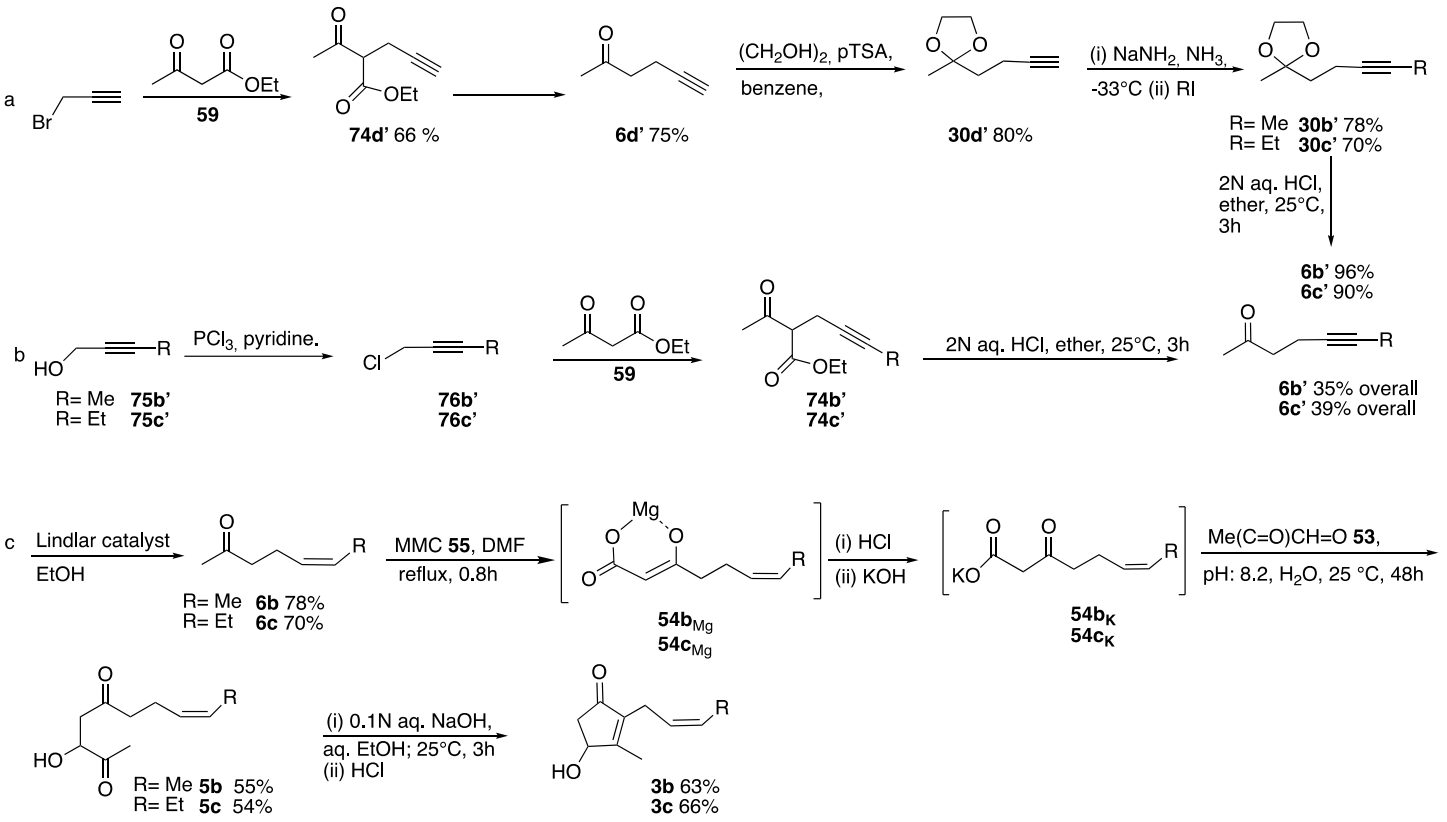
5.1.2 Selected examples. We have selected below, for comparison purposes, some specific syntheses of rethrolones **3** from the hydroxy-substituted 1,4-diketones **5** that we have organized according to the method used to synthesize the β-keto-carboxylates (Scheme 16, entry a_1, entry a_{2a} and entry a_{2c}). They include natural rethrolones such as pyrethrolone **3a** (Scheme 19),[2] cinerolone **3b** (Schemes 18,[2] 21,[47,54] 23[24]) and jasmololone **3c** (Scheme 19),[2] that requires the control of the *Z*-stereochemistry of their side chain at C_f but have presently little economic value, and unnatural ones such as allethrolone **3d** (Schemes 20,[22,26,52,53] 22,[25] 24,[22,34]) and prallethrolone **3d'** (Scheme 24[27]), that miss this stereochemical problem, are commercially viable, and possess a high economic value.

The methods used for controlling the stereochemistry in the synthesis of the natural rethrolone **3a**, **3b** and **3c** have been already discussed in Section 4.2, and are embedded in Schemes 18,[2] 19,[2] 20,[22,26,52,53] 21[47,54] and 23.[24] The strategy used in the "acetylenic route" (Scheme 18)[2] has been compared to that involving instead the "Wittig route" (Scheme 19)[2] although they are presented for different compounds.

The synthetic strategies involved in the "acetylenic route" require at one stage the reduction of the C≡C triple bond to the C=C double bond. This has been achieved at the late stage- (Scheme 21) [26,47] or at early stage- (Scheme 23)[24] of the synthesis. Although most of the yields of individual reactions are good, the overall yields are rather low (a few percent) because these processes imply *linear* approaches that are known to be less efficient than the *convergent* ones.[55]

5.1.2.1 Synthesis of rethrolones 5 employing ketones 6 and magnesium methyl carbonate 55 (MMC, Scheme 16 entry a_1). Amongst the different routes to metal β ketocarboxylates $\mathbf{54_M}$, the one involving the carboxylation of ketone **6** by MMC is the most straightforward (Scheme 16, route a_1).[2,52] It has been used *inter alia* in the synthesis of all the natural pyrethrins (Schemes 18, 19)[2] and offers a number of advantages over the other

methods that requires stronger bases.[47] The reaction carried out at reflux in DMF that is continuously distilled out of the medium (0.5 h),[2] exclusively takes place on the methyl group and provides only the monocarboxylated ketone through a magnesium chelate[2] (**54$_{Mg}$**, Schemes 16, 18, 19).[2] This chelate does not however react with pyruvaldehyde, such a highly electrophilic aldehyde and aldolization requires the exchange of magnesium in **54b$_{Mg}$** for potassium in **54b$_K$**.[2] This has been effectively achieved after acidification of **54$_{Mg}$** by 2 N aq. HCl at low temperature (0-5 °C) followed by titration of the resulting carboxylic acid **56$_H$** with aqueous potassium hydroxide.[2] Although the acetylenic route and the Wittig route have been used for the synthesis of each of the three rethrolones **3a**, **3b**, **3c**, the acetylenic approach suits the synthesis of those rethrolones possessing a dialkyl substituted C=C double bond such as **3b** and **3c** because it is, as already discussed, the most stereoselective one.

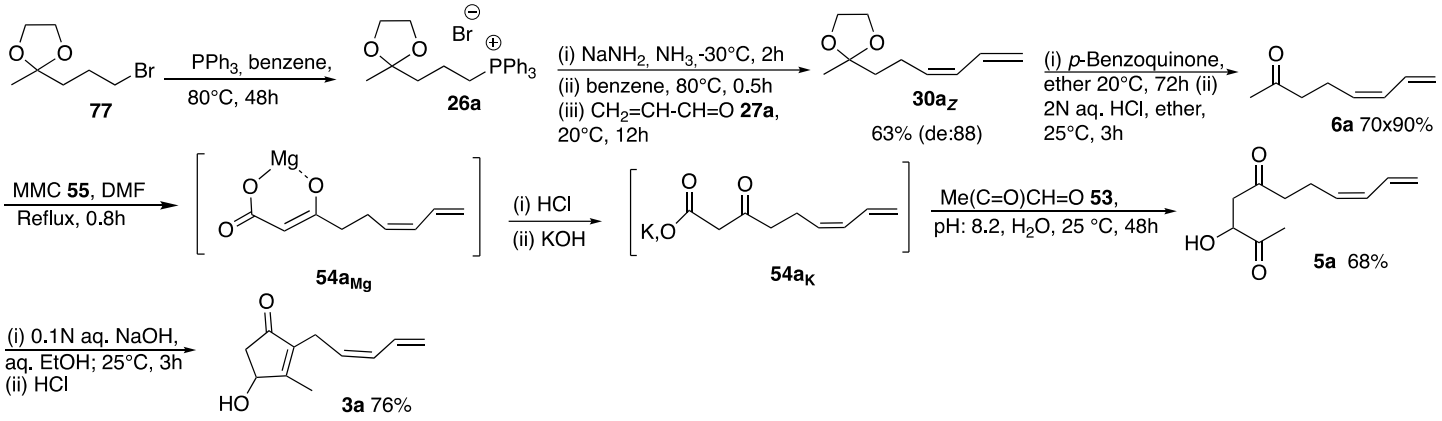


Scheme 18. Synthesis of rethrolones involving an acetylenic intermediate.[2]

The approach described in Scheme 18, entry b, is representative of the ones that will be disclosed in Schemes 20 and 21. It involves as the other key steps (i) the allylation or propargylation of ethyl acetoacetate **59** with an alkenyl or alkynyl halide leading to the alkylated β-keto ester **74** bearing the complete carbon skeleton of the final rethrolones (**3d**, Scheme 20; **3b**, Scheme 21) and (ii) the acid catalyzed ester hydrolysis and decarboxylation leading to the unsaturated methyl ketone **6**, the synthesis of which would have been achieved by the straightforward, but not yet feasible, regioselective monoalkylation of acetone (2-propanone).[48]

It contrasts with the lengthier approach disclosed in Scheme 18, entry a,[2] that also involves the allylation or propargylation of ethyl acetoacetate **59**, and sequential construction of the same side chains using instead a protection/deprotection approach[2] to build the olefinic side chain (Scheme 18, entry a, compared to the shorter approach Scheme 18, entry b).[2]

A closely related stepwise approach has been used to generate (*rac*)-pyrethrolone **3a** that instead uses the Wittig reaction to generate the dienyl methyl ketone **6a** (Scheme 19).

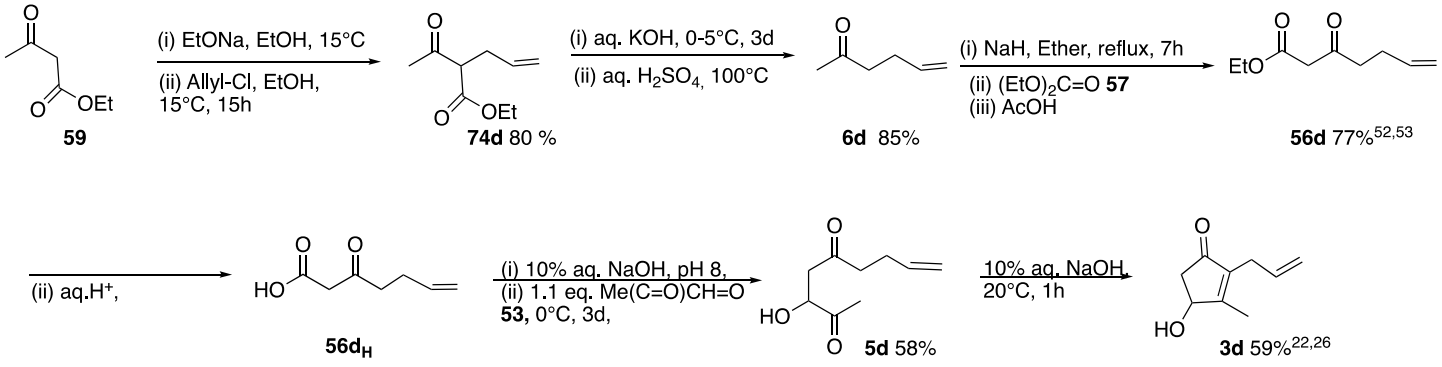


Scheme 19. Diastereoselective synthesis of (*rac*)-pyrethrolone.[2]

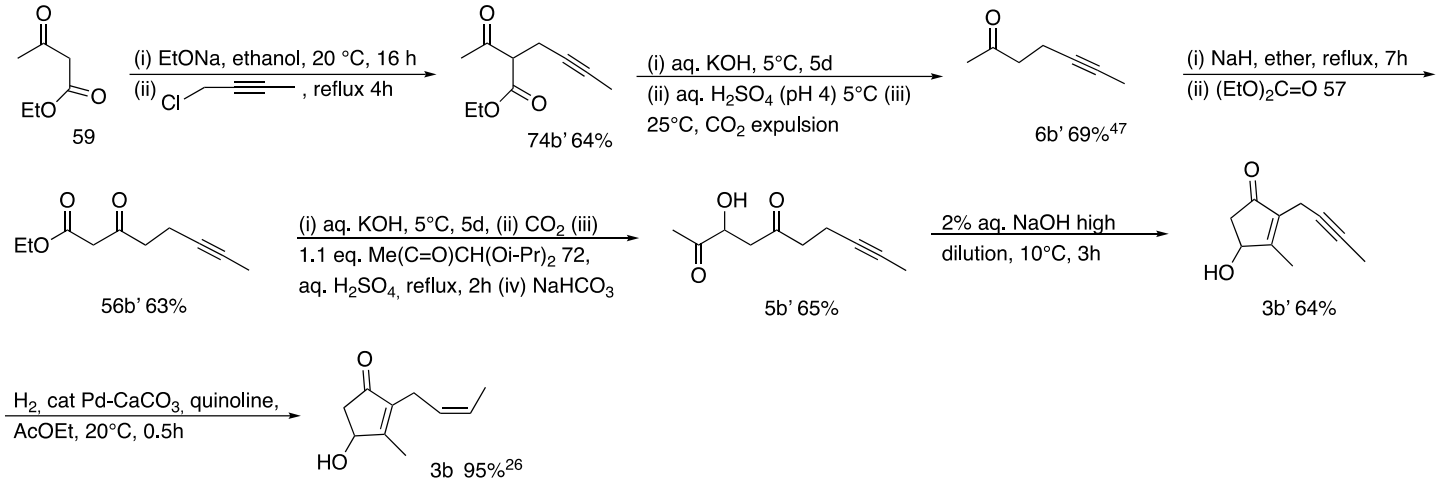
This synthesis takes advantage of (i) the MMC process:[2] (ii) the easy access to the side chain using the "Schlosser salt free trick" from using the phosphonium salt **26a** and acrolein, already discussed in Section 4.2 (Scheme 3), that cannot be achieved using the acetylenic route that would have required the selective hydrogenation of a conjugated an enyne, (ii) the efficient separation of the desired *Z*-isomer **30a**$_Z$ from small amounts of the undesired *E*-isomer **30a**$_E$ from the **30a** mixture using the "Diels-Alder trick" involving *p*-benzoquinone **28b** (Section 4.2., Schemes 4, 19).[2] Related approaches to cinerolone **3b** and jasmolonone **3c,** achieved[2] by simply replacing acrolein by acetaldehyde or propionaldehyde respectively in the Schlosser-Wittig olefin synthesis proved to be less efficient due to the difficulties, in the absence of the "Diels-Alder trick", to achieve efficient separation of the required *Z*- from the small amount of *E*-isomer present in the mixture.[2]

5.1.2.2. Synthesis of rethrolones 5 fom ketones 6 and diethyl carbonate 57 (Scheme 16 entry a$_{2b}$). This approach, related to the previous one, involves two-step-one pot reactions that require the regioselective metalation of the methyl ketones **6** on their methyl groups and their *in situ* carboxylation with ethyl carbonate **57** to produce the corresponding ethyl β-ketocarboxylates. These latter can be purified before saponification leading to the metal β-keto carboxylates precursors of **5**.

The carboxylation was originally achieved under forcing conditions[47] that require enolization of the ketones **6** with a sodium alcoholate in solution of the corresponding alcohol, and condensation of the resulting enolate with ethyl carbonate **57** at reflux for continuous removal of the alcohol. The process has been run more smoothly and at a lower temperature using sodium amide,[35] or better, by adding the ketone dissolved in ether to a refluxing suspension of ethyl carbonate **57** (2 eq.) and sodium hydride (2 eq.) (Schemes 20, 21).[22,47,53]



Scheme 20. Synthesis of allethrolone.[22,26,52,53]

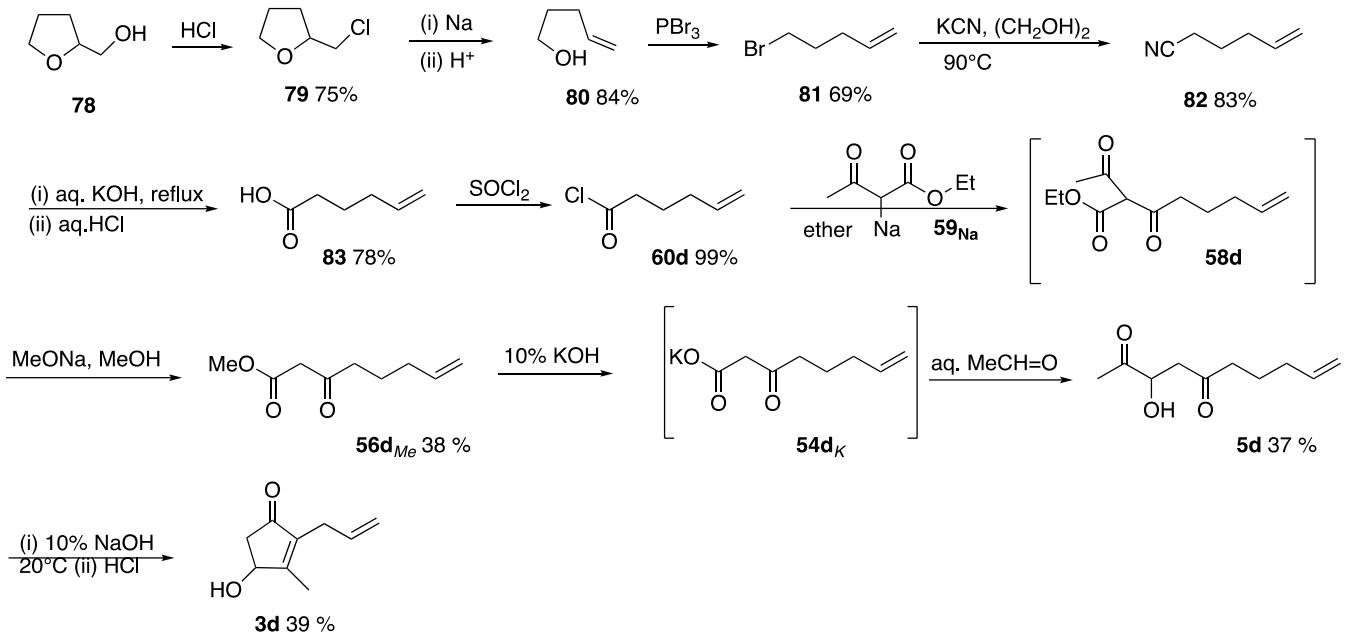


Scheme 21. Synthesis of cinerolone involving an acetylenic intermediate.[26,47]

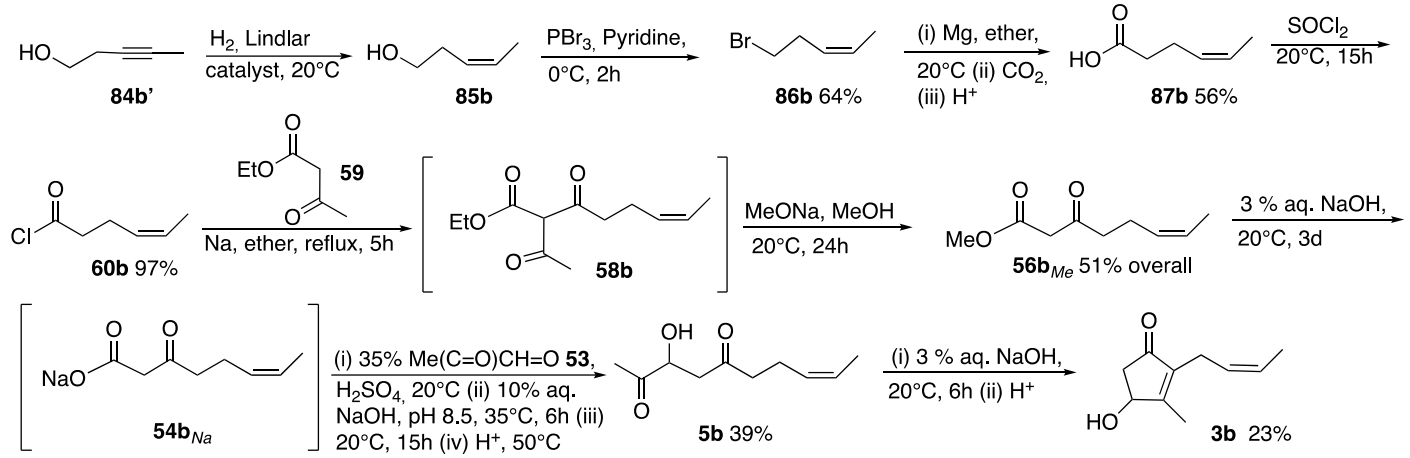
5.1.2.3 Synthesis of rethrolones 5 involving acyl chorides 60 and ethyl acetylacetonate 59 (Scheme 16 entry a_{2c}). Another synthesis of alkyl β-ketocarboxylates **54** also uses ethyl acetoacetate **59** (Schemes 22, 23)[24,25] but differs from the previous ones since it involves its acylation (Schemes 22, 23)[24,25] rather than its alkylation (Scheme 17, 19-21). It produces ethyl 2-acetyl-3-ketooct-7-enoate **58** that on further reaction with metal alcoholates are selectively deacetylated by a method in which the acetyl group on **59** is formally selectively exchanged by another more hindered acyl group (Schemes 22, 23).[24,25]

The synthesis of allethrolone **3d** starts from tetrahydrofurfuryl alcohol **78** that delivers five of the nine carbon atoms required and takes advantage of the β-elimination on the corresponding chloride **79** leading to the synthesis of pent-4-en-1-ol **80** bearing a terminal olefin and precursor of the related unsaturated nitrile **82**.

The synthesis of cinerolone **3b** shown in Scheme 23[24] is even more lengthy. It uses pent-3-yn-1-ol **84b'** as starting material whose reduction with Lindlar catalyst efficiently fixes, at an early stage, the *Z*-stereochemistry of the side chain of **3b** (Scheme 23).[24] Carbonation of the Grignard reagent derived from the related 1-bromo-3*Z*-pentene **86b** produces, after protonation and reaction with thionyl chloride, the acid chloride **60b**.[2]



Scheme 22. Synthesis of allethrolone from 2-hydroxymethyltetrahydrofuran. [25]

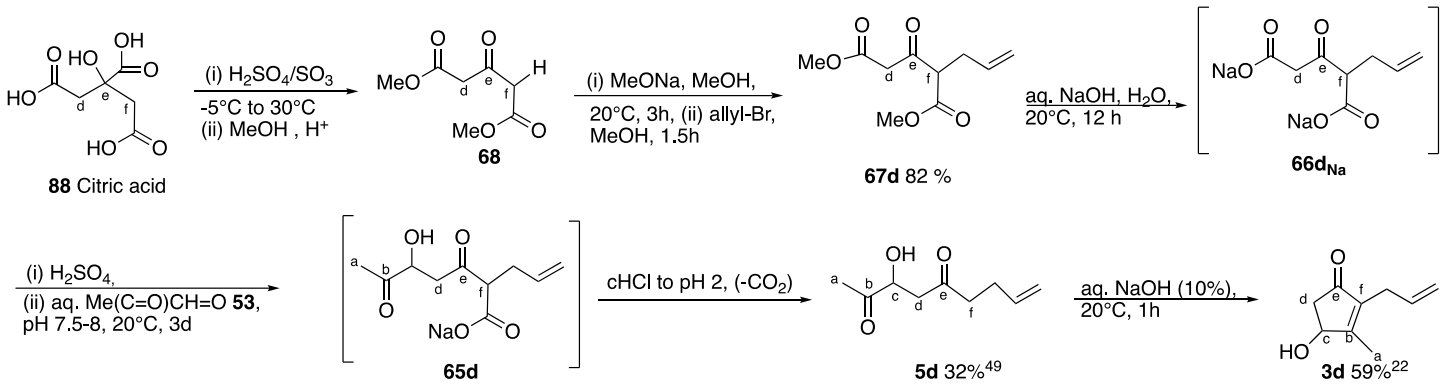


Scheme 23. Synthesis of cinerolone involving an unsaturated β-keto acid.[24]

5.1.2.4 Synthesis of rethrolones 5 involving allyl or propargyl halides and dimethyl acetonedicarboxylate 68 (Scheme 16 entry b). This approach takes advantage of rapid access to the symmetrical dimethyl acetonedicarboxylate (dimethyl 3-oxoglutarate) **68** [54] from the readily available citric acid **88**, that is efficiently alkylated with allyl[49] or propargyl[27] halides, with sodium iodide as catalyst when the chlorides are used (Scheme 24, Scheme 25). It is by far the shortest route to rethrolones and has been successfully applied to the synthesis of allethrolone **3d** (Scheme 24)[22,49] and prallethrolone **3d'** (Scheme 25)[27] that have both economic value and have also been used as valuable precursors of pyrethrolone **3a** and cinerolone **3b** (Scheme 1, entry h), as will be discussed below (Sections 5.7 and 5.8).

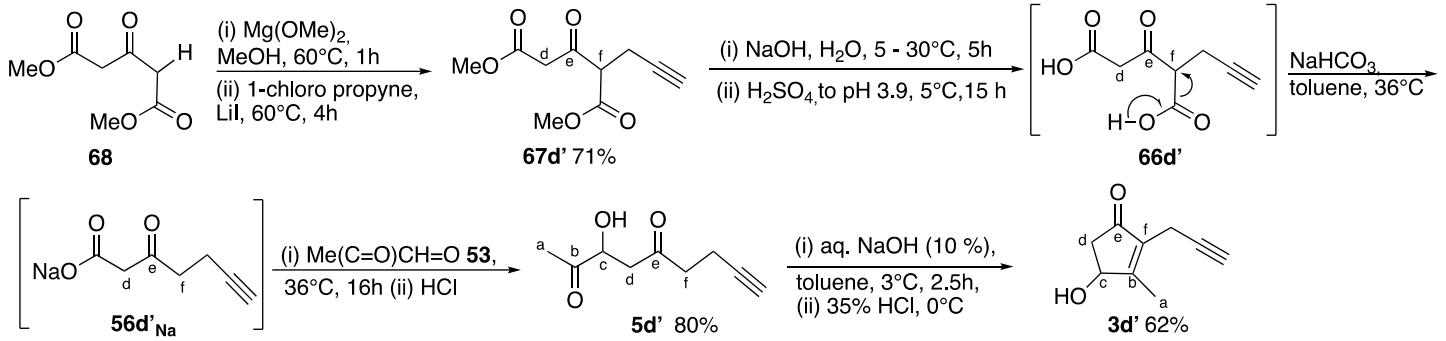
The resulting allyl dimethyl 3-oxo-glutarate **67d**[49] or propargyl dimethyl 3-oxoglutarate **67d'**[27] on sequential reaction with aqueous sodium hydroxide, then with methylglyoxal **53**, provides in one-pot the related 2,5-dioxo-3-hydroxy-8-nonene **5d**[49] albeit in modest yield (32%, Scheme 24) and the 2,5-dioxo-3-hydroxy-8-nonyne **5d'**[27]

in very high yield (80%, Scheme 25) that results from regioselective aldol reaction that takes place from the less hindered of the two sodium β-ketocarboxylates present on each structures **67d** and **67d'**.[27,49] The important difference in yields (32 and 80%) has been attributed[27] to the larger electron withdrawing effect of the 2-propynyl group present on **67d'** favoring the preferential regioselective decarboxylation at C_f (Scheme 25). [27] However careful investigations could suggest another explanation, since the procedures and the processes disclosed by the two groups (compare the proposed intermediates **66d$_{Na}$** and **65d**, Scheme 24 to **66d'**, Scheme 25) are quite different.



88 Citric acid **68** **67d** 82 % **66d$_{Na}$** **65d** **5d** 32%[49] **3d** 59%[22]

Scheme 24. Synthesis of allethrolone from citric acid.[22,49]



68 **67d'** 71% **66d'** **56d'$_{Na}$** **5d'** 80% **3d'** 62%

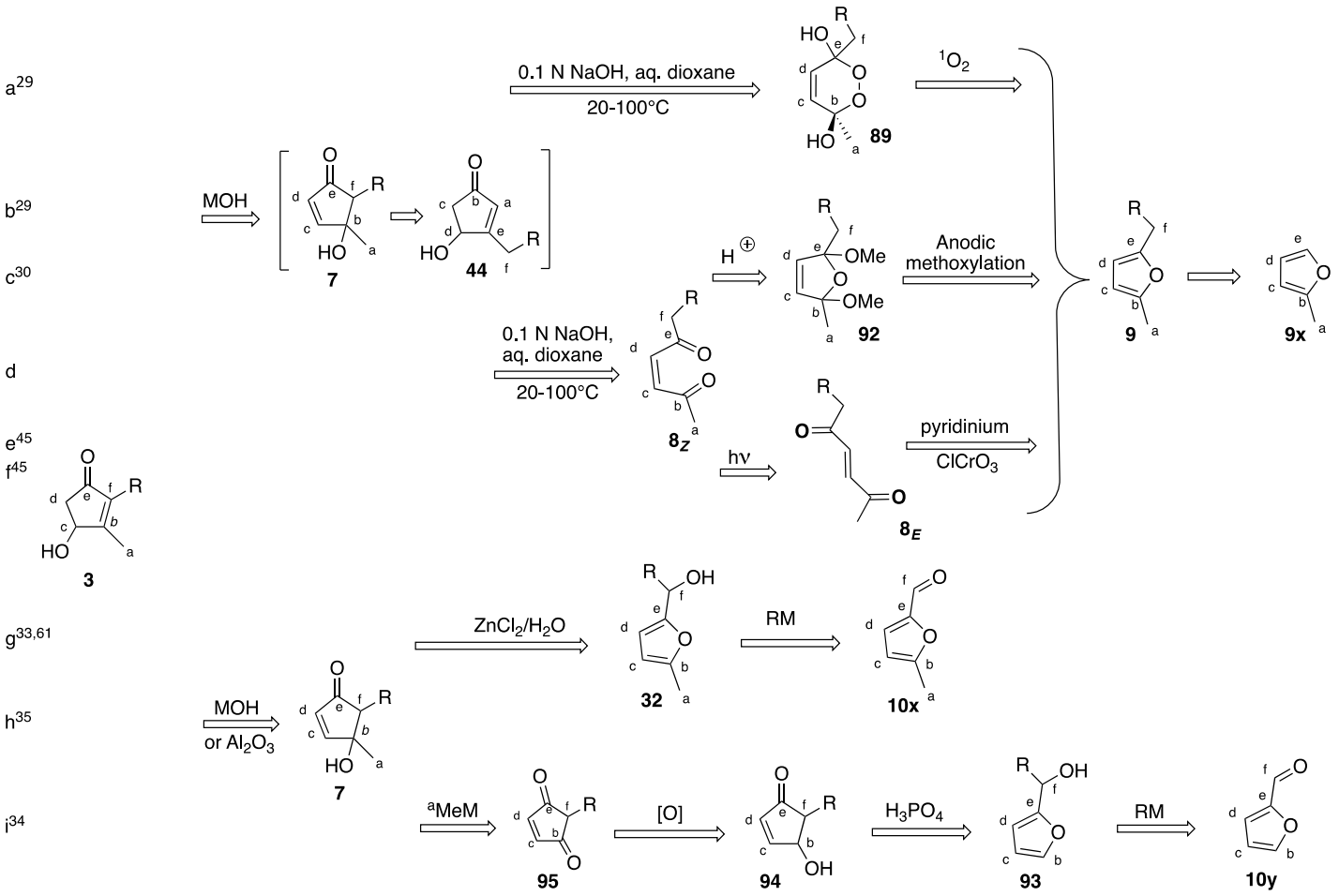
Scheme 25. Synthesis of prallethrolone from dimethyl acetonedicarboxylate.[27]

We would suggest, if either of the syntheses has to be repeated, that the procedure of the Sumitomo Company[27] be followed. This directs: (i) to saponify the diester at around -10 °C by 11% aqueous NaOH solution, (ii) to adjust the pH to 3.9 and then (iii) stir 12 more hours (monodecarboxylation?); (iv) add sodium bicarbonate (to generate **54d'$_{Na}$**) (v) add methylglyoxal 36 °C, 16 h (addition of **54d'$_{Na}$** to methylglyoxal **53** and decarboxylation of the intermediate to **5d'**).

5.2. Synthesis of rethrolones 3 by isomerization of iso-rethrolones 7

5.2.1 Generalities. The approaches are summarized in Scheme 26 and involve the synthesis of rethrolones **3** by isomerization of iso-rethrolones **7** resulting from the aldolization of 3-ene-2,5-diketones arising from ring opening of furan derivatives and involving the formation of the C_f–C_b single bond (Scheme 1, entry b) to allow the set-up of the complete carbon framework of rethrolones **3** very rapidly in semi-convergent ways from furan ring compounds. They lead first to iso-rethrolones (4-hydroxy-4- methyl cyclopent-2-enone) **7**,[55] which are easily

isomerized to rethrolones **3**, to involve two different strategies in which the C_a methyl group on **7** (**3**) is present at the early stage of the synthesis on the furan ring such as 2-methylfuran **9x** (Scheme 26, entry c) or on 2-formyl-5-methylfuran **10x** (Scheme 26, entry g)[33,61] or at a later stage as in Scheme 26, entry i) using furfural **10y** as starting material (Scheme 26, entry i),[34] to take advantage of the aptitude of the furan ring to be (i) easily metallated[29,59] at C-2 (C_b or C_e) then alkylated or formylated or (ii) formylated at C-2 in a straightforward way using the Vilsmeier-Haack reaction.[63,64]



Scheme 26. Retrosyntheses of rethrolones involving furans. [30,33-35,45,61]

Accordingly, the R group present at C_f has been introduced either as an electrophilic entity at C_e on 2-metallo furans (Scheme 26, entry c)[29,59] or as nucleophilic species[33] such as a Grignard reagent on the C_f carbonyl group of furfurals **10** (Scheme 26, entries g,i) to use efficient methods for furan ring opening, producing either a 1,4-diketone or a carbocycle from the heterocycle, especially the transformation of:

(i) dialkyl substituted furans **9** to γ-hydroxycyclopentenones, which requires first an oxidation step. This has been successfully achieved, either by singlet oxygen cycloaddition, 1,4-addition of methoxy groups promoted by anodic oxidation, or using pyridinium chlorochromate (Scheme 26, entries a,c,e),[29,30,45] followed by reaction of the resulting compounds **89**, **92** and **8** under acidic or/and basic conditions (Scheme 26, entries a,c,d).[30,45]

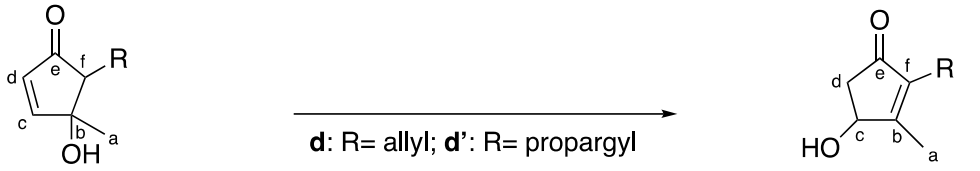
It has been observed that in the transformations implying the intermediate formation of the ene-diones **8**, only the *Z*-isomers $\mathbf{8}_{\boldsymbol{Z}}$, produced under smooth conditions, are prone to produce a carbocycle (**3**, **7** or **44**; Scheme 26) and not their *E*-isomers $\mathbf{8}_{\boldsymbol{E}}$ that are produced (i) on strong acid hydrolysis[30] for example from the dimethoxy

derivative **92** or (ii) on oxidation[45] of 2-methyl-5-allyl furan **9d** and 2-methyl-5-propargylfuran **9d'** with pyridinium chlorochromate (Scheme 26, entry e). In such cases the transformations require an additional photochemical step (Scheme 26, entry f) that allow the contra-thermodynamic isomerization of $\mathbf{8}_{E}$ to $\mathbf{8}_{Z}$ that has been successfully achieved (Scheme 26, entry f).[45]

(ii) furfuryl carbinols **32** (Scheme 26, entry g) and **93** (Scheme 26, entry i) to γ-hydroxycyclopentenones, that involves an acidic medium. [33,34,35] This is efficiently achieved on reaction of protic acids with furfuryl carbinols unsubstituted at C-5 (C_b) on the furan ring such as **93** (Scheme 26, entry i) but requires the presence of zinc chloride for those furyl carbinols bearing a methyl (alkyl group) at C-5 (C_b) such as **32** (Scheme 26, entry g).[33]

Efficient protocols to transform peroxides **89**, enediones **8** and γ-hydroxycyclopent-2-enones **7** to rethrolones **3** are outlined in Scheme 13.

The synthesis of γ-hydroxycyclopent-2-enones (rethrolones) **3** from the peroxides **89**, the enediones **8** and γ-hydroxycyclopent-2-enones (iso-rethrolones) **7** has been efficiently achieved on reaction with dilute aqueous sodium hydroxide, (Scheme 26, entries a,d,h) an aqueous solution of magnesium- or zinc dichloride[35] or even better with alumina.[34] Some results concerning the transformations of the iso-rethrolones **7** to allethrolone **3d** and prallethrolone **3d'** are shown in Scheme 27.[34,35]



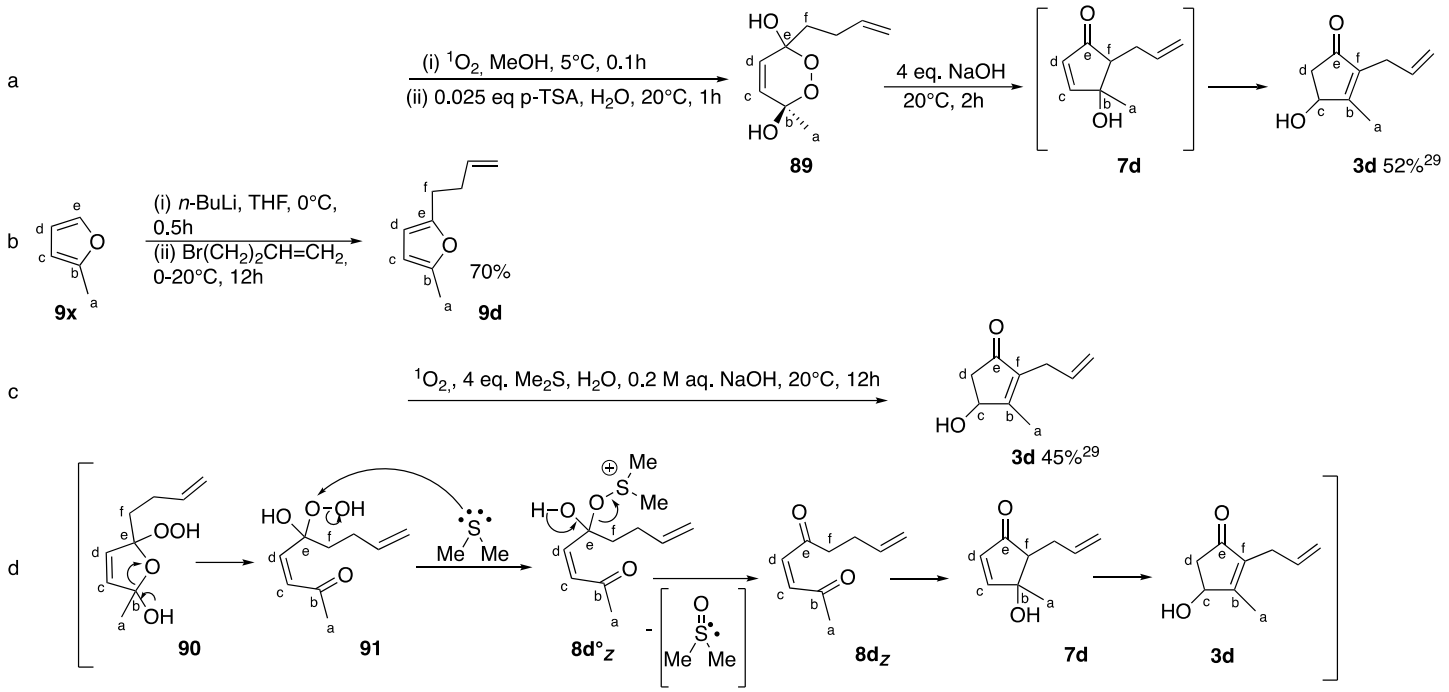
7d 7d' **3d 3d'**

a	Al_2O_3, toluene-ether (1/1), 30°C, 24h	63%[34]	70%[34]
b	5% aq. $NaHCO_3$, 100°C, 1h	75%[34]	
c	1 eq. $MgCl_2.6H_2O$, 0.05M aqueous, pH 7.3, 4h	87%[35]	77%[35]
d	1 eq. $ZnCl_2$, 0.05M aqueous, pH 7.3, 15h	80%[35]	
e	Autoclave, aqueous, 180°C, 6h	95%[36]	

Scheme 27. Isomerization of iso-rethrolones to rethrolones: syntheses of allethrolone and prallethrolone [34-36]

In some cases, such as that in Scheme 26, entry d, the transformation has been achieved in one pot taking advantage of a buffered medium, changing the pH from acidic to basic at the appropriate stage of the process[35] or using high temperature to achieve it at its maximum for each step or in a single step in an autoclave at 180 °C (Scheme 27, entry e).[36]

5.2.2 Selected examples. 5.2.2.1 Synthesis of rethrolones from 2,5-dialkylfurans. 5.2.2.1.1 Synthesis of rethrolones using photochemically generated singlet oxygen. The synthesis of rethrolones using photochemically generated singlet oxygen is a quite convergent approach requiring methylfuran **9x** and homoallyl bromide as readily available starting materials (Scheme 28).[29] It takes advantage of the efficient metalation of the former and alkylation of the resulting organolithium to produce the complete carbon skeleton for example of allethrolone possessing the adequate functionalities at the proper place to perform the transformations that lead to the desired rethrolone **3d** in only a few steps (Scheme 28, entry b).[29]



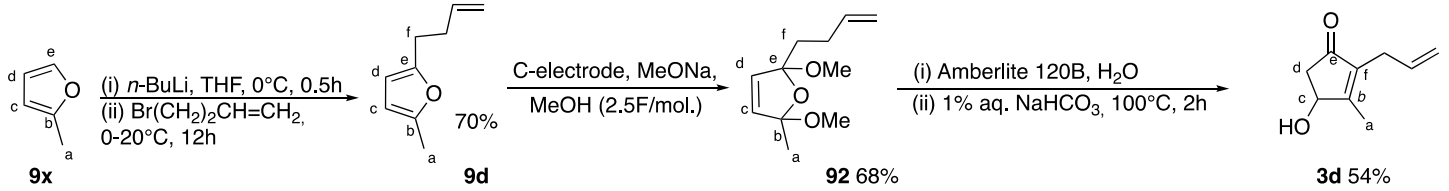
Scheme 28. Synthesis of allethrolone from 2-methylfuran using photochemically generated singlet oxygen.[29]

Although the transformation involving singlet oxygen[29] requires several steps (Scheme 28, entry c),[29] it has been carried in a single pot from the 2-methyl-5-but-3-enylfuran **9d**,[29] by bubbling dioxygen under irradiation in methanol or water containing dimethyl sulfide, in the presence of rose Bengal (10^{-4} M) as sensitizer and sodium hydroxide as a base (Scheme 28, entry c).[29]

The experiment reported in Scheme 28, entry a, reveals the unexpected formation of the endo-peroxy-bis-hemiketal **89** an intermediate never previously observed, which, although not very stable, could be isolated and transformed at room temperature into allethrolone **3d** on reaction with a base.[29]

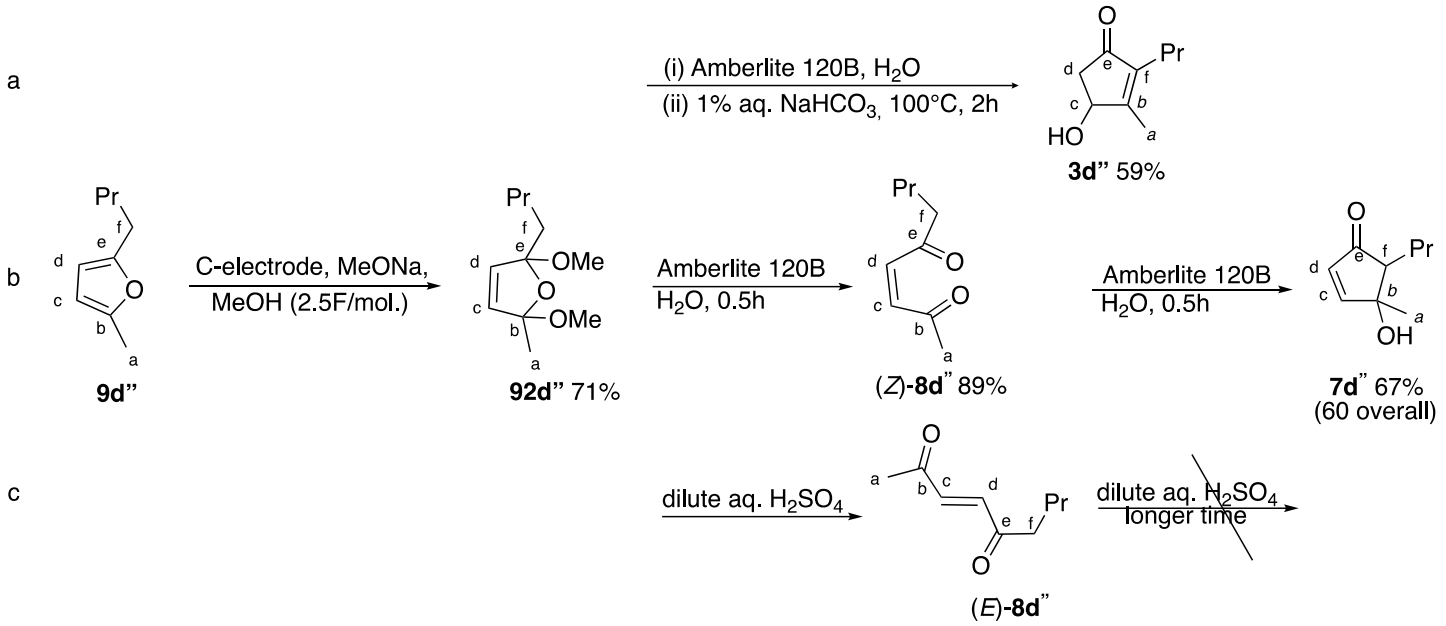
Rationale for the slightly modified process that uses dimethyl sulfide as a reducing agent is shown in Scheme 28, entry d.[29] Thus, the hydroperoxy intermediate **90** resulting from singlet oxygen cycloaddition rearranges to the hemiperoxyketal **91** precursor of the enedione **8d$_Z$** on reduction with dimethyl sulfide, that finally leads to the cyclopentenones **7d**, then **3d**.

5.2.2.1.2 Synthesis of rethrolones using electrochemical oxidation of 2,5-dialkylfurans. The electrochemical approach outlined in Scheme 29 uses the same starting material **9d** as the photochemical and also requires special equipment to perform the electrochemical oxidation.[30] The resulting dimethoxydihydrofuran **92** on sequential reaction with the acidic resin Amberlite 120B at room temperature, that destroys the heterocycle, then with potassium bicarbonate at reflux in water for 2h, that initiates, in competition with its decomposition, the carbocyclisation that leads to the allethrolone **3d** in a single pot[30]



Scheme 29. Synthesis of allethrolone by electrochemical oxidation of 2,5-dialkylfurans.[30]

Some further information about the individual steps has been obtained by carrying out the same transformation on 2-methyl-5-butylfuran **9d"** (Scheme 30).[30]



Scheme 30. Controlling the nature of the products on reaction of a 2,5-dimethoxydihydofuran in acidic media.[30]

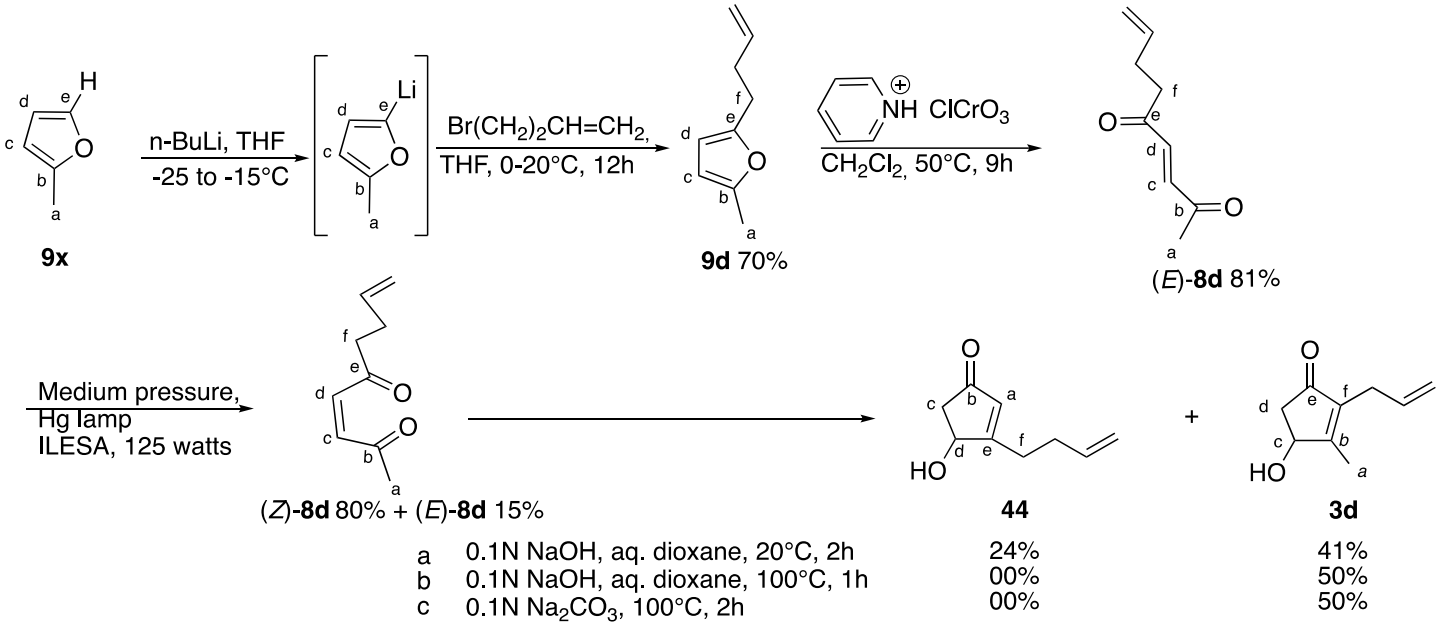
It was found[30] that reacting **92d"** in the presence of the acidic resin Amberlite 120B produces the *Z*-ene-dione (*Z*)-**8d"** after a short time (20 °C, 0.5 h) it further cyclizes to iso-dihydro-allethrolone **7d**" on standing a little more time (0.5 h) under the same conditions (Scheme 30, entry b). Isomerization of **7d**" to dihydroallethrolone **3d**" has been achieved on reaction with aqueous sodium bicarbonate at reflux (compare to Scheme 30, entry a).[30]

Reacting **92d"** with a stronger acid such as dilute sulfuric acid under the same conditions leads instead to the formation of the *E*-isomer (*E*)-**8d"** (Scheme 30, entry c) that no longer cyclizes under acidic or basic conditions.[30]

5.2.2.1.3 Synthesis of rethrolones 3 by pyridinium chlorochromate oxidation of 2,5-dialkyl substituted furans. During the work described above it was found that only the Z-ene-diones **8z** cyclize to hydroxy-cyclopentanones (Scheme 30 entry b) and not their *E*-isomers (*E*)-**8** (Scheme 30 entry c).[29,30] Therefore, the discovery[45] that the latter can be isomerized to their Z-isomers (*Z*)-**8** opened new horizons, allowing the use of other oxidants than the above cited ones. Among them pyridinium chlorochromate proved to be the best,[45] since it is compatible with many other functional groups including the C,C double and triple bonds present in allethrolone and prallethrolone.

Isomerization of (*E*)-**8** to (*Z*)-**8** however requires the use of a medium pressure mercury lamp (ILESA, 125 W) and leads to an 85/15 *Z*/*E*-mixture of isomers (Scheme 31).[45] Access to ene-diones (*Z*)-**8** in neutral media allowed a clear view about the reactivity of such compounds that have been proposed on several occasions as intermediates in the transformation of oxidized furans with acids[30] and bases[29,45] (Schemes 13, 14, 29, 30). It has been found, in accord with related results concerning saturated ene-diones (*Z*)-**8d**", that carbocyclization already takes place at 20 °C, on reaction of **8dz** with 0.1 N aqueous dioxane solution of sodium hydroxide, leading to a mixture of a 4-hydroxy-3-butenyl-cyclopentenone **44d** (on metalation of the methyl group, kinetic product) along with allethrolone **3d** (thermodynamic product) after a short time (Scheme 31, entry a) but to the single "thermodynamic" product if the reaction is instead carried out at 100°C (Scheme 31, entry b).[45]

It may be noticed that the amount of product **3** resulting from thermodynamic control is more important in the case of allethrolone **3d** that for its saturated homologues **3d"** (compare the results in Scheme 31 to those reported in Scheme 14).



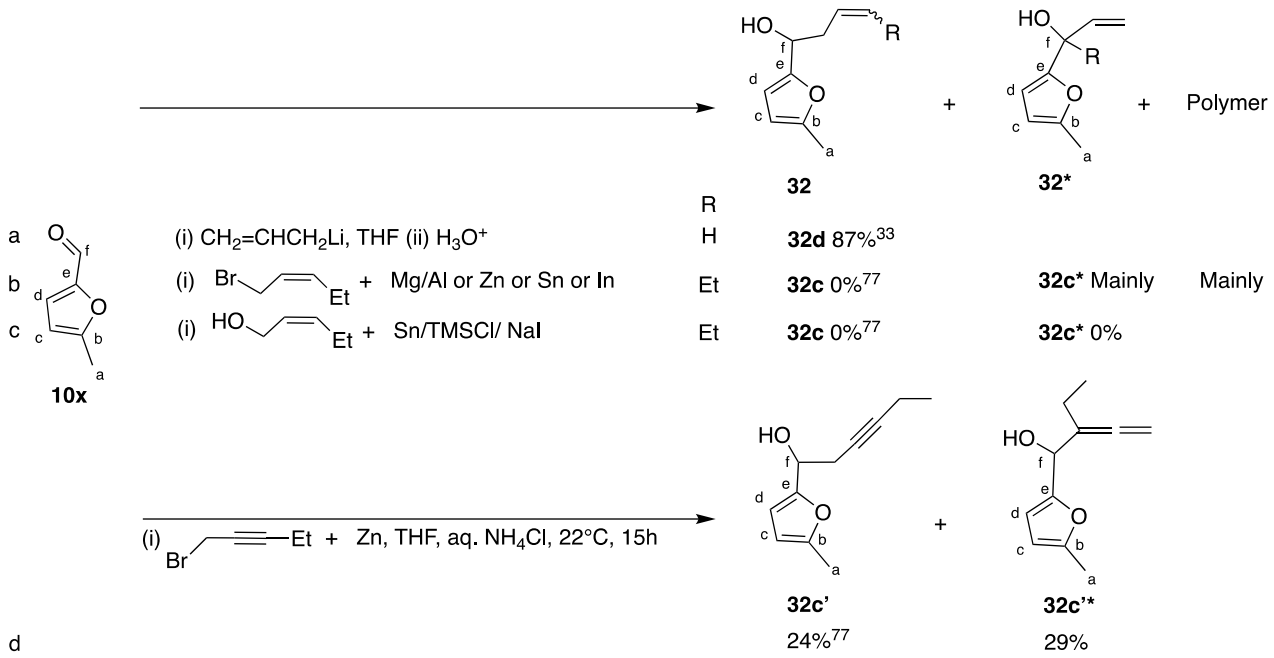
Scheme 31. Photochemically induced contrathermodynamic E/Z isomerization of an enedione and its base promoted carbocyclisation. [45]

5.2.2.2 Synthesis of rethrolones 3 involving furfuryl carbinols. 5.2.2.1.1 Synthesis of rethrolones 3 involving 5-alkyl-2-furfuryl carbinols. This approach takes advantage of the great accessibility of furfuryl aldehyde **10x** by formylation of methyl furan **9x** with chloromethyleniminium salt by the Vilsmeier-Haack reaction[63,64] and its allylation using allyl metals [33,35,36,77] or its propargylation that requires the additional chemoselective dihydrogenation step.[77]

The process has been used successfully for the synthesis of allethrolone **3d** (Scheme 32, entry a),[63,64] and less successfully for jasmololone **3c** (Scheme 32, entry d),[77] since, except for the parent allyllithium (Scheme 32, entry a)[63,64] higher homologs and propargylic analogs suffer from their ambiphilic reactivity that leads to intractable mixtures of regio/stereoisomeric adducts (Scheme 32, entries b,c,d)[77] that unfavorably affects this approach for all the metals and conditions tested.[77]

The transformation of **32d** to the 2-allyl-3-hydroxy-3-methyl-2-cyclopentenone **7d** (the Piancatelli rearrangement) has been primarily achieved in aqueous media at 60 °C using zinc chloride as catalyst (Scheme 33, entry a),[33] and takes place in a different way to the related procedure used in prostaglandin synthesis that takes place with protic acid.[33]

The mechanism in Scheme 33, entry i, has been proposed to explain this in term of thermal electrocyclic conrotatory reaction of a 4π electron system, initiated by electrophilic attack, by the zinc cation, on the oxygen of the hydroxy-group at C_f leading to the carbocation **96d**. Addition of water is expected to produce **97d** that collapses to **98d** then to **99d** to finally produce **7d** (Scheme 32, entry i). The formation of the carbenium ion **96** at C_f probably governs the process leading to a higher yield of **7** if it is well stabilized by, for example, a phenyl group instead of an alkyl group at Cf (Scheme 33, entry i).[33]

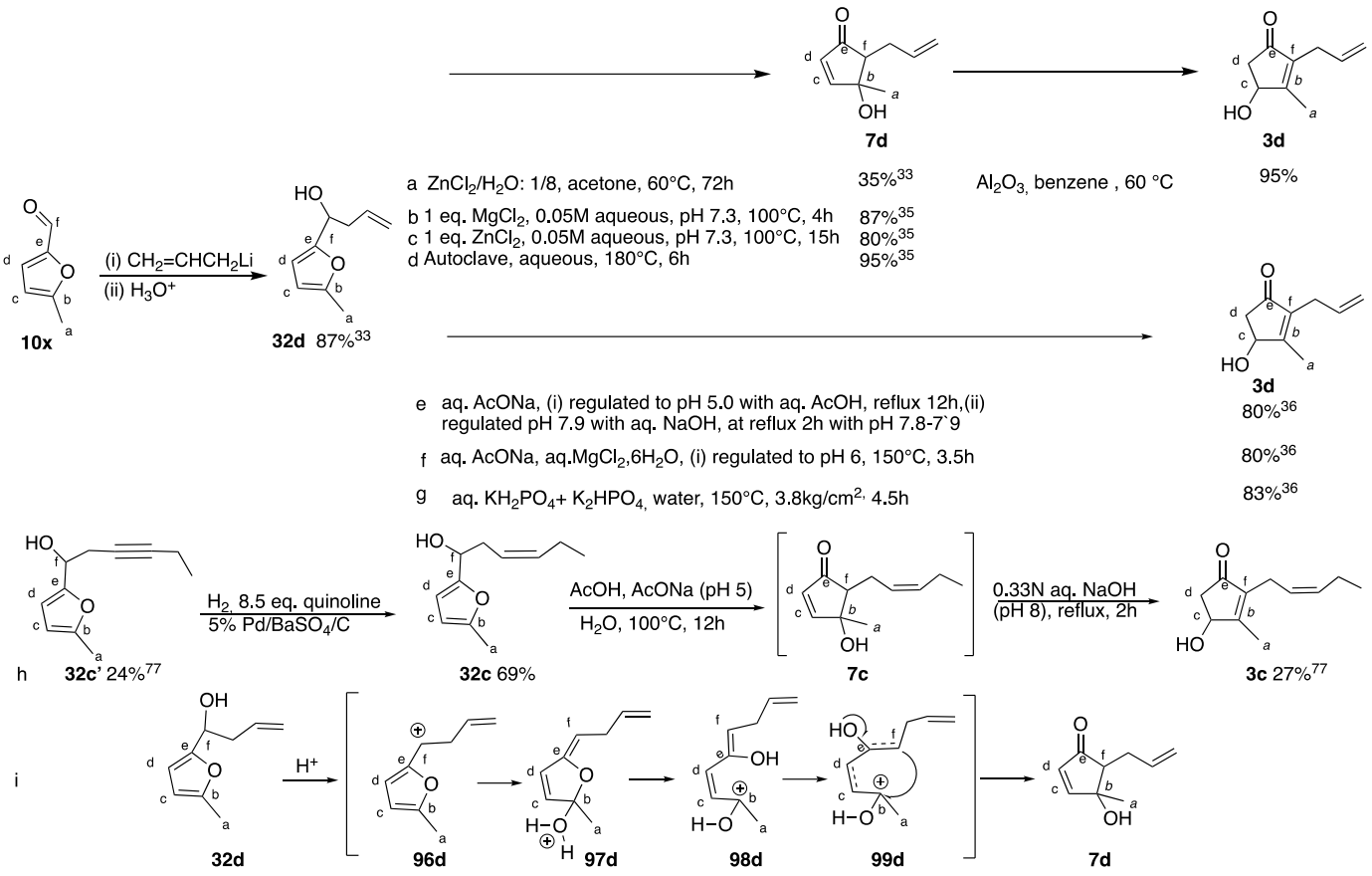


Scheme 32. Reaction of allyl- and propargyl-metals (Li, Mg, Sn, Zn) with 5-methylfurfuryl aldehyde.

The reaction provides **7d** in higher yields if carried out at higher temperature (Scheme 33, compare entry c to entry a) and also occurs with magnesium chloride as catalyst (Scheme 33, entry b).[35] It has also been found[35] that the carbocyclization can be achieved in the absence of an acid catalyst if carried at very high temperature under pressure (Scheme 33, entry d), supporting the more recent observation by Reiser who noticed that rearrangement of 2-furfuryl carbinols efficiently takes place using microwave irradiation in water (closed vessel, 300 W, 200-210 °C, 15 bar) at high dilution to avoid the formation of polymeric by-products.[62]

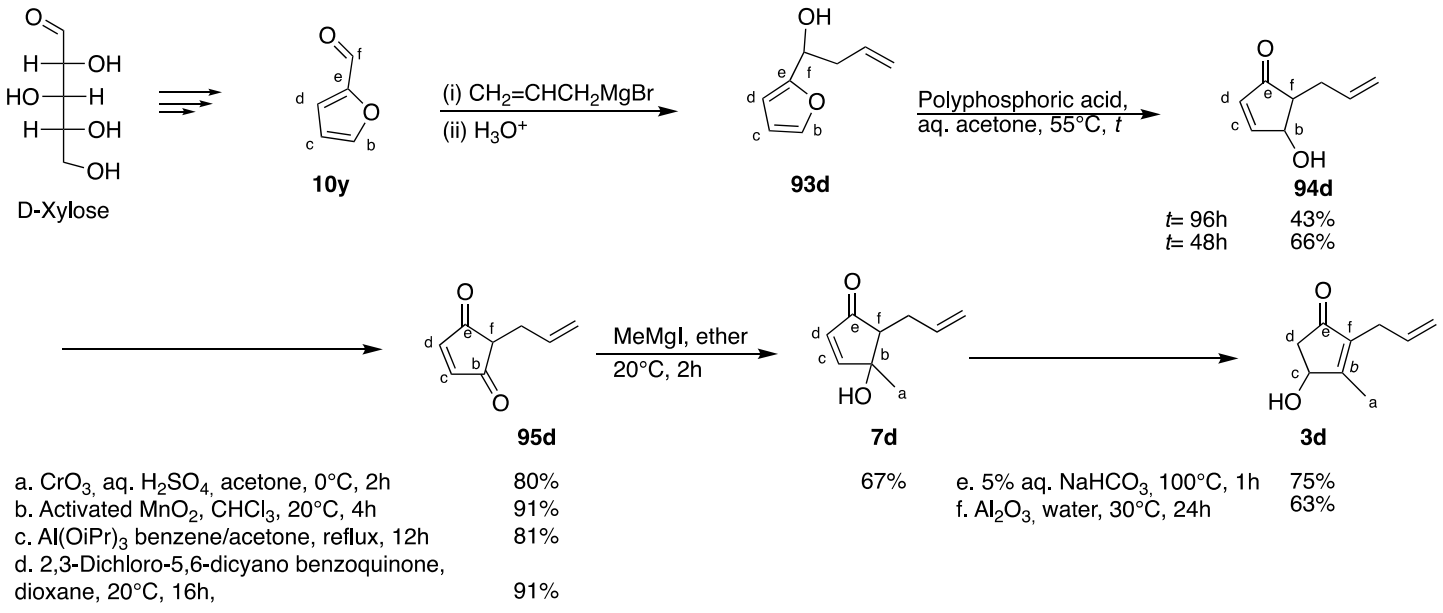
It is interesting to notice that under acidic or neutral, even under drastic conditions, isomerization of iso-allethrolone **7d** to the more stable allethrolone **3d** does not takes place although it occurs smoothly and in almost quantitative yield in the presence of basic alumina at room temperature in an ether-benzene mixture of solvents (Scheme 32, entry a).[32,33] Alternatively the transformation of the furfuryl carbinol **32d** to the allethrolone **3d** has been achieved by Saito[33] in a single pot from the furfuryl carbinol **32d**, in water at reflux, using an acidic pH (5, 12h) at first, then moving to a higher pH (7.9, 2h; Scheme 33, entry e). Use of high temperature and pressure, in the presence of magnesium chloride or a mixture of potassium mono and diphosphates as catalysts allows also the one-pot transformation of **32d** to **3d** (Scheme 33 entries f and g).[36]

The transformation has been applied to jasmololone **3c** but this was obtained in very low overall yield (24-27%; Scheme 32, entry d, Scheme 33, entry h).[77]



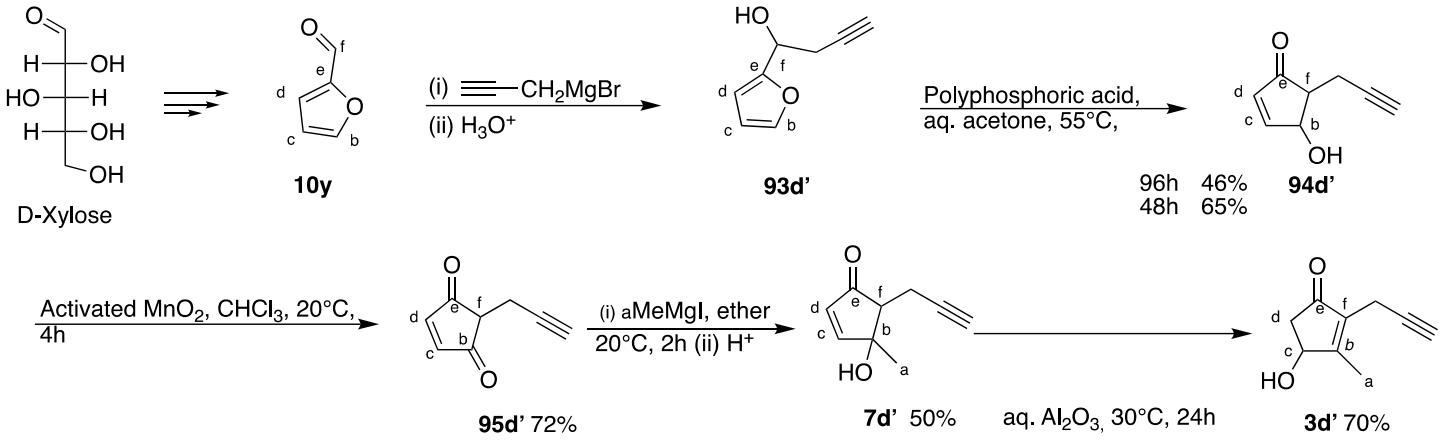
Scheme 33. Synthesis of allethrolone and jasmololone from furfuryl alcohols under controlled conditions.

5.2.2.1.2 Synthesis of rethrolones from furfuryl carbinols 93 involving the intermediate methylation of 4-oxo-2-cyclopentenones 94. A related, somewhat longer approach has been proposed[34] to achieve the synthesis of allethrolone (Scheme 34) and prallethrolone (Scheme 35) from 2-formylfuran **10y** readily available from natural D-xylose.



Scheme 34. Synthesis of allethrolone from D-xylose. [34]

Compared to the approach disclosed above (Sub-section 5.2.2.1.1.), the 2-formylfuran **10y** misses the C_a methyl group that has to be introduced at a later stage. Reaction of allyl or propargyl Grignard reagent to **10y**, followed by acidic treatment of the resulting furfuryl alcohols **93d**, **93d'** (Polyphosphoric acid, aq. acetone, 55°C) directly delivers the 4-hydroxycyclopent-2-enones **94d** (Scheme 34) and **94d'** (Scheme 35) in modest yield after 48h (lower yields for longer reaction times).



Scheme 35. Synthesis of prallethrolone from D-xylose. [34]

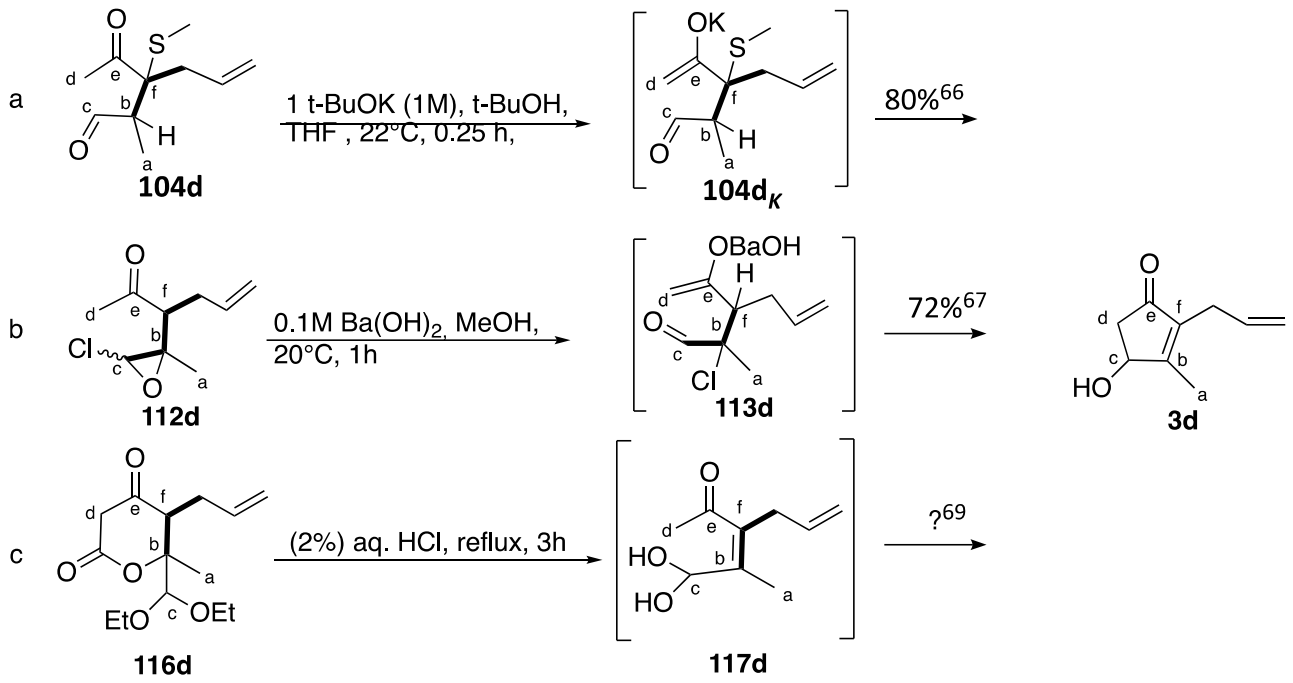
Introduction of the missing C_a methyl group at C_b, has been achieved from **94d** or **94d'** by sequential (i) oxidation to the prochiral diketones **95d** and **95d'** [Scheme 34: chromium trioxide (entry a), activated manganese dioxide (entry b), aluminum tri(isopropoxide) /acetone (the Oppenauer oxidation reaction, entry c); or 5,6-dichloro-5,6-dicyanoquinone (entry d)], and (ii) subsequent nucleophilic mono-addition of methylmagnesium iodide in ether that delivers *iso*-rethrolones **7d** (Scheme 34) and **7d'** (Scheme 35). The reaction of the latter with 5% aqueous solution of sodium hydrogen carbonate (reflux, 1h, 75% yield in **3d**, Scheme 34, entry e) or with 300-mesh activated alumina at lower temperature (30 °C), but for longer time, efficiently achieve their isomerization yielding allethrolone **3d** (63%, Scheme 34, entry f) or prallethrolone **3d'** (70%, Scheme 35).[34]

5.3. Synthesis of the rethrolones by carbocyclisation of 1,4-ketoaldehydes

5.3.1 Generalities. The synthesis of allethrolone **3d** has been achieved by carbocyclisation of a methyl ketone possessing a formyl group at C_b (Scheme 36, entry a)[66] or one of its protected forms (Scheme 36, entries b,c) and implies the formation of the C_c-C_d bond (Scheme 1, entry c).[67,69]

It allows the construction of its carbon framework through a convergent strategy that involves an aldol reaction generating at the same time the C_c–C_d single bond and the hydroxyl at C_c. Depending upon the case the tetra-substituted C_b=C_f double bond is present on the starting material (Scheme 36, entry c)[69] or is produced by β-elimination reaction concomitantly to the aldol reaction (Scheme 36, entries a,b).[66,67]

Note that the formation of the C_f=C_b double bond, present in **3d,** proceeds through an elimination reaction that implies a leaving group present at Cf in the first approach (Scheme 36, entry a)[66] and at C_b in the two latter (Scheme 36, entries b,c).[67,69] and the absence of the highly unstable cyclopentadienone **23d** (Scheme 2) that would have occurred on the elimination of water from a competing crotonization reaction at C_c,C_d.

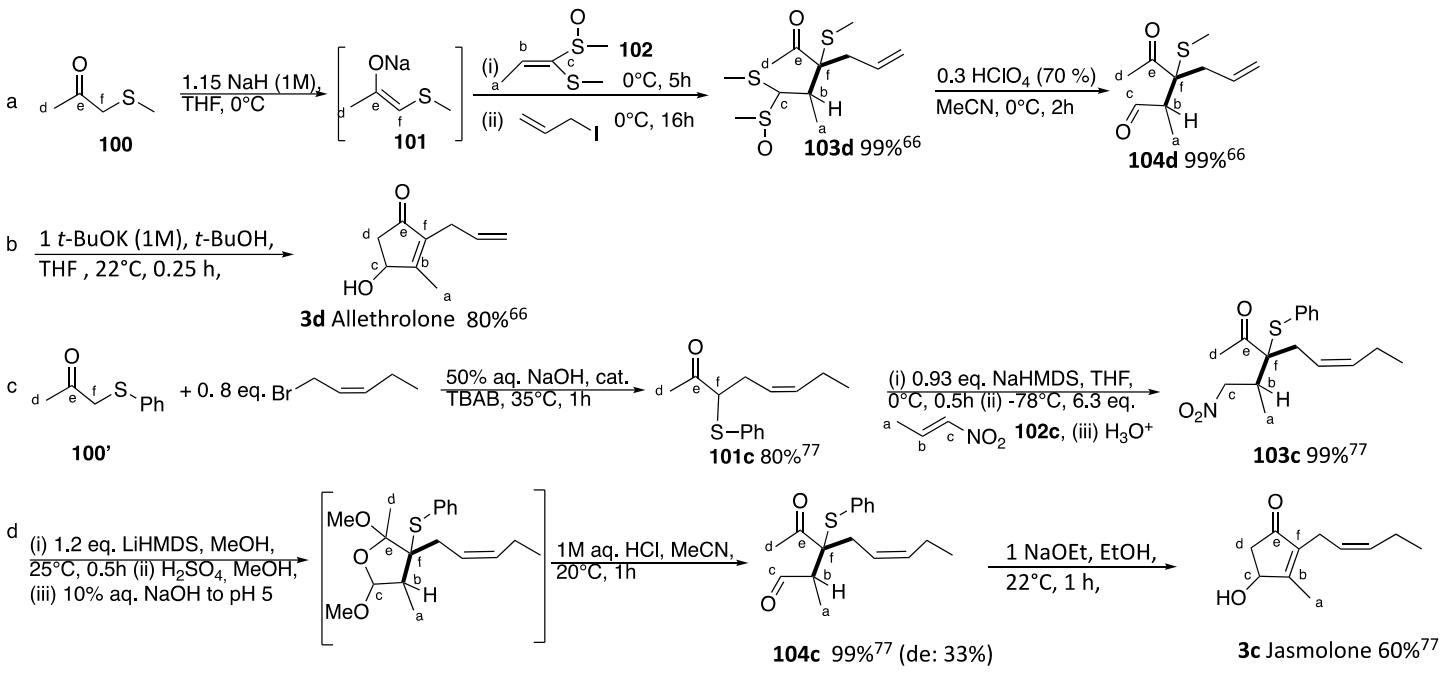


Scheme 36. Syntheses of allethrolone involving an intramolecular aldol condensation with a methyl ketone bearing a formyl group in β-position.[66,67,69]

5.3.2 Selected examples. The approach described[66] in Scheme 37 employs the easily accessible methylthio-acetone **100**. The methylthio group is involved in (i) the regioselective metalation at the C_f carbon, that allows the addition of the resulting enolate across the C=C double bond of the monooxidized ketene thioacetal derivative **102** (ii) the subsequent allylation at C_f with allyl iodide that leads to the highly functionalized **103d** and (iii) the formation of the C_f=C_b double bond by playing sequentially the role of a leaving group, at a last stage leading finally to allethrolone **3d** (Scheme 37).[66] It is noteworthy that (i) that deprotection of **103d** in acidic media generates **104d** that on basic treatment (*t*-BuOK, *t*-BuOH-THF, 22 °C, 0.25 h, 80% yield) allows the formation of the β-ketoalcohol by aldolization without concomitant crotonization reaction but efficient β elimination of the thiol discussed above, and (ii) that this process allows the synthesis of *d,l*-cis-cinerolone **3b** in 75% overall yield when using *cis*-1-iodo-2-butene in place of allyl iodide.[66]

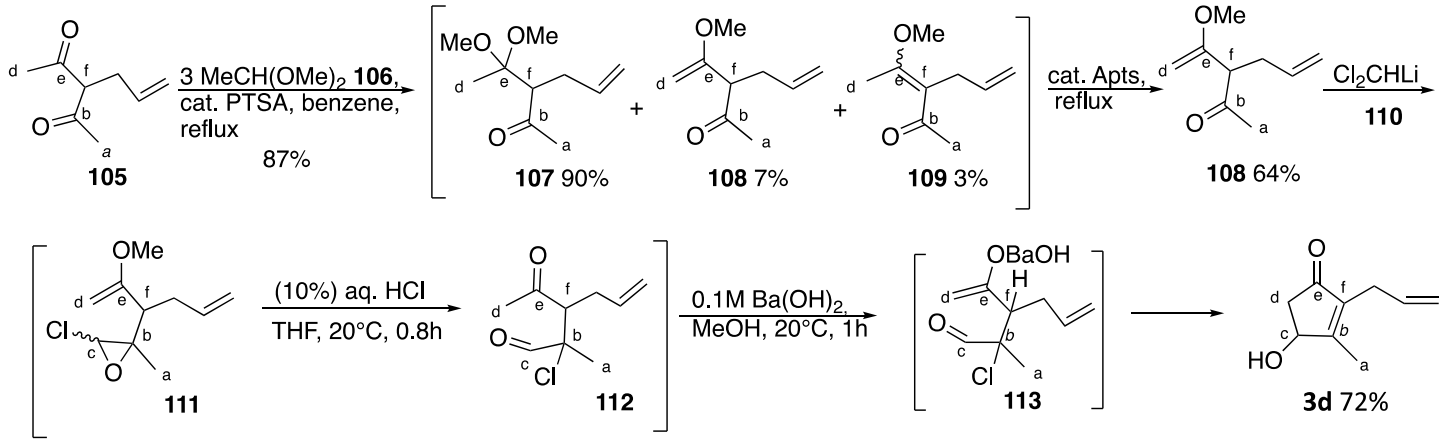
However, it was very recently reported[77] (reference 33 therein) that the authors were unable to extend on **100'**, the phenylthio analog of **100**, the transformation leading originally to **103d**, nor to carry out the carbocyclization of **104c**, the phenylthio analog of **104d**, expected to produce **3c** (Scheme 37, entry a).[66] The latter reaction (**104c** to **3c**) has however been successfully achieved by replacing *t*-BuOK in *t*-BuOH, originally used, by EtONa in EtOH (20 °C, 1 h, Scheme 37, entry d; reference 33 in our reference 77).[77]

In order to bypass the difficulties reported above, and following the same strategy, the authors[77] have trapped the 3-sodio-3-(phenylthio)oct-5-en-2-one with 1-nitropropene **102c**[77] in place of a 1-methylthio-1-methylsulfinyl-propene (Scheme 37, compare entry d to entry a).[66] The next steps to jasmololone **3c** have been adapted accordingly. The transformation of the nitroalkyl group to the corresponding aldehyde involves the Nef reaction[77,131,132,133] that produces the dimethoxytetrahydrofuran intermediate. The latter delivers almost quantitatively the γ-ketoaldehyde **104c** on acidic treatment that has been successfully cyclized to jasmololone **3c**, as reported above, on reaction with sodium ethoxide in ethanol (Scheme 37, entry d).[77]



Scheme 37. Synthesis of allethrolone and jasmololone through an intramolecular aldol condensation involving a methyl ketone bearing a formyl group in β-position.[66,77]

Allethrolone **3d** has been also synthesized from allyl acetylacetone **105** that is only missing the Cc carbon (Scheme 38).[67] This has been introduced by reaction of dichloromethyllithium[68] **110** on the carbonyl groups of **108**. The latter has been generated as well as the vinyl ether **109** on reaction of **105** with methyl orthoformate **106** catalyzed by *p*-toluenesulfonic acid (PTSA).[67] Interestingly, the presence of the vinyl ether **109** does not affect the next steps.



Scheme 38. Synthesis of allethrolone from a 2,4-pentanedione involving an intramolecular aldol condensation.[67]

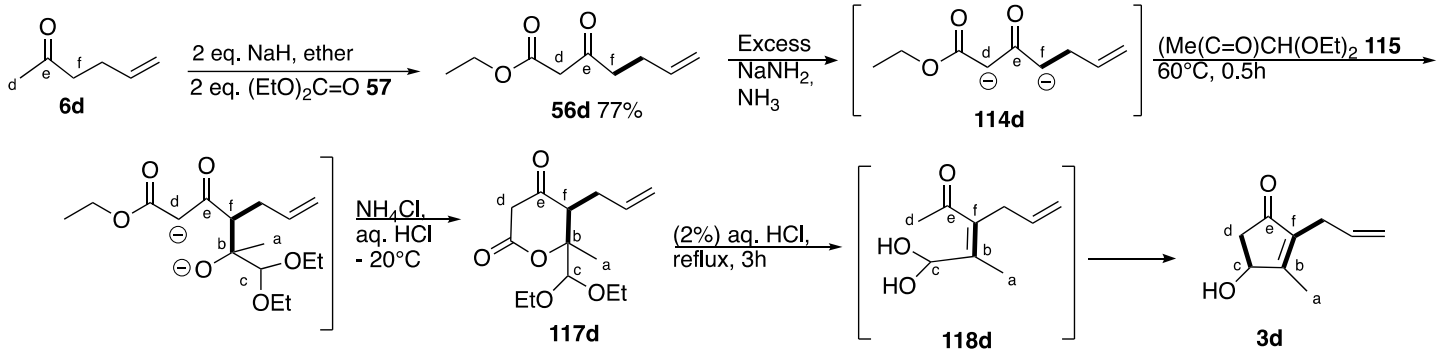
The addition of the dichloromethyllithium on to the carbonyl group of the methyl ketone **108** finally leads to the chloroepoxide[67]**111** that was not isolated but was transformed, in high yield, in the same pot, to allethrolone **3d** on sequential reaction with (i) aqueous hydrochloric acid that transforms the vinyl ether to the

methyl ketone and the chloro-epoxide moiety to the α-chloro-aldehyde, leading to the intermediate **112** and (ii) barium hydroxide in methanol that delivers **3d** from the barium enolate **113**.[67]

A related series of reactions, performed from acetylacetone and 2-butynyl *p*-toluenesulfonate, allowed the synthesis of *d,l*-cis-cinerolone **3b**.[67] It requires at one stage the selective hydrogenation of the C≡C triple bond to the *cis*-disubtituted double bond using the Lindlar catalyst.[2]

5.3.2.3. The synthesis[69] shown in Scheme 39 is published in a patent, and although each reaction is clearly described none of the yields is reported. As with the other syntheses in this section, the construction of the carbon framework is very rapidly achieved using the aldol reaction involving the dianion **114d**[70] derived from the β-keto ester **56d** with the diethyl acetal of pyruvaldehyde **115**. This approach reverses the reactivity of pyruvaldehyde by exposing to the aldol process its keto carbonyl group rather that of its formyl group as in the usual approaches shown for example in Scheme 20 (Section 5.1.2.2). that use the sodium salt **56d*K*** of the same β-keto ester **56d** and pyruvaldehyde **53**, the precursor of the acetal **115**.

Smooth acid hydrolysis at low temperature of the resulting adduct **116d** leads to the β-oxo-lactone **117d** that on subsequent acid catalysis at reflux of the water solvent leads, in a single pot, to allethrolone **3d** (Scheme 39).[69] The process involves on **117d** (i) the hydrolysis of the acetal moiety that delivers the postulated aldehyde hydrate and the lactone ring opening inducing a β elimination reaction resulting in the formation of the Cb-Cf and then a decarboxylation reaction leading to the generation of the methyl ketone producing the intermediate **118d** (Scheme 39).[69]



Scheme 39. Synthesis of allethrolone involving two consecutive aldol condensations.[69]

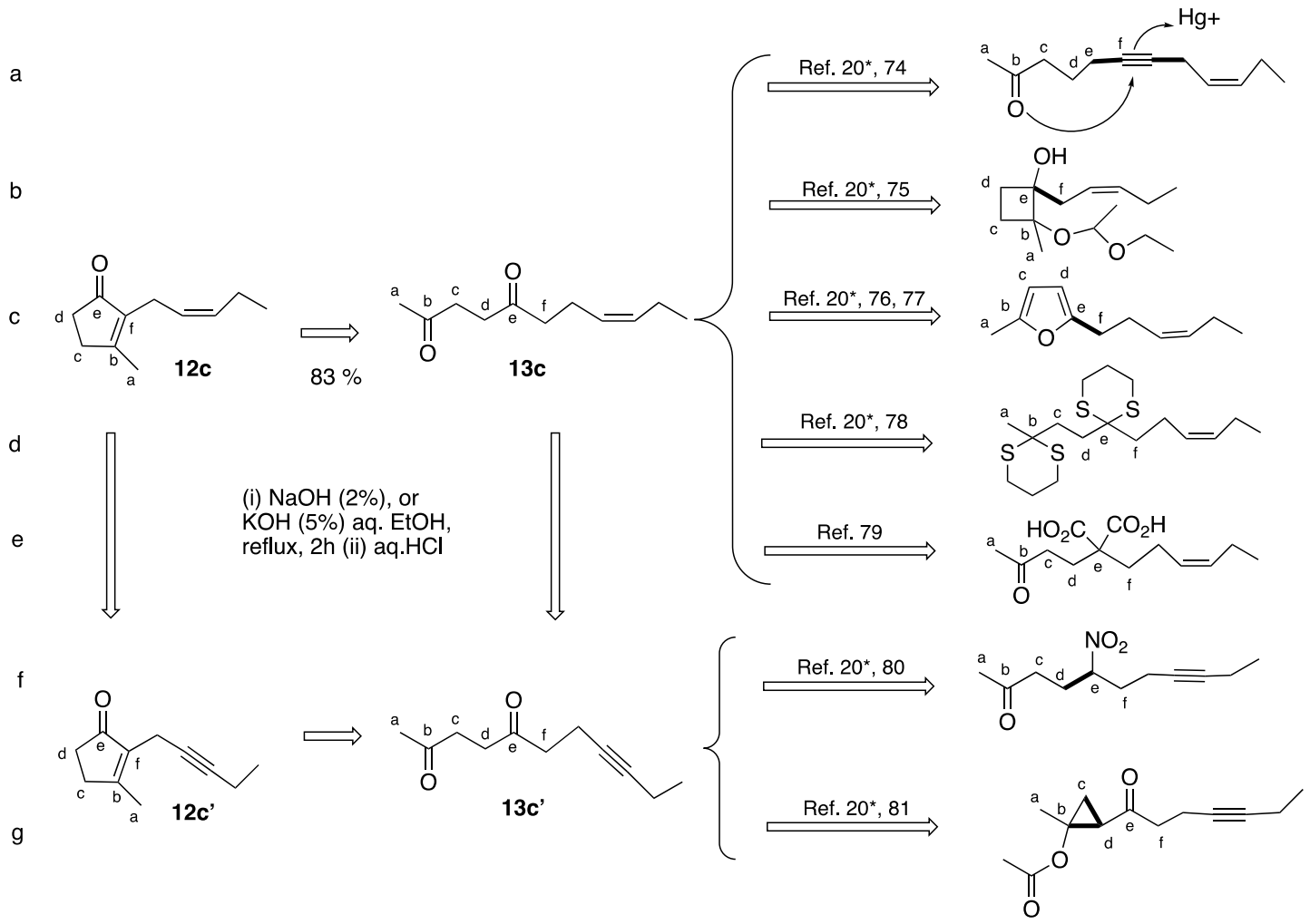
5.4. Synthesis of rethrolones by selective oxidation of preformed rethrones

Among the different strategies proposed for the synthesis of rethrolones, that involving the selective oxidation at C_c of cyclopentenones **12**, is very attractive since several synthetic methods to such compounds, as for example that of jasmone **12c**, have been devised (Scheme 1, entry d).

5.4.1 Syntheses of Jasmone 12c. Some of the retrosynthetic routes to jasmone **12c** that involve an aldolization reaction from the unsaturated β-diketones **13c** bearing a C=C double bond or **13c'** possessing a C≡C triple bond have been collected in Scheme 40 (entries a-e), [20,22,28,44,74-82] and Scheme 40 (entries f,g),[20,79,80] respectively. Although there are few variations for the formation of the cyclopentane ring using the aldol reaction (Section 4.3),[18,20,28] a wide variety of synthetic routes to their diketone precursors have been published. They include (a) The regioselective addition of water on a C≡C triple bond promoted by mercury salt and directed by complexation of the mercury salt by the carbonyl group of the methyl ketone (Scheme 40, entry a),[74] (b) The ring opening of β-alkoxy-cyclobutanol (Scheme 40, entry b) ,[75] (c) The acid catalyzed ring opening of furans (Scheme 40, entry c), [28,44,76] (d) The hydrolysis of thioketals (Scheme 5, entry d), [78] (e) The electrolytic di-

decarboxylation of β diesters (Scheme 40, entry e), [79] (f) The Nef reaction involving the transformation of a nitro group to a carbonyl group (Scheme 40, entry f), [80] and (g) The cyclopropane ring opening of a β alkoxy-cyclopropyl ketone (Scheme 40, entry g). [81]

The last two approaches require an extra step to produce jasmone **12c** that involves the dihydrogenation of the C≡C triple bond to the Z-C=C double bond using hydrogen and Lindlar catalyst.[4]



Scheme 40. Some retrosynthetic routes to jasmone involving the formation of the five membered ring.[20,74-81]

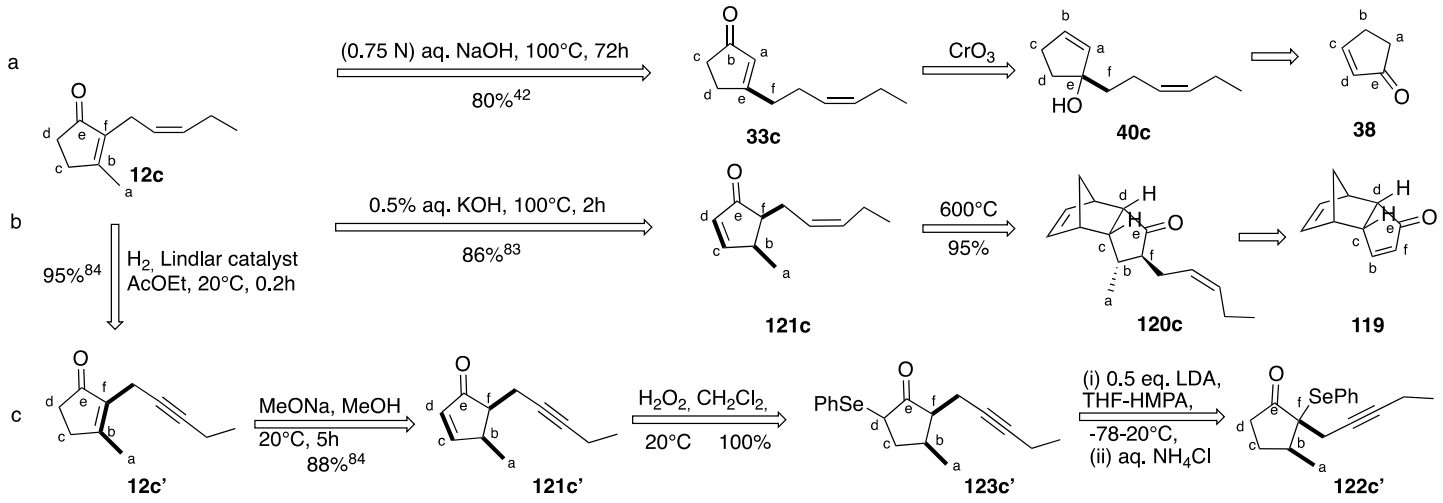
The synthesis of jasmone **12c** that has also been achieved by base-catalyzed isomerization of an existing cyclopentenone such as that of **33c** (Scheme 41, entry a),[42] **121c** (Scheme 41, entry b)[83] and **121c'** (Scheme 41, entry c) [84] opens access to new strategies reminiscent of those that have been described for the synthesis of rethrolone **3** (Section 4.3).

The isomerization processes used for these syntheses of *cis*-jasmone involves two completely different pathways in which either a rearrangement takes place in which (i) extensive changes occur since not only is the C_f carbon present on the side chain in **33c** inserted into the five membered of jamone **12c,** but also the oxygen of the carbonyl carbon is no longer attached to C_b (in **33c**) but to C_e (in **12c**) (Scheme 41, entry a),[42]or (ii) the C_c,C_d double bond present on the five-membered ring of **121c** migrates to the C_b,C_f location in jasmone **12c** (Scheme 41, entry b)[42] or its related unsaturated analogue **12c'** from **121c**' (Scheme 41, entry c).[84]

Both transformations are base-catalyzed and generate **12c** or **12c'** that possess more stabilized C=C double bonds since they are more alkyl-substituted than that present on the starting materials (Scheme 41). However, whereas the former implies a retroaldol reaction that reorganize the related carbon framework bond (Scheme 41, entry a),[42] the latter, at least formally, involves the migration of a C=C double bond (Scheme 41, entries b,c) [83,84] that can be also achieved by heat (sealed Pyrex tube, 220°C).[83]

The synthesis of jasmone **12c** that involves the intermediate **33c** (Scheme 41, entry a)[42] is reminiscent of that shown in Scheme 11 and discussed there. It takes advantage of the 1,2-addition of the (*Z*)-3-hexenyllithium across the C=O double bond of cyclopentenone and oxidation of the resulting alcohol with chromium trioxide that takes place with a concomitant rearrangement leading to **33c**.[42] The whole process finally leads to jasmone **12c** in 29% overall yield (Scheme 41, entry a).[42]

The route to jasmone **12c** reported by Stork[83] (Scheme 41, entry b), requires further comment since the starting material, the tricyclodecadenone **119**, plays the role of the extremely reactive cyclopentadienone. Dialkylation of the conjugated C=C double bond leading to **120c** involves the 1,4-addition of methyl cuprate and the allylation of the related lithio-enamine that prevents the formal O-allylation that is operative on the related ketone enolate.[83,85] Deprotection of the "protected C_c=C_d double bond" from **120c** to **121c** is achieved through a retro Diels-Alder reaction[83,86,87] that involves flash thermolysis (600°C). This method does not favor the migration of the resulting C=C double bond from C_c,C_d in **121c** to C_b,C_f **12c** that effectively takes place at much lower temperature (100 °C) or under different experimental conditions (Scheme 41, entry b).[83]



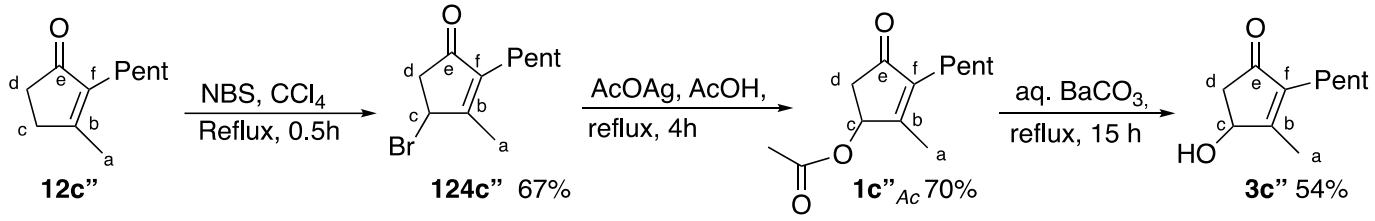
Scheme 41. Retrosynthetic routes to jasmone involving a preformed cyclopentane ring.[42,83,84]

The isomerization of the cyclopentenone **121c'** to **12c'** precursor of jasmone **12c** was not originally planned by Liotta (Scheme 41, entry c) but an adaptation to the context of an unexpected reactivity.[84]

The presence of the phenylseleno group at C_f on the 2-phenylseleno cyclopent-2-enone **48** was strategically planned to soften that position and favor its propargylation leading to **122c'**. It was planned to produce, after oxidation, the related selenoxide particularly prone to eliminate[88,89,90] with a hydrogen located on a β-carbon (C_b) in the suitable syn-relationship to produce the required C_f=C_b double bond present in jasmone **12c** (Scheme 41, entry c). Apparently, the reaction takes another course when applied to **122c'** since the elimination occurs instead from the side chain leading to an exocylic conjugated enyne moiety. In order to circumvent this problem preliminary treatment of the α-seleno-ketone **122c'** with base was used to isomerize it to the α-seleno ketone **123c'** bearing the phenylseleno-group at C_d (Scheme 41, entry c).[84] The latter on oxidation with hydrogen

peroxide quantitatively collapses to the cyclopentenone **121c'** (Scheme 41, entry c),[84,88-90] precursor of **12c** by base-promoted migration of the endocyclic C=C double bond from the least stable C_c,C_d to the more stable C_b,C_f one (Section 4.3).

5.4.2 Synthesis of rethrolones 3 from rethrones 12. 5.4.2.1 Generalities. This approach to rethrolones **3** involves the selective oxidation of rethrones **12** at C_d an endocyclic allylic position. Such transformation that has been first carried out on cinerone **12c"** that bears a saturated side chain at C_f, has been achieved using the three-step sequence that involves allylic bromination[71] at C_d by *N*-bromosuccinimide (NBS) leading to **124c"** followed by regioselective substitution using silver acetate that leads to the acetate **1c"*Ac***, and to the alcohol **3c"** on saponification using barium carbonate (Scheme 42).[71]

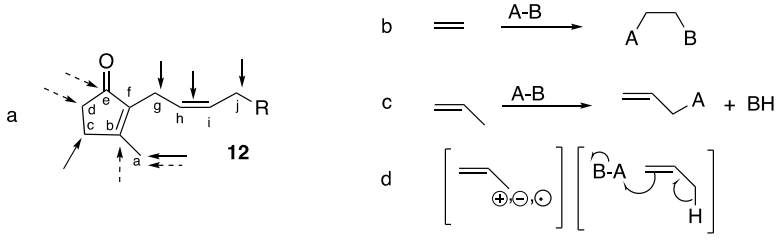


Scheme 42. Synthesis of cyclopentenolones from cyclopentenones by regioselective allylic oxidation.[71]

However, application of this process to analogous compounds possessing an unsaturation in the side chain attached at C_f such as on pyrethrolone and cinerolone failed.[52,72,73] It was for example reported[73] that treatment of cinerolone with lead tetraacetate in benzene, cupric bromide in chloroform and ethyl acetate, *t*-butyl peracetate and cuprous chloride in benzene, *t*-butyl chromate in carbon tetrachloride or selenium dioxide in aqueous ethanol did not allow the oxidation at C_c.[73]

In fact, rethrones possess several potential reactive sites shown on Scheme 43, entry a, that involve either their C_b=C_f or the C_h=C_i double bonds (Scheme 43, entry b) or their allylic positions at C_a, C_c, C_j and C_g that is bi-allylic (Scheme 43, entries c,d). The C_e=O carbonyl group is susceptible of 1,2-addition of nucleophilic species and favors at the same time the 1,4-addition at C_b and the enolization at C_d, C_c and C_a. The *Z*-stereochemistry of the exocyclic C_h=C_i double bond confers a higher reactivity than its *E*-isomer, tending to favor electrophilic addition reactions or reaction at C_j and C_g that can also result from an ene reaction (Scheme 43, entry d).

It should however be noted that although still no suitable reagent able to carry out the required transformation at C_c has been discovered, in *Chrysanthemum cinerariifolium* Nature has achieved it both regio- and stereo-selectively.[1,94]

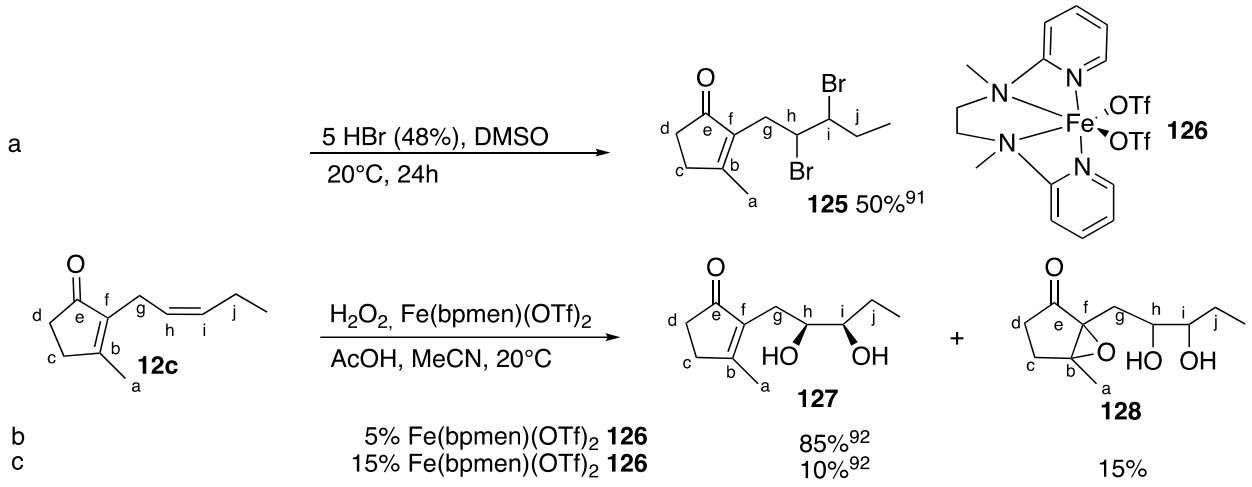


Scheme 43. Potential reactive sites of rethrones, generic reactions and potential intermediates

5.4.2.2 Chemical-reagents. Bromine, generated by oxidation of hydrobromic acid (Scheme 44, entry a),[91] or

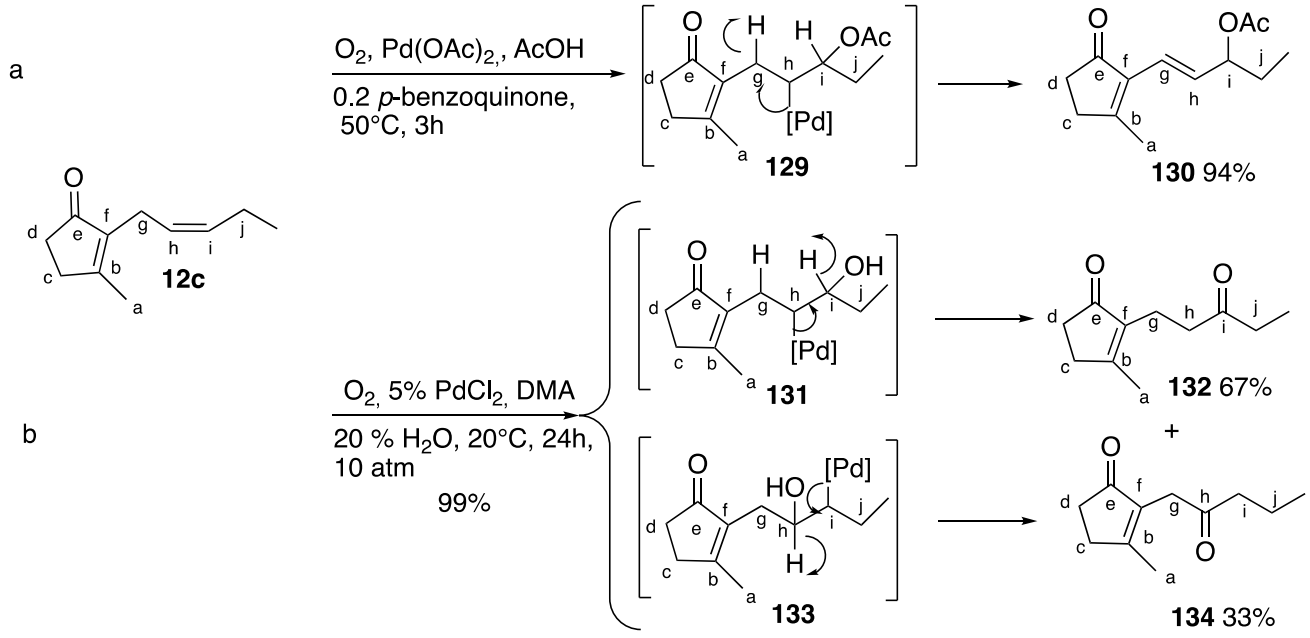
hydrogen peroxide in the presence of an iron catalyst [Fe(bpmen)(OTf)$_2$] **126** (Scheme 44, entry b)[92] react with *cis*-jasmone **12c** to produce the exocyclic dibromide **125** or the diol **127**.

The reaction of hydrogen peroxide regioselectively occurs on the exocyclic C_h=C_i double bond, especially when the oxidation is performed in the presence of 5% catalyst **126** (Scheme 44, entry b).[92] It is poorly selective and leads to a mixture of the diol **127** and the epoxy diol **128** in poor overall yield, if higher amount of **126** (15%) is used (Scheme 44, entry c).[92] Note that in such a case the reaction proceeds differently on the two C=C double bonds, producing a diol on C_h,C_i and an epoxide on C_b,C_f.[92]



Scheme 44. Behavior of *cis*-jasmone towards bromine and hydrogen peroxide.[91,92]

The reaction also takes place on the exocyclic double bond when *cis*-jasmone **12c** is reacted with dioxygen in the presence of palladium acetate and *p*-benzoquinone in acetic acid (Scheme 45, entry a),[93] but the resulting *Z*-allylic acetate **130**, obtained in excellent yield, results from regioselective addition of palladium acetate followed by regioselective β-elimination of palladium hydride that takes place away from the acetyl group.

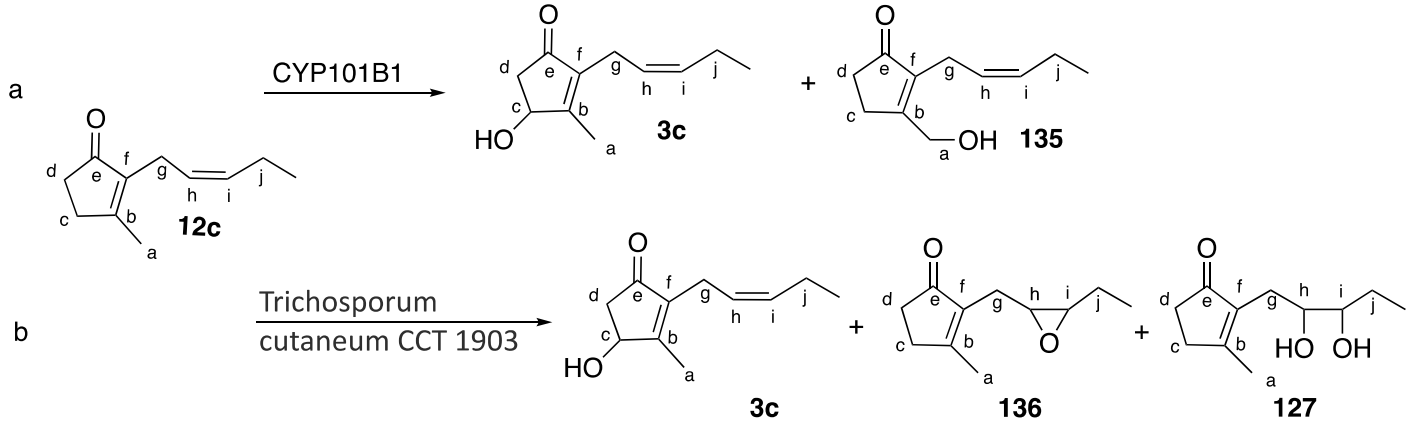


Scheme 45. Behavior of *cis*-jasmone towards dioxygen.[93]

The reaction involving palladium dichloride in a mixture of acetic acid and DMA is no longer regioselective and provides a mixture of exocyclic diketones **132** and **134** (Scheme 45, entry b).[93] They are expected to result from a non-regioselective addition of "palladium hydroxide" followed in each case by a regioselective β-elimination of palladium hydride, with departure of the hydrogen on the same carbon as the hydroxyl group (Scheme 45, entry b).[93] The presence of at least 10% of water is crucial to the success of the reaction, that takes place with good conversion after only 8 h (91%). It has been also reported that the oxygen content on the ketone carbonyl group comes from both the dioxygen and the water.[93]

5.4.2.3 Bioreagents. Bio-reagents, especially those present in *C. cinerariifollium*,[94] are however able to achieve the required endocyclic allylic oxidation of *cis*-jasmone **12c** that chemical reagents have, so far, been found unable to perform. This proved to be the role of the cytochrome P450 (CYP) oxidative hydroxylase present in the plant, whose coding gene has been identified. [94]

It has been found that other microorganisms also possess the aptitude to perform the same transformation, although less regioselectively, on *cis*-jasmone **12c**. Thus, the monooxygenase enzyme CYP101B1, from *Novosphingobium aromaticivorans* DSM12444, catalyzes the oxidation of *cis*-jasmone **12c** mainly to jasmololone **3c** with concomitant formation of a minor amount of 11-hydroxy-*cis*-jasmone **135** resulting from oxidation at its other allylic position on the C_a methyl group (Scheme 46, entry a),[95] and although jasmololone **3c** is produced[96] on reaction of *cis*-jasmone **12c** with *Trichosporum cutaneum* CCT 1903 whole cells, 7,8-epoxyjasmone **136** and 7,8-dihydroxyjasmone **127** are produced concomitantly in lower amounts (Scheme 46, entry b).[96] Related results have been obtained by reacting other fungal strains such as *Penicillium*, *Absidia*, *Syncephalastrum*, *Botrytis*, *Aspergillus*, *Cunninghamella*, *Chaetomium*, and *Didymosphaeria*.[97] It is unfortunate that very little has been reported on the stereochemical outcome LF conversions by such species, that should have produced enantiopure compounds.



Scheme 46. Behavior of *cis*-jasmone towards represenative bio-reagents.[96,97]

5.5. Synthesis of rethrolones by 1,4-cycloaddition of singlet oxygen to substituted cyclopentadienes

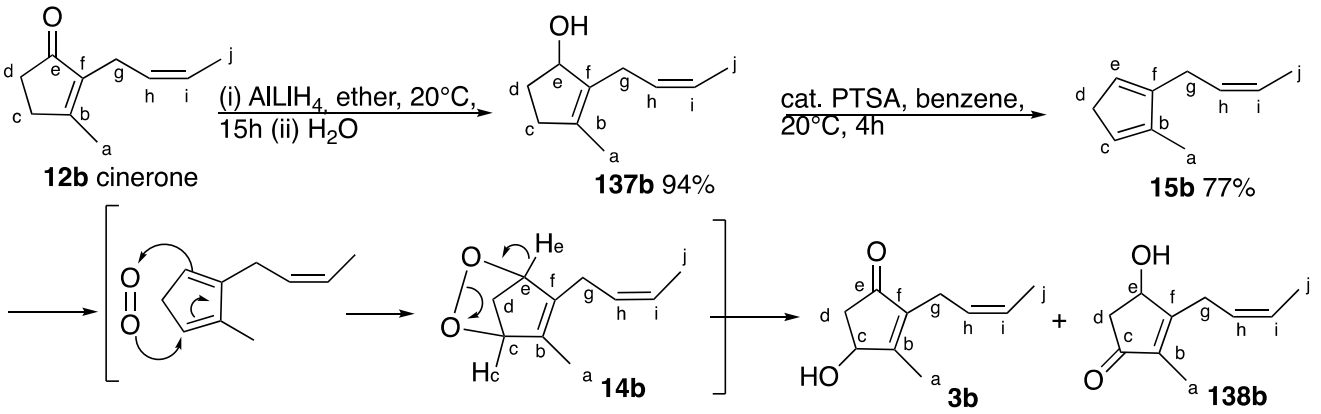
These reactions were shown in Scheme 1, route e.

Since selective oxidation of the cyclopentane ring of cyclopentenones **12** at C-4 has not yet been achieved efficiently, another approach, shown in Scheme 47, has been proposed that takes advantage of the 1,4-addition of singlet oxygen to dienes, already discussed in Section 5.2 on furans that also possess the diene moiety (Scheme 28).[29]

To be successful this approach requires (i) an efficient regioselective synthesis of the cyclopentadiene (**15b**) with the proper substitution at the correct positions, (ii) successful 2+4 cycloaddition of singlet oxygen to the

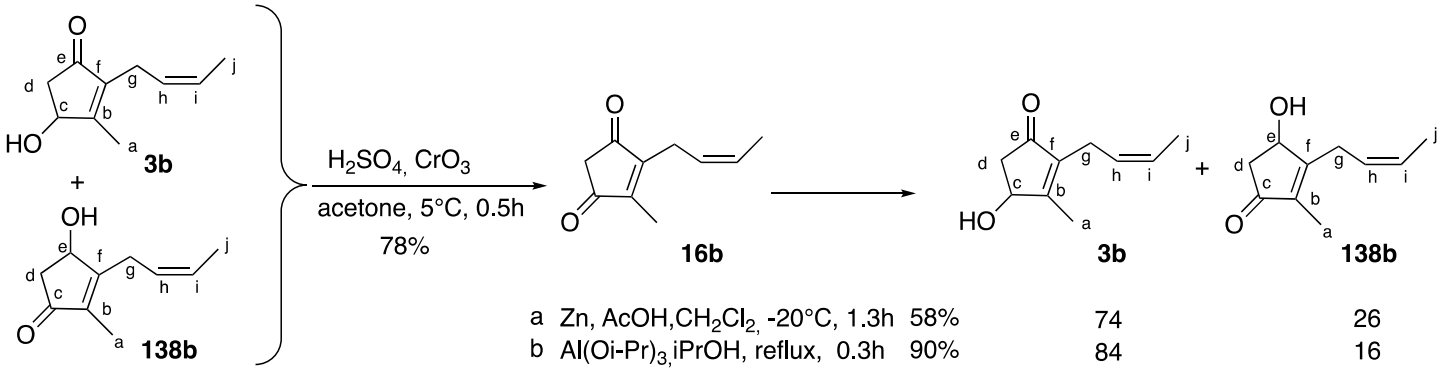
cyclopentadiene, and (iii) regioselective decomposition of the bicyclic peroxide that should provide the β-hydroxycyclopentenone **3b** and not its isomer **138b** (Scheme 47).

Reduction of the carbonyl group of the enone **12** to the allyl alcohol **137b** using lithium aluminum hydride and activation of its hydroxyl group with an acid catalyst delivers at room temperature the required diene **15b** regioselectively (Scheme 47).[73] Cycloaddition of singlet oxygen to the diene leads, after treatment with basic alumina,[98*] to an intractable mixture of regioisomeric rethrolone **3b** and **138b** in extremely poor yield when singlet oxygen is produced photochemically (Scheme 47, entry a)[73] and in modest yield from a process using hydrogen peroxide and sodium hypochlorite (Scheme 47, entry).[73,99]



Scheme 47. Synthesis of cinerolone by cycloaddition of singlet oxygen to a cyclopentadiene.[73]

The rethrolone **3b** has been generated[73] from this mixture with much better selectivity by introducing an additional two-step sequence (Scheme 48) that involves oxidation of the **3b**+**138b** mixture by the Jones reagent[73,100] followed by a Meerwein-Ponndorf-Verley reduction using aluminum isopropoxide (Scheme 48, entry b).[73,101] The reduction is modestly regioselective (dr: 68%) but it occurs in much better yield and higher regioselectivity than when zinc is used instead.[73] It is interesting to notice that over-reduction to the diol does not occur in those two processes. The regioselectivity observed is derived from the difference in steric hindrance between the methyl group at C_b and the butenyl group at C_f of **16b**.

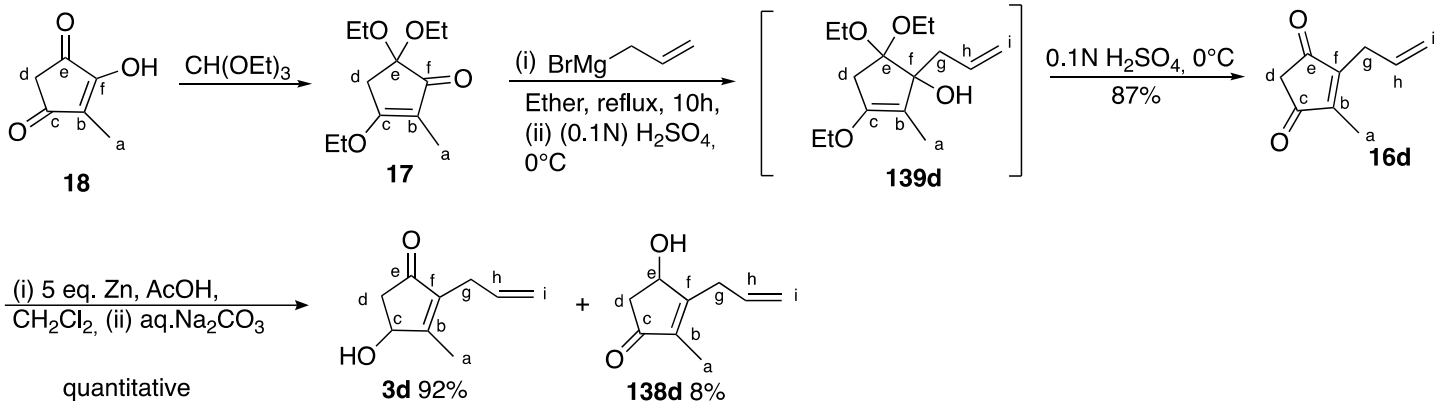


Scheme 48. Synthesis of cinerolone by regioselective reduction of a cyclopent-2-ene-1,4-dione.[73]

5.6. Synthesis of rethrolones by regioselective reduction of cyclopent-2-ene-1,4-diones

This transformation involving the regioselective reduction of cyclopent-2-ene-1,4-diones **16**, planned in Scheme 1, entry f, and shown[102] in Scheme 49, is extremely convergent - by far more so that the previous ones (Schemes 47, 48) but it shares with them the problems of regioselectivity associated with the reduction of the β-diketones **16** at the last step (Scheme 49, compare Scheme 48, entry a).

The synthesis takes advantage of (i) the easy transformation of triketone **18** to the β-alkoxy-enone **17** on reaction with triethyl orthoformate,[102] (ii) The efficient 1,2-addition of allylmagnesium bromide that takes selectively place on the carbonyl group whose reactivity resembles that of an ester (to which it is vinyloguous), and (iii) The selective rearrangement that smoothly takes place on the resulting adduct **139d** on acid-catalyzed hydrolysis that leads to the diketone **16d** with the complete carbon framework of allethrolone **3d** in very few steps.[102]



Scheme 49. Synthesis of allethrolone by regioselective reduction of a cyclopentenedione.[102]

Regioselective reduction of the less hindered carbonyl group (closer to the methyl group) is best achieved using an excess of zinc and acetic acid in dichloromethane (Scheme 49).[102] Although the conditions are very close to those of Scheme 48, entry a, and the starting material almost identical, there is a discrepancy involving the reduction of the 1,3-diones **16** that apparently occurs in much higher yields when performed on **16d** (100% instead of 58%) and with higher regiocontrol (de 84 instead of 68) than that involving the enedione **16b** (Scheme 49; compare Scheme 48, entry a).

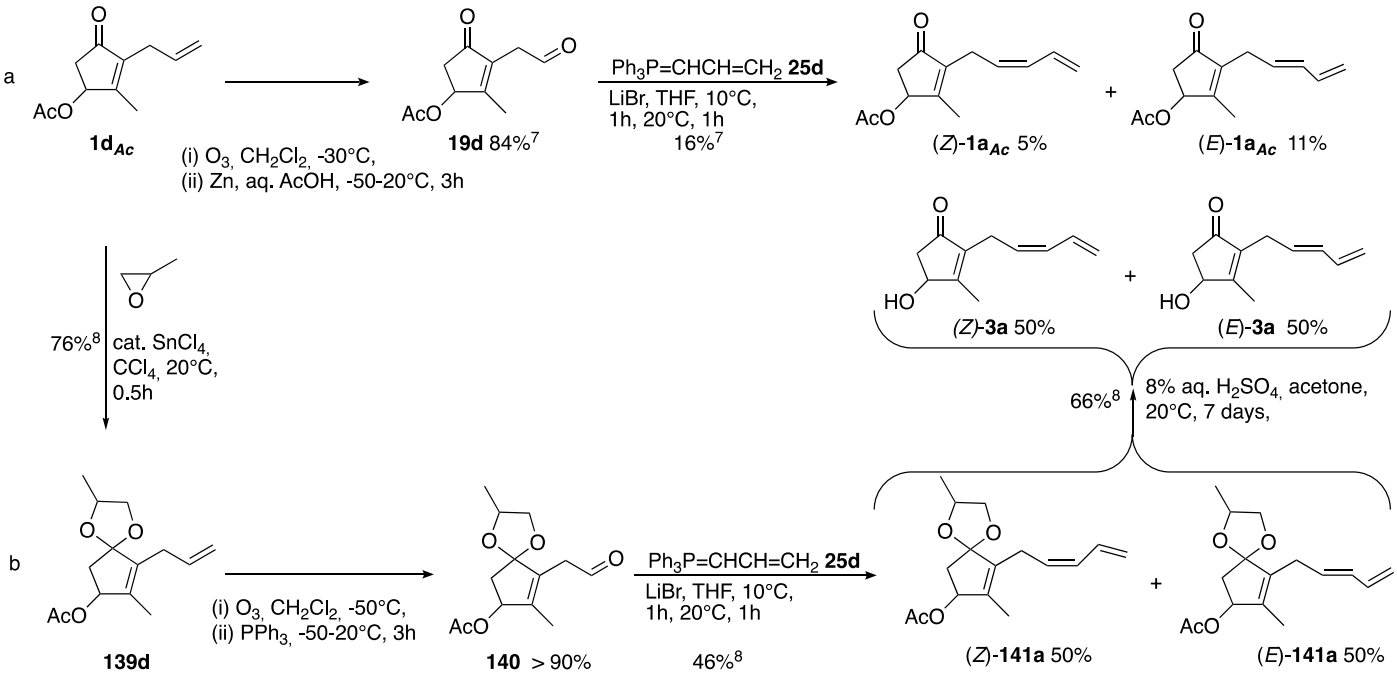
5.7. Stereoselective synthesis of rethrolone side-chains from allethrolone

This synthetic strategy (Scheme 1, entries g and h) allows access to the series of natural rethrolones such as pyrethrolone **3a**, cinerolone **3b** and jasmololone **3c**, allethrolone **3d** or prallethrolone **3d'**, that already possess almost all the required carbon framework. It avoids following the lengthy routes that have been already reported above.

Access to all those compounds from common commercially available enantiopure intermediates offers an opportunity to market their chrysanthemate esters (related pyrethrin **1a**, cinerin **1b** or jasmolin **1c**) as mixtures mimicking the natural composition in *C. cinerariifolium*, adapting to the trend to use natural products, avoiding the constraints from growing the plant for two years, and avoiding the presence of allergens (see Chapter 1 of this series).[1]

The synthesis of rethrolone side-chains from allethrolone **3d** has been successfully achieved by degradation and rebuilding of its allylic side chain (Scheme 1, entry g).

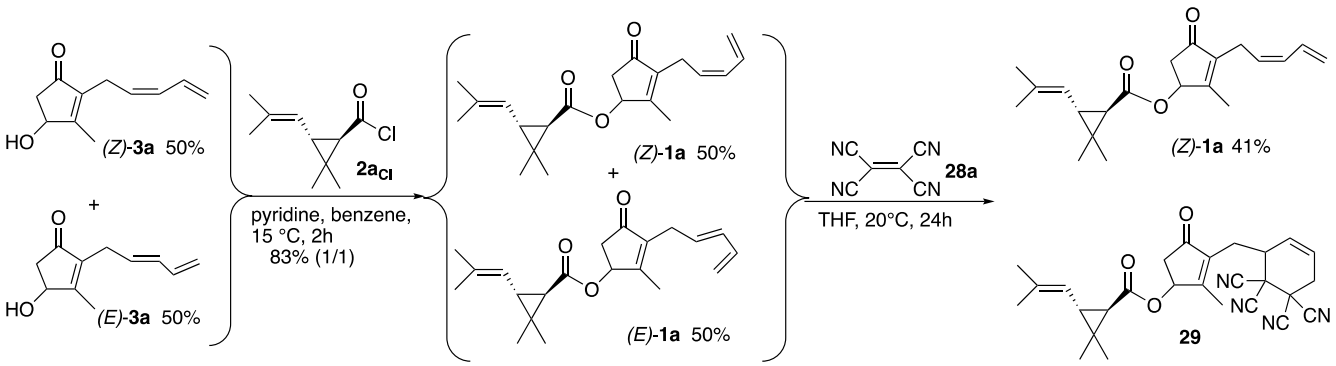
5.7.1 Transformations involving allethrolone and a Wittig reaction. The first approach involves the transformation of the commercially available allethrolone **3d**, to pyrethrolone **3a** (Scheme 50, entry a).[7] It was achieved, but in very poor overall yield (13%), from the acetate **1d*Ac*** via a two-step sequence that involves (i) its "reductive ozonolysis" [(i) O_3, CH_2Cl_2, -30 °C, (ii) Zn, aq. AcOH, -50 to 20 °C, 3 h] leading to the aldehyde **19d**, followed by (ii) a Wittig reaction employing the ylid **25d** derived from the allylic triphenylphosphonium bromide **26d** and n-butyllithium in THF that provides a Z/E (30/70) mixture of the pyrethrolone acetate **1a$_{Ac}$** (Scheme 50, entry a).[7] Results proved even worse when **19d** is generated from **1d*Ac*** by the two step one pot sequence involving osmium tetroxide/periodate methods instead($NaIO_4$ aq., OsO_4 THF, 20 °C, 24 h, 58% yield) since the aldehyde, formed in reasonably good yield, decomposes on attempt at purification.[7] The authors also tried unsuccessfully on a model[7] to improve the *Z*-content of the resulting olefinic compounds by reacting aldehyde with the same ylide **25d**, generated using the "non salt" method published by Schlosser,[9,106] but that apparently works only with "non-conjugated ylides".



Scheme 50. Synthesis of pyrethrolone from allethrolone by modification of the side chain.[7,8]

The same sequence of reactions applied to **139d,** a derivative of allethrolone **3d** protected both on its hydroxyl group as an acetate and on its carbonyl group as a dioxolane, leads to a substantial improvement in the yield as well as unexpectedly improves the ratio of the desired *Z*-stereoisomer (Scheme 50, entry b; compare entry b to entry a).[8] The increase (30%) in this step does not improve the whole process too much since it requires (i) the use of two more steps that results in lowering the overall yield by 50%, (ii) to tolerate an unusually long reaction time for the deprotection of **141** to **3a** (7 days!, Scheme 50, entry b), and (iii) a tedious separation of the desired pyrethrolone stereoisomer **3a*Z*** from the E+Z mixture that uses chromatography on silver nitrate impregnated support.[8]

Otherwise, the stereoisomeric mixture of *d,l*-**3a** resulting from deprotection of **141** (Scheme 34 entry b) was esterified[8] with *d-trans*-chrysanthemic acid chloride **2a*Cl*** (Scheme 51) and the pyrethrin **1a$_Z$** possessing a *Z*-allethronyl moiety was isolated as shown.



Scheme 51. Synthesis of pyrethrin from a cis/trans mixture of pyrethrolone.[8]

Purification of the pyrethrin **1a$_Z$ w**as successfully achieved after reacting the resulting mixture with tetracyanoethylene **28a** that exclusively reacts on the undesired pyrethrin **1a**$_E$ stereoisomer and leads to the Diels-Alder cycloadduct **29** since it is the only diene that allows a strainless *S-cis*-conformation required for the cycloaddition to occur (Scheme 51; for related work see Scheme 3), leaving the **1a**$_Z$ free from **1a**$_E$.

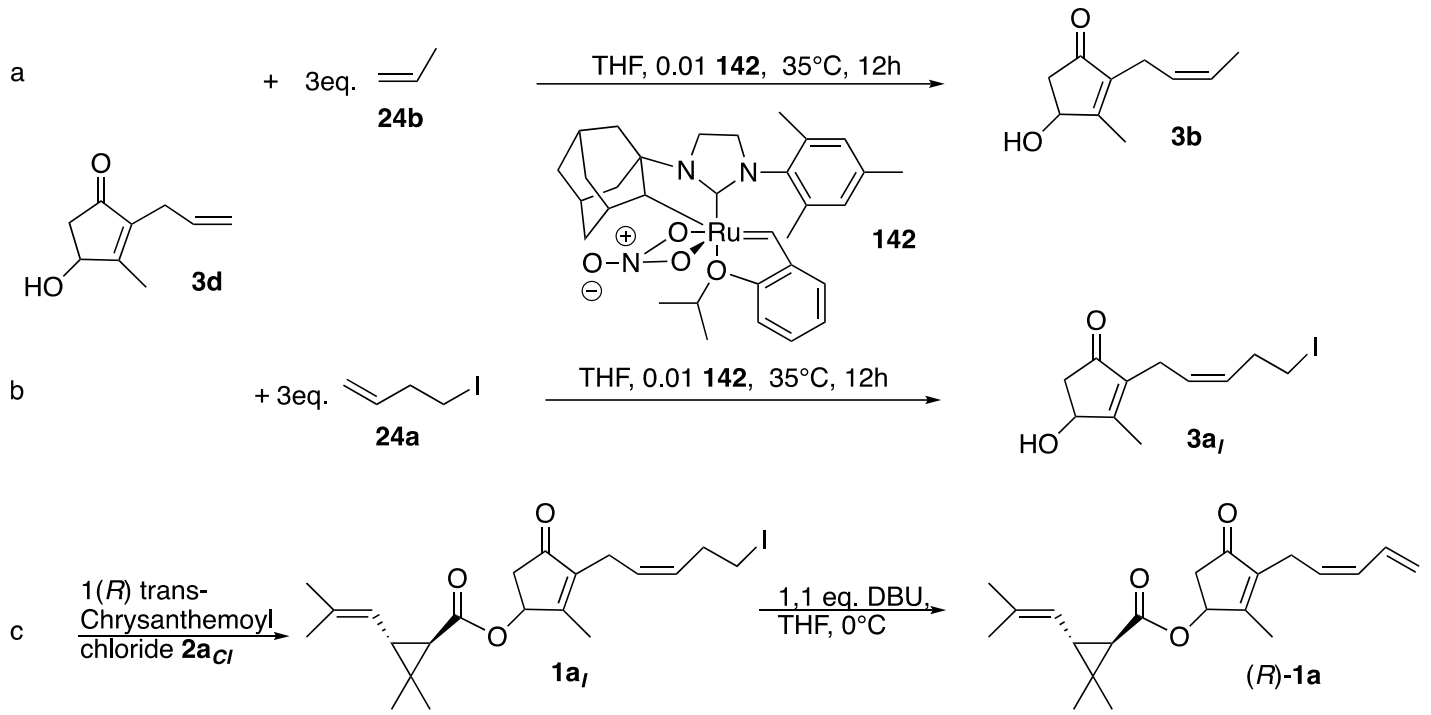
5.7.2 Transformations involving allethrolone and a metathesis reaction. The second and briefer transformation of allethrolone **3d** to cinerolone **3b** and jasmololone **3c** takes advantage of the olefin cross-metathesis reaction that occurs in a single step through a trans-alkylidenation reaction exchanging, the methylene group of the former **3d** by the ethylidene or propylidene group to produce **3b** and **3c**. Although the metathesis reaction has been well established for many years, the stereocontrol of the resulting olefinic compound, especially if the *Z*-stereochemistry is required, as is the case with natural rethrolones, has not yet reached today's requirements, even if considerable progress has been achieved.[13,14,15]

Thus, the patent[12,13] disclosing the results gathered in Scheme 52 that neither reports yields nor the stereochemical outcome of the reactions has to be taken cautiously and can be viewed only as a collection of pertinent references on the subject.

The ruthenium catalyst **142** [13,14] selected by the authors of the patent[12] has been previously used by Grubbs[15] to synthesize insect pheromones possessing a *Z*-C=C disubstituted double bond in about 75% yield and only 70% diastereoselectivity, from seed-oil derivatives such as oleyl alcohol and 11-eicosenol. We therefore could assume that their results are of the same order that makes their approach far from attractive. Furthermore, although these transformations use a few percent catalyst, its high molecular weight and absence of information about its recovery and recycling are not encouraging.

The process described in the patent allows the one step synthesis of cinerolone **3b** (Scheme 52 entry a)[12] and jasmololone **3c**,[12] has not however been used to synthesize pyrethrolone **3a** but the related pyrethrin I **1a** (Scheme 52, entry c).

Allethrolone **3d** has been reacted, in the presence of the ruthenium catalyst **142**, with an excess of 1-iodobut-3-ene **24a** that results in the synthesis of the rethrolone **3a**$_I$ possessing the homoallyl iodide group on its side chain (Scheme 52 entry b).[12] Esterification with chrysanthemoyl chloride **2a**$_{CI}$ leads to the ester **1a**$_I$ precursor of pyrethrin I on base promoted elimination of hydrogen iodide (Scheme 52, entry c).[12] Regrettably, the yields of the different steps and the nature of the by-products formed are again not disclosed.[12]



Scheme 52. Synthesis of cinerolone and pyrethrin from allethrolone by olefin cross-metathesis reactions.[12]

5.8. Stereoselective synthesis of rethrolone side-chains from prallethrolone

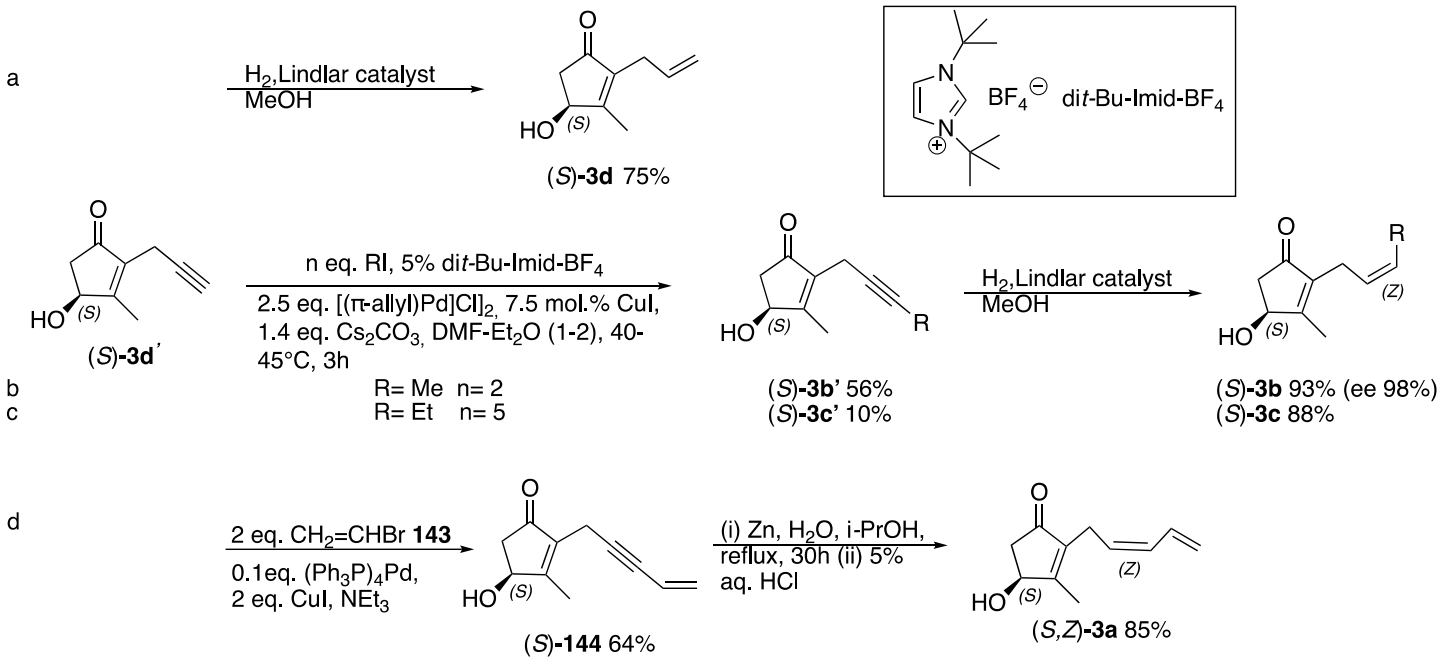
This procedure employs the stereoselective synthesis of rethrolone side chains from prallethrolone **3d'**, by sequential metalation, alkylation or vinylation, then hydrogenation of their side chains (Scheme 1, entry h).

The syntheses[3] of the unnatural enantiopure allethrolone (*S*)-**3d** and of the natural cinerolone (*S*)-**3b** and pyrethrolone (*S*)-**3a**, have been efficiently achieved from prallethrolone (*S*)-**3d'**. These transformations take advantage of (i) the availability of prallethrolone (*S*)-**3d',** an industrial compound accessible in large quantities and high enantiomeric purity, (ii) the presence on its structure of almost all the appendages present in other rethrolones as well as a terminal C≡C triple bond that, without the need for protection/deprotection, allows procedures to: (a) *adjust* the length of its side chain by alkylation (Scheme 53, entries b,c) or vinylation (Scheme 53, entry d), taking advantage of the Sonogashira cross coupling reaction[103] to generate the related to (*S*)-**3b'** and (*S*)-**3a'** possessing a C≡C triple bond on the side chain, and (b) *allow* their dihydrogenation leading to the compounds possessing the related C=C double bond (Scheme 53, entries a-d), with the required *Z*-stereochemistry in high yield and high regioselectivity (Scheme 53, entries b-d), even from the ene-yne (*S*)-**3a'** precursor of enantiopure pyrethrolone (*S*)-**3a**. Some specific comments on each of these two key steps will be disclosed in Subsections 5.8.1 and 5.8.2.

5.8.1 Alkylation and vinylation of 3d'. It has been achieved using the Sonogashira reaction[103] that offers the advantages of experimental simplicity, high atom-economy and functional-group tolerance and typically employs a palladium and a copper catalyst to couple terminal alkynes.[123] The conditions originally disclosed by Sonogashira proved suitable for the vinylation of prallethrolone (*S*)-**3d** that finally leads to pyrethrolone **3a**, and was achieved in reasonable yield using vinyl bromide **143**, Pd(0) in the presence of copper iodide as catalyst and a tertiary amine such as Et_3N or *i*-Pr_2NEt as a base (Scheme 53, entry b),[3] but did not proved suitable for the alkylation of (*S*)-**3d'** leading finally to cinerolone **3b** and jasmololone **3c**.[3]

It was however found that the conditions of the modified Sonogashira reaction reported by Fu[123] that involves a Pd/N-heterocyclic carbene-based catalyst, is suitable for the methylation of prallethrolone (*S*)-**3d'**

leading to (*S*)-**3b'** the precursor of cinerolone (*S*)-**3b** (Scheme 53, entry b). Those conditions proved[3] however inefficient for its ethylation to (*S*)-**3c'**, the precursor of jasmololone (*S*)-**3c**, due to the well-known competing β-hydride elimination reaction (Scheme 53, entry c).



Scheme 53. Synthesis of allethrolone, cinerolone, jasmololone and pyrethrolone, from prallethrolone.[3]

5.8.2 Hydrogenation of the C≡C triple bond of 3d' and 144. The last step of the process requires the chemo- and stereo-selective dihydrogenation of the terminal (Scheme 53, entry a) or disubstituted (Scheme 53, entries b,c) C≡C triple bonds present on the cyclopentenolones (*S*)-**3a'**, (*S*)-**3b'**, (*S*)-**3c'**. It has been already discussed in Section 4.2 and has been successfully achieved conventionally, in up to 85% yield, by reacting dihydrogen in the presence of the Lindlar catalyst [Pd-$CaCO_3$ poisoned by $Pb(OAc)_2$].[4,26,77]

These conditions do not apply to the chemo- and stereo-selective dihydrogenation of the C≡C triple bond of the ene-yne (*S*)-**144d**.[3,4,26,77] Related conditions that involve the use of Pd-catalysts[4] poisoned by quinoline, manganese chloride in the absence or presence of quinoline, 5% Pd-$BaSO_4$-(6 eq.)-quinoline or $NaBH_4$-BF_3·Et_2O lead besides the desired pyrethrolone **3a**, to some jasmololone **3c** resulting from an over-reduction of the terminal C=C double bond and the recovery of some starting material (*S*)-**144d.**[3]

The required transformation of the eneyne (*S*)-**144d** to pyrethrolone **3a** has been nevertheless successfully performed in up to 85% yield, using activated Zn in isopropanol (100°C, 30 h; Scheme 53, entry d),[3] a reaction previously used to reduce the triple bonds to Z-C=C double bonds in long chain conjugated fatty acids (Section 4.2).[5]

This approach to rethrolones from prallethrolone (*S*)-**3d'** is probably the most convergent although it does not allow the synthesis of jasmololone **3c** in reasonable yield.

6. Synthesis of Enantiopure Natural and Unnatural Rethrolones from Racemic Compounds

Although enantiopure aldol reactions have been recently reported (see below), they are far from being efficient and have not been applied to synthesis of rethrolones as we shall see in Chapter 7. Therefore, resolution of a

racemate remains the only viable solution that has been used in industrial synthesis. The first approaches rely on separation by crystallization of diastereoisomeric mixtures with the requirement that the resulting separated isomers must be separable into the resolving agent and the required enantiomer without affecting the fragile cyclopentenolone moiety that is sensitive to basic media that favor both epimerization and the formal elimination of water leading to the extremely reactive cyclopentadienone intermediate (see below).

The second type of approach deals with the enantioselective hydrolysis of racemic esters or enantioselective acylation of one of the two enantiomers of the rethrolones using lipases.

In the last group successful approaches that will be discussed, involves:

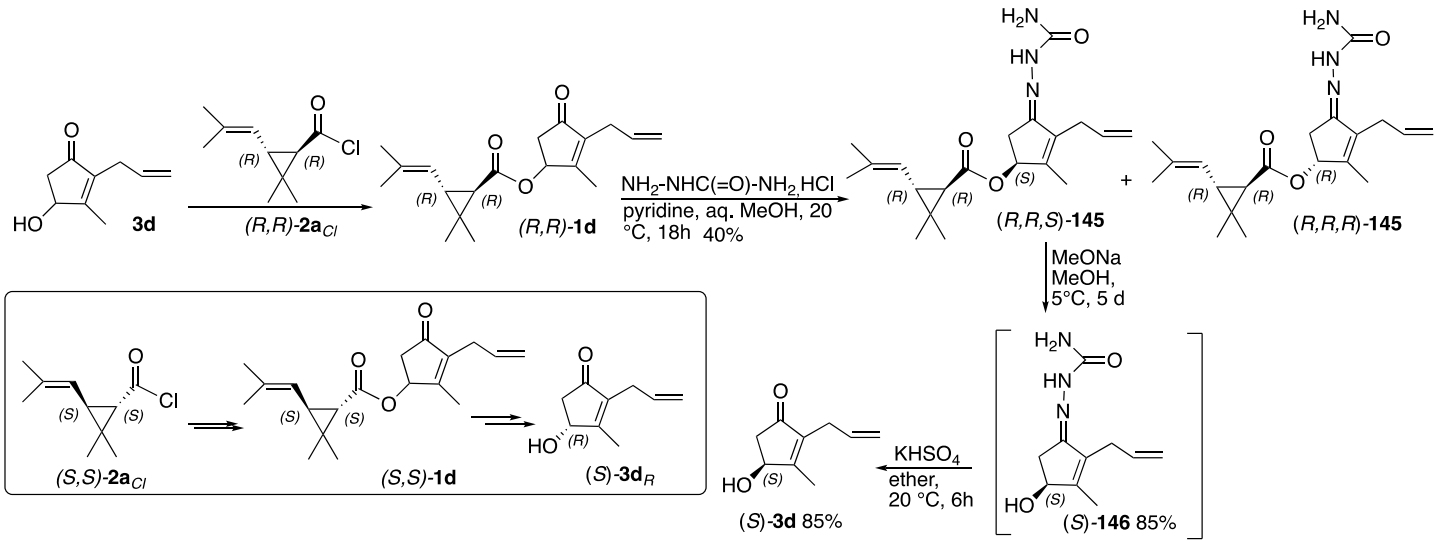
(i) Isolation in pure form of the unwanted (*R*)-rethrolone and its recycling to the (*S*)-enantiomer or

(ii) racemization of the remaining rethrolone and performing a subsequent resolution round.

6.1. Isolation of enantiopure (*S*)-rethrolones from racemates by crystallization of diastereoisomeric mixtures

This is the traditional, classical resolution method. The first separation[104] involves the reaction of racemic allethrolone **3d** with *d*-(*R,R*)-*trans*-chrysanthemic acid chloride (*R,R*)-**2a**$_{Cl}$ leading to the diastereoisomeric (*R,R,S*)- and (*R,R,R*)-allethrins **1d**. Successful separation of stereoisomers is not achieved at this stage but on the related diastereoisomeric semicarbazones **145** that can be differentiated by crystallization, leading to the isolation of the pure diastereoisomer **145**$_S$ (Scheme 54).[104] Treatment of the latter sequentially in basic media for a long time (five days) to cleave the ester bond, then in slightly acidic media to regenerate the carbonyl group from the semicarbazone **146**$_S$ intermediate, leads to the isolation of the *d*-(*S*)-allethrolone enantiomer **3d**$_S$ in quite good overall yield and recovery of the *d*-(*R,R*)-*trans*-chrysanthemic acid **1a** that can be isolated for reuse (Scheme 54).[104]

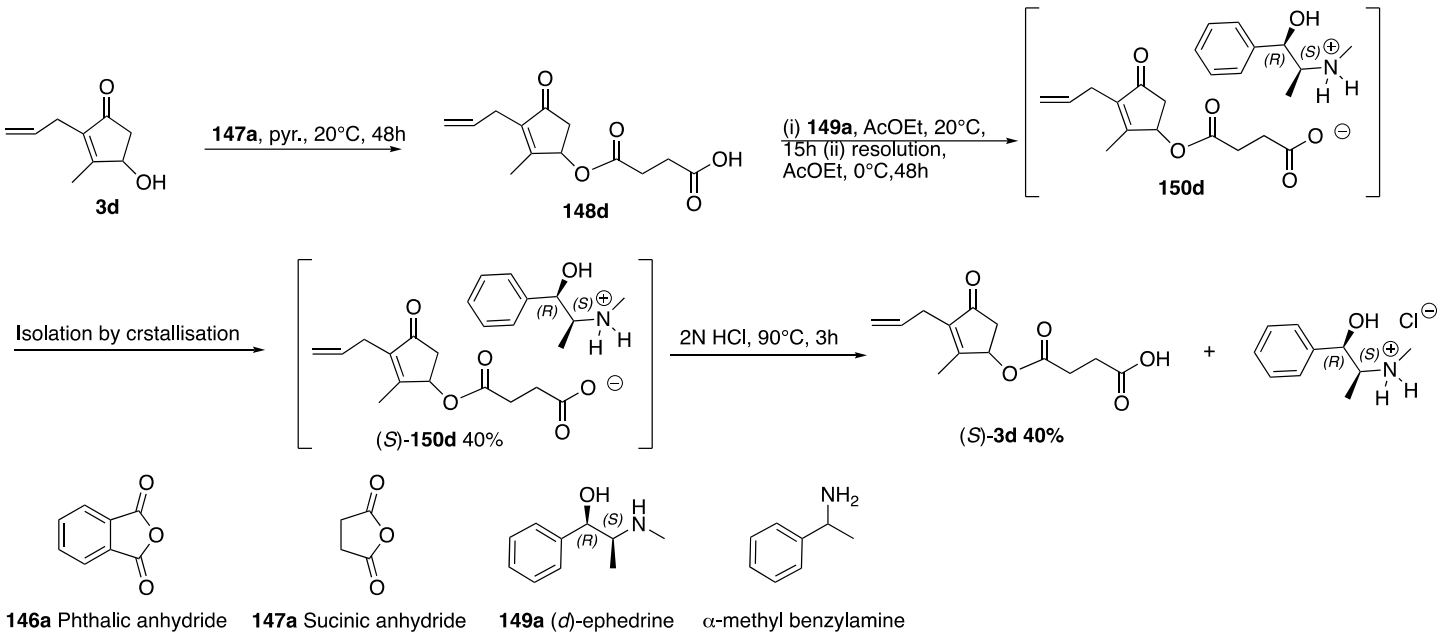
The partially resolved allethrin semicarbazone remaining after separation of *d*-allethrolone does not allow the extraction of pure l-allethrolone.[104] The latter can however be isolated in pure form by resolution of allethrolone **3d** with *d*-(*S,S*)-*trans*-chrysanthemoyl chloride (*S,S*)-**2a**$_{Cl}$ instead (Scheme 54, framed).[104]



Scheme 54. Resolution of allethrolone using 1*R-trans* chrysanthemic acid.

Isolation of the required allethrolone enantiomer (*S*)-**3d** has been successfully achieved for industrial purposes in other ways:

(i) on esterification of the racemate with succinic anhydride **147a**[105,106] or phthalic anhydride **146b**[107] and resolution of the resulting esters with a enantiopure amine such as (*d*)-ephedrine **149a** with the succinate **148d** (Scheme 55)[105,106] and α-methyl benzylamine[107] or α-phenyl- or α-*p*-tolyl-ethyl benzylamine for the phthalate.[107] Thus*, (d)*-ephedrine **149a** allows the almost quantitative separation of the succinate (*S*)-**150d,** then the recovery of S-allethrolone (*S*)-**3d** as disclosed in Scheme 55.

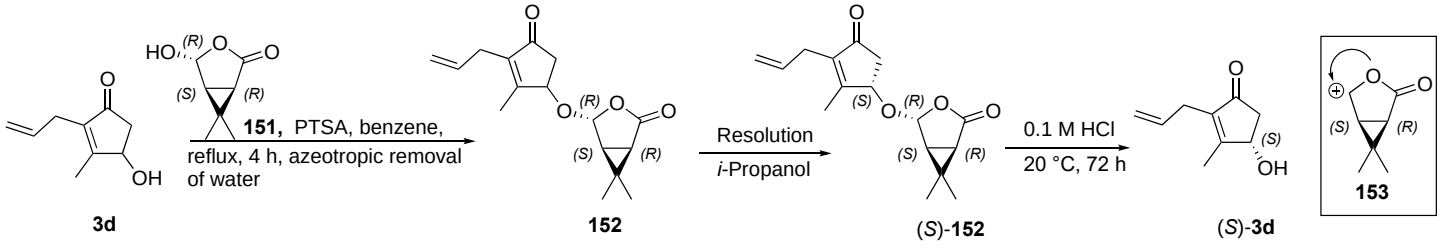


Scheme 55. Resolution of allethrolone using ephedrine.[105,106]

(ii) on performing an unusual type of acetalization using biocartol **151** as a resolving agent (Scheme 56).[108] The ease of formation of **152** from biocartol **151** in acidic media and the very mild conditions used for the regeneration in the same media of each of the diastereoisomers after resolution, offers an advantage for recovery of the base-sensitive allethrolone. This behavior is related to the efficient stabilization of the same carbonium ion **153** on departure of the protonated hydroxyl group from **151** or of the protonated allethronyl group from **152**.

This is probably one of the most convenient resolution approaches since the intermediate **152** on which resolution takes place is produced in a single step from allethrolone, and enantiopure biocartol **151** used as resolving agent has been a valuable intermediate in one of the industrial synthesis of chrysanthemic acid and deltamethrinic acid carried out by the former Roussel-Uclaf Company and is recovered in the process.[105]

Accordingly, (*R,S,R*)-**151** allows, after acetalization with racemic allethrolone, resolution of the resulting mixture in isopropanol and acid hydrolysis, then isolation of the enantiopure (*S*)-allethrolone (*S*)-**3d**.

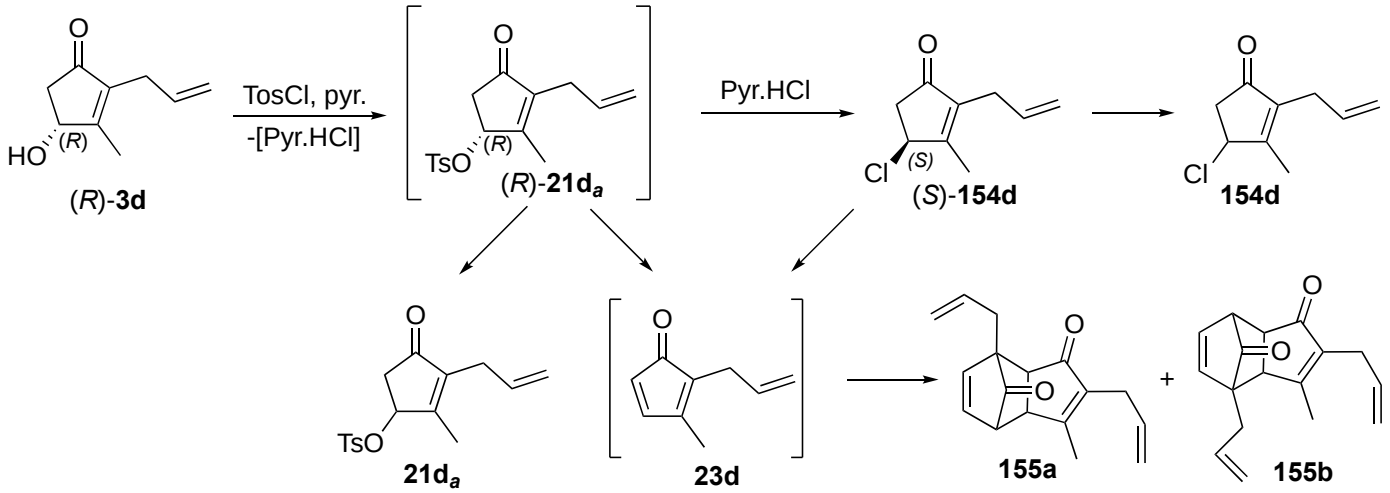


Scheme 56. Resolution of allethrolone using biocartol.[105]

6.2. Recycling the unwanted rethrolone (*R*)-enantiomer to its (*S*)-enantiomer

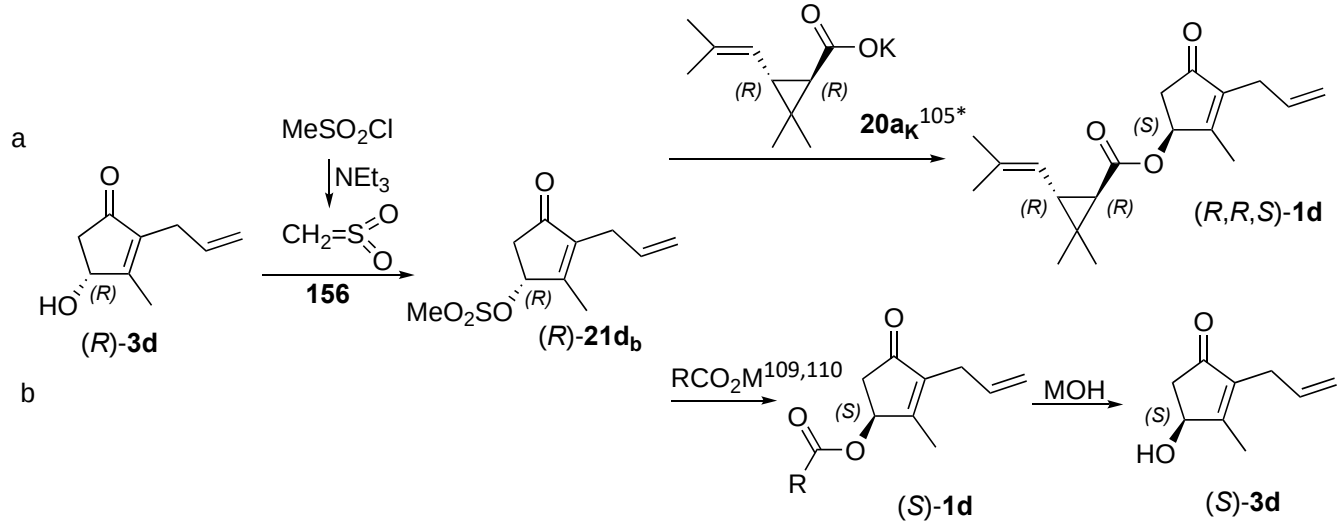
(*R*)-Allethrolone enantiomer (*R*)-**3d** resulting from the resolution process as a by-product has been reused according to two different strategies involving both the inversion of the configuration at the allylic C-4 carbon and usually achieved via the sulfonates (*R*)-**21** (Section 4.1, Scheme 2).[105]

The transformation of the alcohol (*R*)-**3d** into its tosylate (*R*)-**21**$_a$ is not an easy task. When carried out in the presence of pyridine under the usual conditions the reaction leads to a series of compounds that include: (i) the chloride (*S*)-**154d** resulting from the substitution of the tosylate intermediate (*R*)-**21d**$_a$ by the chloride ion present in the reaction mixture, and also (ii) the dimers **155** that are formed by the [4+2]-cycloaddition of the anti-aromatic dienone **23d** resulting from the competing elimination reaction on **21d** and **154** (Scheme 57).[105]



Scheme 57. Unsuccessful outcome of tosylation of allethrolone.[105]

To avoid these side reactions the alcohol (*R*)-**3d** has been instead transformed into its mesylate (*R*)-**21d**$_b$ on reaction with the sulfene **156** formed from the reaction of triethylamine with methanesulfonyl chloride (Scheme 58).[105] Its reaction with potassium chrysanthemate **20**$_K$ occurs with net inversion of configuration and leads to allethrin (*R,R,S*)-**1d** (Scheme 57, entry a).[105] Using instead of a metal carboxylate and performing a subsequent saponification reaction leads instead to allethrolone (*S*)-**3d** resulting from a net inversion of configuration on (*R*)-**3d** (Scheme 57, entry b).[109,110]



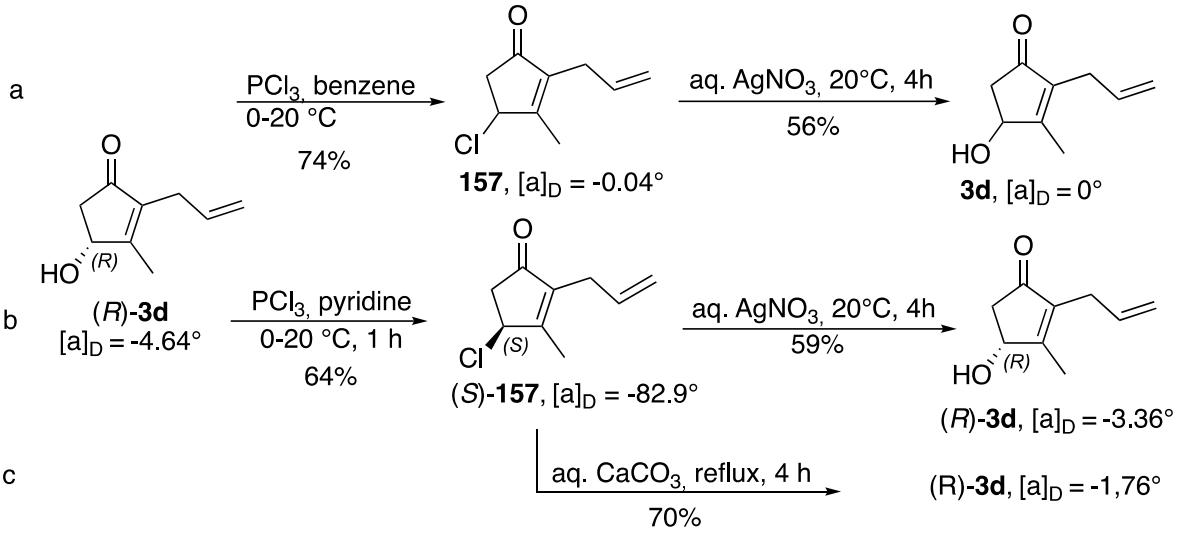
Scheme 58. Synthesis of (*S*)-allethrin and (*S*)-allethrolone from (*R*)-allethrolone.[105,109,110]

Related substitutions at the allylic carbon of activated rethrolones **3** will be reported below (Schemes 60, 61, 62).

6.3. Racemization of rethrolones

Another approach involves the racemization of (*R*)-allethrolone or of the residue left after resolution of the racemate and recovery of the (*S*)-allethrolone, in order to initiate a subsequent resolution step.[111]

This racemization has been successfully achieved on reaction of allethrolone $\mathbf{3d}_R$ with zinc chloride, phosphorus trichloride, phosphorus oxychloride or phosphorus pentachloride in benzene and subsequent reaction of the resulting chloride **157** (74, 80 and 71% yield respectively) with aqueous silver nitrate (20 °C, 4 h, 56-59%; Scheme 59, entry a).[112]



Scheme 59. Racemization of (*R*)-allethrolone in a two-step process involving 4-chlorocyclopentenone.[112]

It was found that the solvent has a profound effect on the stereochemical course of the reaction of (*R*)-**3d** with phosphorus trichloride.[112] Thus, use of pyridine instead of benzene as the solvent produces the allethronyl chloride (*S*)-**157** with net inversion of configuration rather than racemization (Scheme 59, entry b, compare entry a).[112] Subsequent treatment of (*S*)-**157** with aqueous silver nitrate at 20 °C leads to allethrolone (*R*)-**3d** with modest stereocontrol (ee: 72%, Scheme 59 entry b) implying an inversion of configuration. The same reaction using aqueous calcium carbonate not only requires a higher temperature (100 °C) but also leads to allethrolone (*R*)-**3d** with poor stereocontrol (ee 38%, Scheme 59, entry c compare entry b).[112]

6.4. Synthesis of enantiopure rethrolones from racemates using lipases

6.4.1 Generalities. Resolution of racemates using lipases offers the advantage of minimal manipulations during the enantioselective hydrolysis of their esters, usually rethrolonyl acetates or the enantioselective esterification of rethrolones using vinyl acetate.[113]

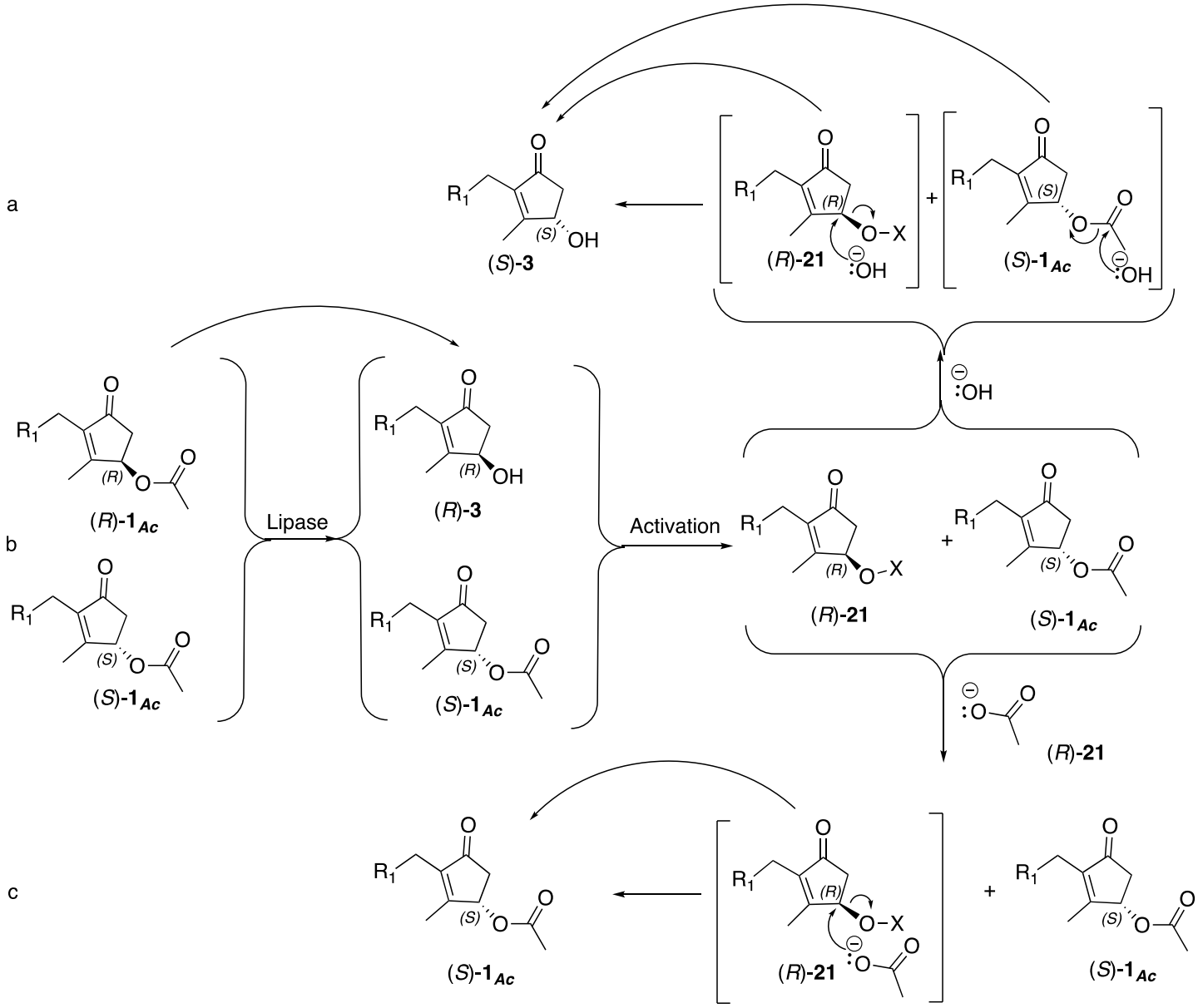
Nearly a hundred microorganisms: bacteria (*B. subtilis* IFO-3026), yeasts (*Kloeckera corticis* IFO-0868), actinomycetes (*Streptomyces griseofuscus* IFO-12870), and moulds (*Aspergillus niger* IFO-6342), have been found to hydrolyze, usually enantioselectively, prallethrolonyl- $\mathbf{1d'}_{Ac}$ and allethronyl acetates $\mathbf{1d}_{Ac}$.[114-116] The (*R*)-acetates (*R*)-$\mathbf{1d}_{Ac}$ are preferentially hydrolysed[114] to the corresponding rethrolones (*R*)-**3** by most of the

microorganisms, with the exception of a few yeasts such as *K. corticis* IFO-0868, whereas the acetates (*S*)-**1d**$_{Ac}$ remain untouched (Scheme 60).

In order for an efficient procedure to be operated, depending upon the case, the mixture of the enantiopure alcohol (*R*)-**3** and of the rethronyl acetate (*S*)-**1**$_{Ac}$ formed by the reaction of the lipase should be either transformed *in situ* into a single alcohol (*S*)-**3** or a single acetate (*S*)-**1**$_{Ac}$.

Thus, for a successful process the hydroxide ion should exclusively react by substitution at the C_c carbon of (*R*)-**21** and invert the stereochemistry there to produce (*S*)-**3** exclusively and exclusively saponify (*S*)-**1**$_{Ac}$ present in the medium to complement the production of (*S*)-**3** (Scheme 60, entry a).

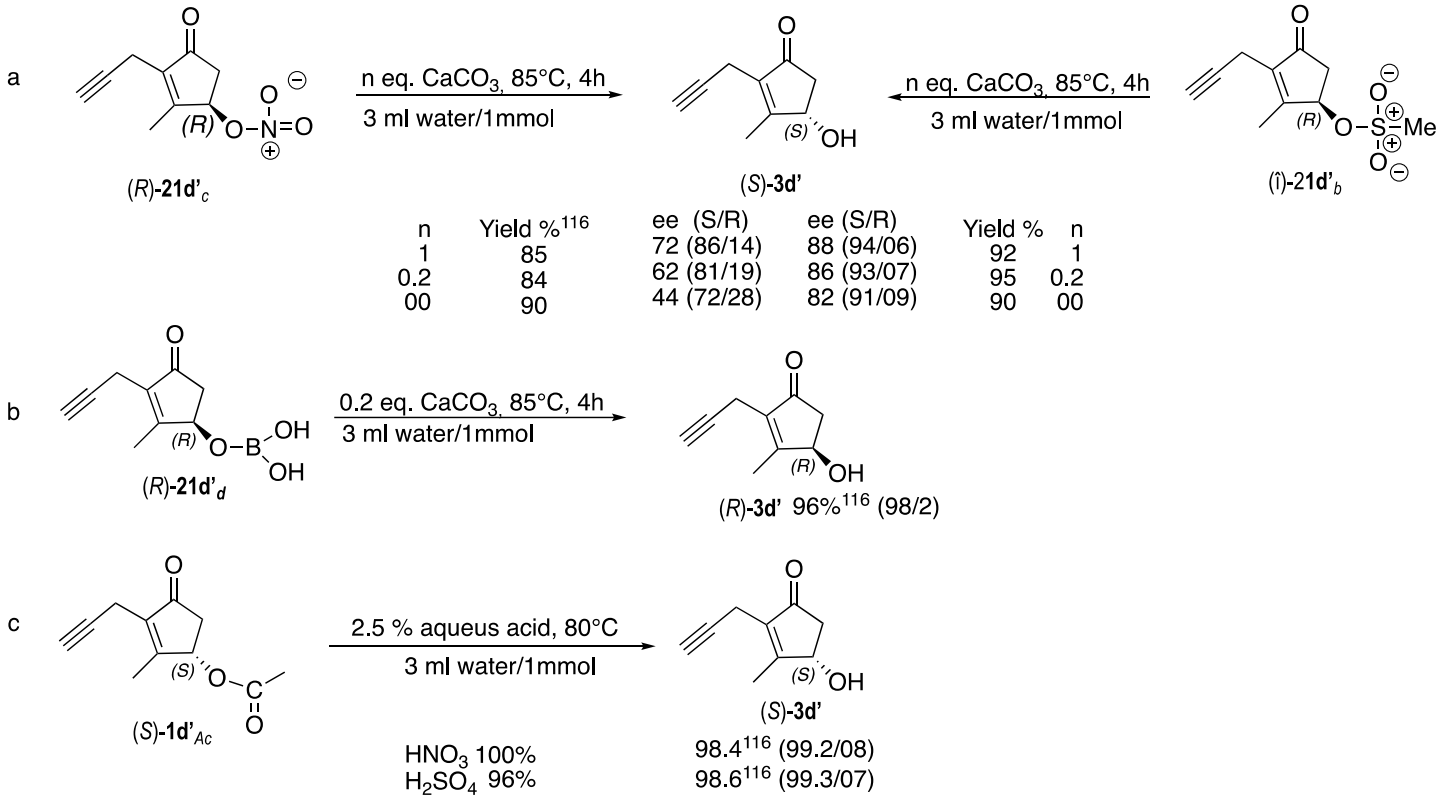
In the complementary approach involving the substitution of the activated alcohol (*R*)-**21** by a metal acetate, the conditions used should favor the inversion of configuration at C_c to complement the rethronyl acetate (*S*)-**1**$_{Ac}$ present in the medium (Scheme 60, entry b).



Scheme 60. Resolution of cyclopentenolones by lipases and recycling the unwanted enantiomer.

The selection of the activating group (X, Scheme 60) to generate a better leaving group on rethrolones **3** namely allethrolone **3d** and prallethrolone **3d'**,[105,111,113,114-116] should be done keeping in mind these requirements. Specific results are presented in Schemes 61,62.

Thus (*R*)-**3d** and (*R*)-**3d'** present in the crude mixtures resulting from the enantioselective hydrolysis of the related racemic rethronyl acetates **1d**$_{Ac}$ or **1d'**$_{Ac}$ or as a single compound have been reacted[114,115,116,117] with mesyl chloride (Scheme 61, entry a), [109,110,116] fuming nitric acid (Scheme 61, entry a),[116] boric acid in benzene under azeotropic reflux (Scheme 61, entry b),[116] or azodicarboxylate-triphenyl phosphine under the conditions of the Mitsonobu reaction[114] (Scheme 62) to produce the corresponding prallethrolonyl mesylate (*R*)-**21d'**$_b$,[109,110,116] -nitrate (*R*)-**21d'**$_c$,[116] and -borate (*R*)-**21d'**$_d$.[114] Note that all transformations disclosed above, except the one involving the Mitsonobu reaction[114] (Scheme 62), do not affect the stereochemistry at the carbon to which the hydroxyl group is attached. The Mitsonobu reaction[117] which involves azodicarboxylate and triphenyl phosphine however produces the corresponding acetate (*S*)-**1d'**$_{Ac}$ in a single step with complete inversion of the configuration through the intermediate **21d'**$_e$ that, interestingly, possesses the original stereochemistry.[114]



Scheme 61. Saponification of enantiopure pyrethrolone esters.[116]

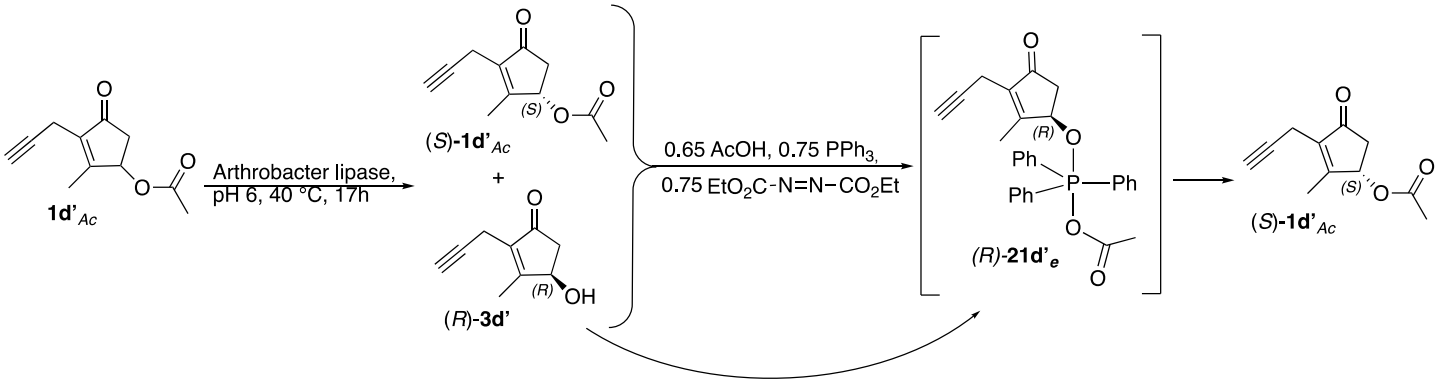
The prallethrolonyl derivatives **21d'**$_b$,[109,110,116] (*R*)-**21d'**$_c$[116] (Scheme 61, entry a) and **21d'**$_d$ (Scheme 61, entry b),[116] have been subsequently reacted with aqueous calcium carbonate at 85°C and, except for the prallethrolonyl borate **21d**$_d$,[116] found to produce the corresponding prallethrolone (*S*)-**3d'** with net inversion of the configuration at the substituted carbon (Scheme 61).

Under the same conditions the enantiopure prallethronyl borate **21d'**$_d$ (Scheme 61, entry b)[116] and prallethrolonyl acetate **1d'**$_{Ac}$ produces prallethrolone **3d'** with complete retention of configuration suggesting that the later reaction occurs by the selective attack on the boron or on the carbonyl group carbon of the

corresponding borate or acetate. It has been reported that prallethronyl acetate is (*S*)-**1d'$_{Ac}$** is also transformed to prallethrolone (*S*)-**3d'** with net retention of configuration in acidic aqueous media (Scheme 61, entry c).[116]

6.4.2 Selected examples of transformation of racemic rethrolones to a single enantiomer in overall yields exceeding 50%. Typically, the lipase from *Arthrobacter* species offers, among the 100 enzymes tested, the advantage to perform the hydrolysis of the racemic prallethrolonyl acetate **1d'$_{Ac}$** leading to selective saponification to the prallethrolonyl acetate (*R*)-**1d'**$_{Ac}$ leading to (*R*)-prallethrolone (*R*)-**3d'** and providing as well the enantiopure prallethrolonyl acetate (*S*)-**1d'**$_{Ac}$.

The lipase from *Arthrobacter* was found to perform the reaction with (i) the highest yield, (ii) the highest enantiomeric excess and (iii) the lowest amount of enzyme. A few comparative results are collected below: (a) substrate conc.: 8.8 w/v%, (b) reaction time: 23h, (c) temperature, 40 °C, (d) pH 7.0: *Arthrobacte*r sp. required: 3 mg, (*R*)-**3d'** 50% yield, ee 98.8 (Scheme 62); *Achromobacter* sp. required: 100 mg, (*R*)-**3d'** 33% yield, ee: 95.2; *Pseudomonas fluorescens* required: 6 mg, (*R*)-**3d'**: 47% yield, ee: 94,8).[154] It has been also reported that the rate of hydrolysis increased with chain length from acetate to caprylate but decreased with caprate.[155]

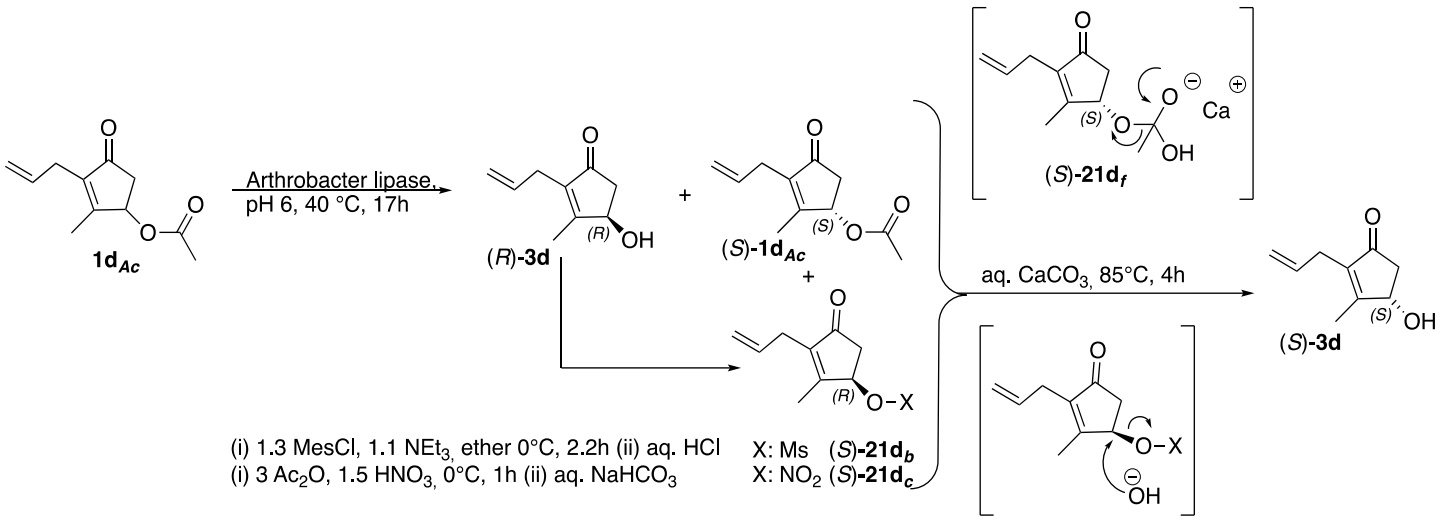


Scheme 62. Single-pot resolution of prallethronyl acetate and recycling of the unwanted enantiomer using an *Arthrobacter* lipase and a Mitsonobu reaction. [114,156]

Combining the lipase resolution with the Mitsonobu reaction, as seen in Scheme 62, leads to the conversion, in a single pot, of the racemic prallethrolonyl acetate **1d'**$_{Ac}$ into the enantiopure prallethrolonyl acetate (*S*)-**1d'**$_{Ac}$. Hydrolysis of the resulting mixture in acidic aqueous media (Scheme 61, entry c), allows, the conversion of the racemic acetate **1d'**$_{Ac}$ to the (*S*)-prallethrolone (*S*)-**3d'** in excellent yield and very high overall stereocontrol (ee: 93.6%), without any separation. [156]

Arthrobacter lipase efficiently performs the enantioselective hydrolysis of racemic allethrolonyl acetate **1d**$_{Ac}$ (Scheme 63).[157] The reaction is usually carried out at 40 °C and pH 6 and provides (*R*)-allethrolone (*R*)-**3d** in good yield (43%−50% maximum) with high enantiomeric excess (98.4%) and recovery of the (*S*)-allethrolonyl acetate (*S*)-**1d**$_{Ac}$ (53%) after 17 h.

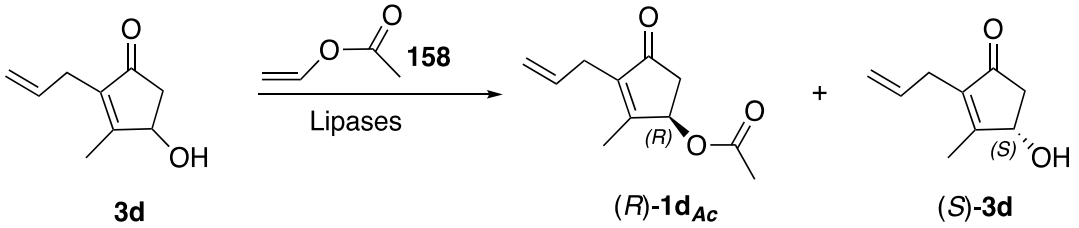
Reacting the resulting mixture of (*S*)-allethronyl acetate (*S*)-**1d**$_{Ac}$ and bio-saponified (*R*)-allethrolone (*R*)-**3d** with mesyl chloride or nitric acid then with aqueous calcium carbonate at 85 °C for 4 h allows the formation of enantiopure allethrolone (*S*)-**3d** by concomitant saponification of the allethrolonyl acetate (*S*)-**1d$_{Ac}$** as well as substitution by the hydroxyl ion of the (*R*)-allethrolonyl mesylate (*R*)-**21d$_b$**,[116] or allethrolonyl nitrate (*R*)-**21d$_c$**[116] with net inversion of the configuration there (Scheme 63).



Scheme 63. Single-pot resolution of allethronyl acetate and recycling of the unwanted enantiomer using *Arthrobacter* lipase and mesyl chloride. [157]

Manipulations of the lipases have been carried out to, *inter alia*, (i) improve their enantioselectivity, their activity, and their reuse and (ii) facilitate the recovery of the products.[118,119,120,121,122]

Lipases are also able, in the presence of vinyl acetate **158**, to transform (*R*)-allethrolone (*R*)-**3d** to its acetate (*R*)-**1d**$_{Ac}$ leaving untouched its (*S*)-stereoisomer (*S*)-**3d** (Scheme 64).[118,119,120,121,122]



Scheme 64. Enantioselective acylation of racemic allethrolone.

Enantioselective acylation of racemic allethrolone has been successfully achieved by *Arthrobacter* lipase and *Pseudomonas* lipase using vinyl acetate **158** as both the acyl donor and organic solvent. They lead to the (*S*)-allethrolone (*S*)-**3d** with ee up to 99%.[118,120] The V_{max} of modified *Pseudomonas* lipase, coated by didodecyl *N*-D-glucono-L-glutamate as synthetic surfactant, was improved by as much as 160 times over the native lipase in spite of a similar K_m. It allows 40% conversion in 20 h leading the acetate (*S*)-**1d**$_{Ac}$ (ee 100%) with concentration in substrate as high as 1 M and 1.0 mg/ml of coated lipase.[118]

Immobilization of *Arthrobacter* lipase has been performed by deposition on grafted diatomaceous material,[120] encapsulation in hydrophobic sol-gel materials,[121] and onto glutaraldehyde-activated amino-silica gel.[122] For example the *Arthrobacter* lipase[120] immobilized on diatomite grafted by methacryloxypropyl-, vinyl-, octyl-, dodecyl-, and γ-(aminopropyl)-glutaraldehyde leads to excellent enantioselective transformations (E≥400, instead of E = 85 for the free enzyme), yielded the highest activity with a recovered activity of 8.5-fold of total activity and 85% of initial activity remaining even after 10 days.[120]

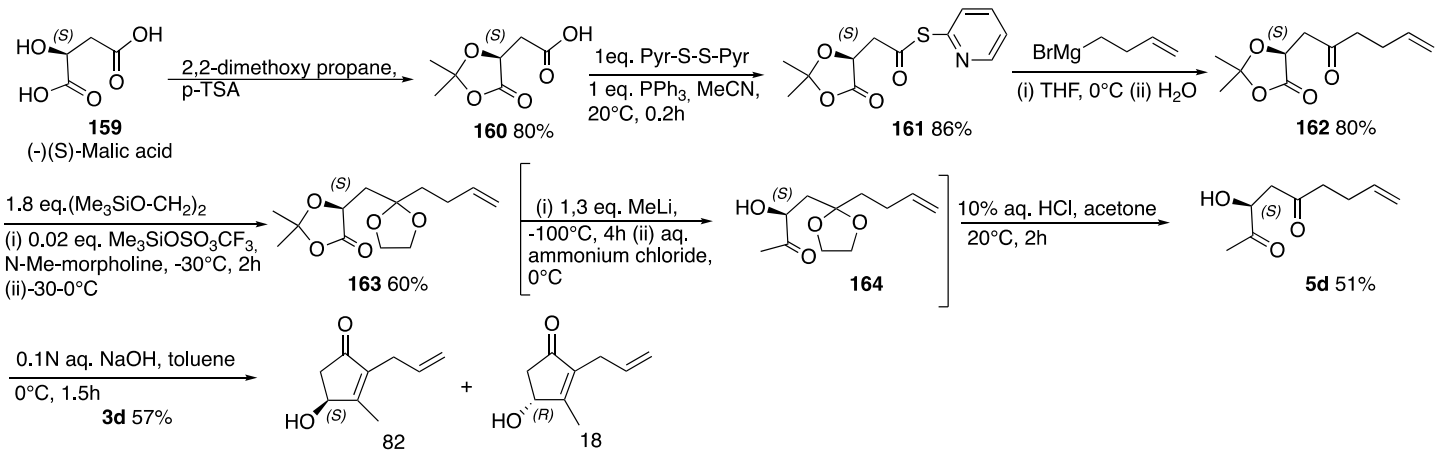
7. Enantioselective Syntheses of Rethrolones

Only few enantioselective syntheses of rethrolones have been reported. It could have been interesting to know about the stereochemical outcome of the bio-oxidation of jasmone to jasmololone, but not only were the reported reactions not highly regioselective, but little has been published on their stereochemical outcome (Subsection 5.4.2).[94-97]

Most of the recent work has been concentrated on the most "classical" synthesis of rethrolones, that implies decarboxylative aldolization reaction involving the formation of their C_b=C_f double bond (Section 5.1).

The first approach, shown in Scheme 65,[124] uses (*S*)-malic acid as starting material and a series of reactions that involve engaging first the hydroxy groups of the alcohol and of the acid to form the lactone **160**.[125] Activation of the remaining carboxylic acid group in **160** to the thiol ester **161** allows the regioselective addition of the but-3-enyl bromomagnesium Grignard reagent leading to the ketone **162** in high yield.[124]

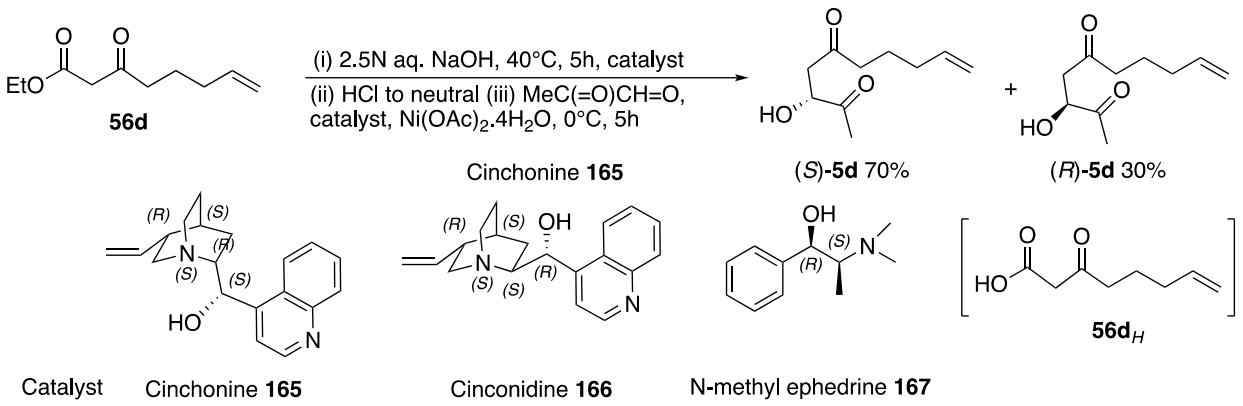
Selective protection of the just-formed ketone carbonyl group as dioxolane, followed by reaction of methyllithium with the lactone carbonyl group of **163**, leads to the enantiopure methyl ketone **164**, that after deprotection of the built-in dioxolane moiety in acidic media delivers the enantiopure (*S*)-hydroxy diketone **5** in 51% yield and high stereocontrol**.**[124]



Scheme 65. Enantioselective synthesis of allethrolone from (*S*)-malic acid. [124]

Unfortunately however, the cyclization of the last to the cyclopentenolone **3** under the usual conditions (0.1 N aqueous NaOH) is accompanied[124] by racemization probably due to a retroaldol reaction (ee: 64%) (Scheme 65). This could perhaps be prevented by protecting the hydroxyl group of (*S*)-**5d** since it has been found with a compound possessing a related structure that esterification of its hydroxyl group takes place without epimerization.[126]

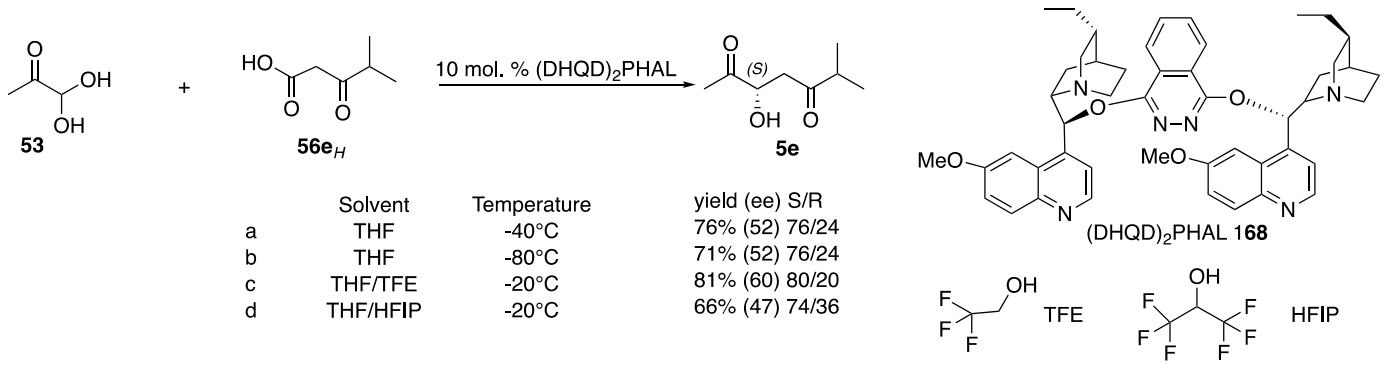
Another even more interesting approach involves[127] an organocatalytic asymmetric decarboxylative aldol reaction promoted by cinchonine **165**, chinchonidine **166** or *N*-methylephedrine **167** on the β-keto esters **56d** and **56d'** leading to **5d** and **5d'**, precursor of allethrolone **3d** and prallethrolone **3d'** with modest stereocontrol (ee: 40%). Nickel acetate has been used[128] to complex around the nickel, the enolate, the chiral catalyst and the methylglyoxal to favor the reaction and to enhance the formation of a rigid transition state promoting a better enantioselectivity compared to reactions performed in its absence.



Scheme 66. Enantioselective decarboxylative aldol condensation using enantiopure amino-alcohols. [127]

Since then, related reactions involving methylglyoxal **53** in organocatalytic asymmetric (i) decarboxylative aldol reaction (Scheme 67)[126] or (ii) aldol reaction (Scheme 68),[129] have been reported but unfortunately cannot be used to synthesize rethrolones due to the limitations disclosed in the related publications.

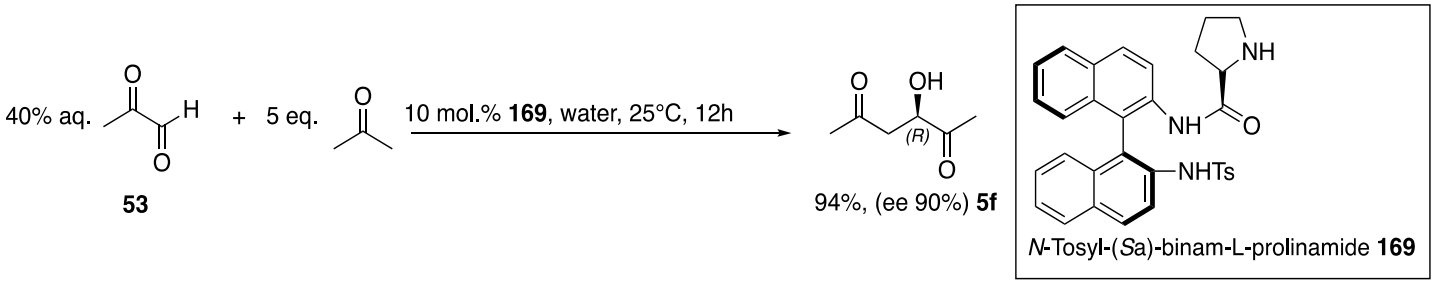
It was for example found[126] that the modified cinchona alkaloid $(DHQD)_2PHAL$ **168** (Scheme 67) is far superior to an anthraquinone or a pyrimidine ligand to promote enantioselective aldol reactions carried out in THF in the presence of trifluoroethanol (TFE, Scheme 67)[126] and even the enantiomeric excess never exceeded 60% in THF (Scheme 67, entry c) that proved to be far better than dichloromethane or acetonitrile (Scheme 67).[126]



	Solvent	Temperature	yield (ee) S/R
a	THF	-40°C	76% (52) 76/24
b	THF	-80°C	71% (52) 76/24
c	THF/TFE	-20°C	81% (60) 80/20
d	THF/HFIP	-20°C	66% (47) 74/36

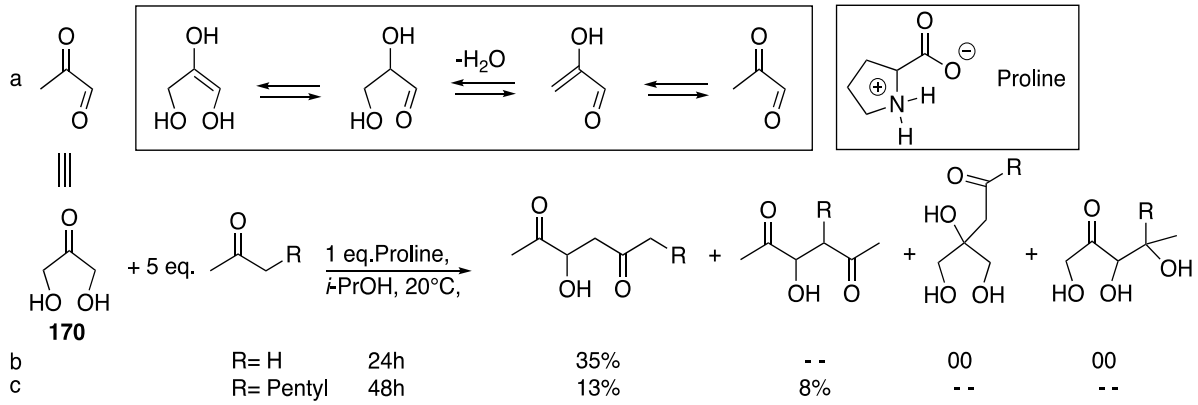
Scheme 67. Enantioselective decarboxylative aldol condensation catalyzed by a cinchona alkaloid. [126]

The enantiomeric excess is far better[128] on reaction of acetone with methylglyoxal **53** catalyzed by prolinamide derived from binaphthylamine **169** when carried out in aqueous medium. It has been reported that the chirality of the proline directs the nature of the enantiomer **5f** produced and that the highest enantioselectivity is achieved with a catalyst whose composition includes the matching combination of L-Pro and (S_a)-binam **169**, much higher than when L-proline alone is instead used. Unfortunately, however although the process has been successfully extended[128] to aldehydes and cyclic ketones, it does not go well with methyl alkyl ketones that are requested starting materials for the synthesis of rethrolones.



Scheme 68. Enantioselective aldol condensation catalyzed by a prolinamide derived from binaphthylamine.[129]

Finally, the reaction recently published and shown in Scheme 69[130] describes an organocatalyzed aldol reaction that uses 1,3-dihydroxyacetone **170** as a substitute for methylglyoxal and although proline is used as a chiral substance it is not clear if a enantiopure product is formed since no asymmetric induction is reported.[130] Furthermore, it is interesting to notice that although cross aldol reaction is not regiospecific (Scheme 69, entry c),[130] aldol reactions involving directly 1,3-dihydroxyacetone have not been observed.[130]



Scheme 69. Aldol reactions involving 1,3-dihydroxyacetone as surrogate for methylglyoxal. [130]

8. Conclusions

Isolation of rethrolones (pyrethrolone **3a**, cinerolone **3b**, jasmololone **3c**) besides chrysanthemic acid **2a** on hydrolysis of natural pyrethrins has opened doors for intensive research both in academia and industry. Unfortunately, the chemical structure determination of rethrolones was incorrect in several aspects (regio and stereochemical grounds) and therefore early syntheses produced regio and stereoisomers instead. Discovery of analogs (allethrin **1d**, prallethrin **1d'**) possessing less elaborated structures on their alkoxy portion (allethrolone, **3d** prallethrolone **3d'**) but similar biological behavior for domestic uses leads to their industrialization [allethrin **1d** (1953); (*S*)-bioallethrin (*S*)-**1d** (1970), prallethrin **1d'** (1980).[134,135] The great availability, at low cost, of large quantities of prallethrolone **3d'**, the presence on its structure of a terminal C≡C triple bond, and availability of an arsenal of synthetic methods able to allow its functionalization regio- and stereoselectively, have promoted prallethrolone as the key starting material for the synthesis of the natural pyrethrolone **3a**, cinerolone **3b** as well as the unnatural allethrolone **3d** a commercial insecticide. It does not allow however the synthesis of jasmololone **3c.**

The considerable amount of work described in this review now allows, at relatively low cost, the commercialization of mixtures of man-made pyrethroids mimicking the exact natural composition of ground pyrethrum flowerheads in insecticides, thus avoiding spraying uselessly the natural compounds. It suggests an even more ecological approach that Nature can achieve for this specific use.

Various strategies developed for the synthesis of natural (**1a**-**1c**) and unnatural (**1d**, **1d'**) rethrolones have been disclosed. They almost all involve building the cyclopentane ring with the required γ-hydroxy α,β-enone moiety possessing the natural stereochemistry. These approaches rely on the aldol reaction[136,137] both for building the required skeleton, often through its decarboxylative version,[138] and to generate the cyclopentene moiety through its intramolecular version followed by the crotonization process. The aldol reaction is one of the most basic reactions in organic synthesis and it also plays a crucial role in Nature.[138]

The construction of the side chain at C-2 on the five-membered ring has been one of the main concerns, especially the control of the stereochemistry for the naturally derived pyrethrolone **3a**, cinerolone **3b** and jasmololone **3c**. Although the Wittig olefination reaction and olefin metathesis have been used for that purpose, the hydrogenation of the acetylenic functionality proved by far the most efficient approach and prallethrolone **3d'** the most suitable precursor. The related strategy, at the difference of the earlier ones, involves the control the stereochemistry of the side chain and even the construction of its complete carbon content at the last stage of the synthesis of the rethrolone.

Rethrolones are part of a wider family of cyclopentanones that include prostaglandins that play an important role in inflammation and birth control in mammals, and jasmone that occupies a privileged position in perfumery and has an important economic value. Jasmone has been identified as an intermediate in the biosynthesis of pyrethrins, its regioselective hydroxylation being a key step. Since several syntheses of jasmone are known, including industrial ones, it would seem obvious to use the same strategy to produce pyrethrins. Unfortunately, however, oxidation does not occur at the required location and instead takes place either by addition on the exocyclic double bond or by allylic oxidation there. It could be suggested that performing the oxidation on a dehydrojasmone possessing a less reactive exocyclic triple bond in place of the double bond would allow the required endocyclic allylic oxidation.

9. Acknowledgements

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