Pyrethroid insecticides.
Chapter II: Synthesis of rethrolones

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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
Table of Contents

1. Introduction
2. Generalities Concerning Rethrolones as Partners in Pyrethrin and Pyrethroid Synthesis
3. Synthetic Strategies in the Synthesis of Rethrolones
4. Solutions to Generic Problems involved in the Synthesis of Rethrolones
   4.1. Strategies to access enantiopure (S)-rethrolones
   4.2. Strategies to control the Z-stereochemistry of the C-2 side chain of rethrolones and rethrones
   4.3. Strategy and practice with intramolecular aldol-reactions leading to rethrolones and rethrones
5. Synthesis of Rethrolones
   5.1. Synthesis of rethrolones by carbocyclisation of 1,4-diketones
      5.1.1 Generalities
      5.1.2 Selected examples
         5.1.2.1 Synthesis of rethrolones 5 employing ketones 6 and magnesium methyl carbonate 55 (MMC, Scheme 16 entry a1)
         5.1.2.2 Synthesis of rethrolones 5 from ketones 6 and diethyl carbonate 57 (Scheme 16 entry a2b)
         5.1.2.3 Synthesis of rethrolones 5 involving acyl chlorides 60 and ethyl acetylacetonate 59 (Scheme 16 entry a2c)
         5.1.2.4 Synthesis of rethrolones 5 involving allyl or propargyl halides and dimethyl acetonedicarboxylate 68 (Scheme 16 entry b)
   5.2. Synthesis of rethrolones 3 by isomerization of iso-rethrolones 7
      5.2.1 Generalities
      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
            5.2.2.1.2 Synthesis of rethrolones using electrochemical oxidation of 2,5-dialkylfurans
            5.2.2.1.3 Synthesis of rethrolones 3 by pyridinium chlorochromate oxidation of 2,5-dialkyl substituted furans
         5.2.2.2 Synthesis of rethrolones 3 involving furfuryl carbinols
            5.2.2.2.1 Synthesis of rethrolones 3 involving 5-alkyl-2-furfuryl carbinols
            5.2.2.2.2 Synthesis of rethrolones from furfuryl carbinols 93 involving the intermediate methylation of 4-oxo-2-cyclopentenones 94
   5.3. Synthesis of rethrolones by carbocyclisation of 1,4-ketoaldehydes
      5.3.1 Generalities
      5.3.2 Selected examples
   5.4. Synthesis of rethrolones by selective oxidation of preformed rethrones
      5.4.1 Syntheses of Jasmone 12c
      5.4.2 Synthesis of rethrolones 3 from rethrones 12
         5.4.2.1 Generalities
         5.4.2.2 Chemical-reagents
         5.4.2.3 Bioreagents
   5.5. Synthesis of rethrolones by cycloaddition of singlet oxygen to substituted cyclopentadienes
   5.6. Synthesis of rethrolones by regioselective reduction of cyclopent-2-ene-1,4-diones
   5.7. Stereoselective synthesis of rethrole hem side chains from allethrolone
5.7.1 Transformations involving allethrolone and a Wittig reaction
5.7.2 Transformations involving allethrolone and a metathesis reaction
5.8. Stereoselective synthesis of rethrolone side chains from prallethrolone
  5.8.1 Alkylation and vinylation of 3d'
  5.8.2 Hydrogenation of the C≡C triple bond of 3d' and 144
6. Synthesis of Enantiopure Natural and Unnatural Rethrolones from Racemic Compounds
  6.1. Isolation of enantiopure (S)-rethrolones from racemates by crystallization of diastereoisomeric mixtures
  6.2. Recycling the unwanted rethrolone (R)-enantiomer to its (S)-enantiomer
  6.3. Racemization of rethrolones
  6.4. Synthesis of enantiopure rethrolones from racemates using lipases
    6.4.1 Generalities
    6.4.2 Selected examples of transformation of racemic rethrolones to a single enantiomer in overall yields exceeding 50%
7. Enantioselective Syntheses of Rethrolones
8. Conclusions
9. Acknowledgements
References

1. Introduction

As was pointed out in the first chapter, pyrethrins (natural) and pyrethroid (synthetic/non-natural) insecticides 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).

Figure 1. Structures of some of the most bioactive natural and synthetic pyrethrins and pyrethroids. Note that due to CIP priority rules, the (1R,3R) 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-vinylcyclopropanecarboxy 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)-configured 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.

![Figure 2. Structures of the acid and alcohols and cyanohydrin components of some natural and synthetic pyrethrins and pyrethroids.](image)

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 alcolholates, 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 Pyrethin 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, jasmolalone 3c, cinerolone 3b pyrethrolone 3a, (ii) enantiopure (S)-allethrolone (S)-3d as well as (S)-prallethrolone (S)-3d', (S)-jasmolalone (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. 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)-configured and that of the side chain that as already mentioned is (Z)-configured. Unfortunately however, the correct stereochemistry at both sites was not properly determined until quite lately. 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 stereocchemistry 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 theCc–Cd bond;

5.4. Oxidation at Cc of preformed rethrone 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 permethrin (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”
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, before the cyclization leading to the cyclopentenolone is achieved (Scheme 1, entries a-c), or at a late stage (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 (Scheme 3, Routes i) or an olefination reaction that brings together two sp² carbons to create the C=C double bond with the Z-stereochemistry either using a Wittig (Scheme 3, Route ii) or a metathesis reaction (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. Reduction by metals usually leads to the formation of a C=C double bond with the E-stereochemistry, and catalytic hydrogenation, although producing the Z-stereoisomer, is often contaminated by products resulting from over-hydrogenation. The use of Lindlar’s poisoned palladium catalyst to avoid over-reduction of the Z-unsaturated intermediate proved very efficient especially for the reduction of yrones 6′ or alkyalted prallethrolone derivatives 3′ (Scheme 3, Routes i). This reaction does not however apply to the reduction of the 1-en-3-yne, precursor of pyrethrolone 3a, for which zinc/HCl in isopropanol has proved to be the reagent of choice (See below, Scheme 53, entry d) in a reaction that occurs stereoselectively.

The Wittig reaction is highly regioselective but does not usually proceed stereoselectively. Nevertheless the “salt free” version, discovered by Schlosser then revisited by Corey, allows reasonable stereocontrol favoring the synthesis of the Z-stereoisomer of β-dialkyl substituted olefins (de: 88%). 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) is insoluble and can be separated by filtration or using a solvent that sequesters the cation in situ (e.g. DMSO, dimethyl sodium or butyllithium in HMPA). 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. 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.
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.\(^1,^7\) 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 stereocntrol is far from perfect.\textsuperscript{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).\textsuperscript{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\textsuperscript{18-20} that allows the formation of either the C\textsubscript{r}–C\textsubscript{b} bond (Scheme 1, entry a, route (i); entry b, route (iii)) or the C\textsubscript{c}–C\textsubscript{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\textsuperscript{12}, especially jasmone\textsuperscript{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.\textsuperscript{19}

![Scheme 5](image-url)

\textbf{Scheme 5.} Aldolization-crotonization reactions leading to cyclopentenolones from 2-hydroxy-1,4-diketones.\textsuperscript{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)\textsuperscript{2,21-26} or -alkynes 5b’ (Scheme 5, entry c)\textsuperscript{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).\textsuperscript{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’\textsuperscript{28,29,30,31} that implies a different mechanism in which the aldol reaction is followed by a rearrangement (Scheme 6, entries a,b).\textsuperscript{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.\textsuperscript{33-36}

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\textsuperscript{37-44} 12, especially cis-jasmine 12c,\textsuperscript{40,42-44} a constituent of jasmine oil, an intermediate in the biosynthesis of pyrethrolone 3a and jasmolone 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.\textsuperscript{37-39,41}

The carbocyclisation reaction of 5-oxo-methyl ketones has been originally described on saturated derivatives by Blaise\textsuperscript{37} and extended later by Hunsdiecker.\textsuperscript{38-40} It accepts wide structural variation (Schemes 5-7) but requires, as shown by Blaise,\textsuperscript{37} Hunsdiecker\textsuperscript{39} and LaForge,\textsuperscript{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.\textsuperscript{23} The reaction is best carried out in water\textsuperscript{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\textsuperscript{23} or borax\textsuperscript{39} but in the latter cases requires a high temperature (200 °C) in an autoclave to proceed (Scheme 7, entry b).\textsuperscript{39}
Scheme 7. Base promoted regioselective aldolization-crotonization of 1,4-diketones.\textsuperscript{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).\textsuperscript{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” on reaction of 13d” with sodium deuteride in deuterated water for even less than a minute (Scheme 8, entry a).\textsuperscript{41} Performing the reaction for a little longer leads to deuterated cyclopentenones 12d” and 33d” in almost quantitative yields (0.25h, Scheme 8, entry b).\textsuperscript{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”.\textsuperscript{41}

Scheme 8. Base-promoted regioselective aldolization-crotonization of nona-2,5-dione in deuterated medium.\textsuperscript{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:

(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.”

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-H2O, 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 synthesized42 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-butylcyclopentanone 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 found42 that the cyclopentenone 33"d" bearing a butyl substituent at C-3 (C₆) does not lead to its isomer 12"d" possessing two alkyl substituents on the cycle (a propyl at C-2 (C₅) and a methyl at C-3 (C₆)) 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 found42 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, H₂O, 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 C₆ 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

![Chemical structure](attachment:image.png)

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Product</th>
<th>Yield (as %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>C₃H₇</td>
<td>1% aq. Na₂CO₃, 100°C, 2h</td>
</tr>
<tr>
<td>b</td>
<td>C₃H₇</td>
<td>1% aq. Na₂CO₃, 100°C, &lt;2h</td>
</tr>
<tr>
<td>c</td>
<td>C₃H₇</td>
<td>Amberlite 120B, H₂O, 0.5h</td>
</tr>
<tr>
<td>d</td>
<td>C₁₀H₂₁</td>
<td>0.1N aq. NaOH, dioxane, 100°C, 1h</td>
</tr>
<tr>
<td>e</td>
<td>C₁₀H₂₁</td>
<td>0.1N aq. NaOH, dioxane, 20°C, 2h</td>
</tr>
</tbody>
</table>

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 120³⁰ (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 ZnCl₂·H₂O, 100 °C, 1 5h;³³,³⁵ MgCl₂·H₂O, 100 °C, pH 7, 50 h³⁵) and basic conditions (NaHCO₃, H₂O, 100 °C, 1 h;³⁴ Na₂CO₃, H₂O, 100 °C, 1 h;³⁰ Al₂O₃, benzene, reflux³²,³³).

It has been found that reacting the ene-1,4-diones 8z 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 8z respectively from their methyl (Cₐ) and methylene group (C₆).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 8z 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 Cc,Cd followed by water elimination at Ca,Ce (Scheme 13, entry c). In such case the departing group (OH) is sufficiently poor that enolate equilibration is considerably more rapid than elimination. Therefore, the transition state for dehydration reflects the thermodynamic considerations which favor the formation of the more substituted double bond in (3 from 42).

Scheme 15. Directed isomerization of cyclopentenolones.

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 (Scheme 15 entry b). This has been ascribed 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 Ce and the side chain at Ca (that leaves one face of the cyclopentenone entirely unhindered). This problem which is not apparently observed in the iso-rethrolone series 7, 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).

Finally, the aldol reaction has been also used to produce rethrolone 3 by forming the Cc–Cd 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 C₅=C₆ 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)-bioallethrin 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 \( \beta \)-oxocarboxylates 54 or of the \( \beta \)-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 \( \beta \)-oxocarboxylates 54 (Scheme 16, route a) each step (i) the synthesis of the adduct 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 \( \beta \) 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 \( \beta \)-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 \( \beta \)-ketocarboxylates 54 (or their enolates) tend to be protonate leading to the corresponding acids 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 73\(_m\) requires its protonation followed by decarboxylation of the resulting acids 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. 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, 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), or to use its protected form as its bisulfite combination or its diethyl or diisopropyl acetals that are expected to be decomposed in acidic media just before reacting (Scheme 21). 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 56 using sodium or potassium hydroxide in water at room temperature “for a few days” according to “the cold saponification protocol” (Scheme 16, route a2, Schemes 17, 21, 24, 25, 24, 22, 23, 24, 25, 27) or by (ii) titration using potassium hydroxide of the corresponding acids 56 obtained by acidification of the magnesium ketocarboxylates 54Mg (Schemes 16, route a1, 18, 19) or sodium or potassium β-ketocarboxylates 54Na or 54K (Schemes 16, route a2, 20). It has been also noticed that decarboxylation of 87H 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%-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 a3, entry a2a and entry a2c). They include natural rethrolones such as pyrethrolone 3a (Scheme 19), cinerolone 3b (Schemes 18, 21, 23, 24, 22, 23, 24) and jasmololone 3c (Scheme 19), that requires the control of the Z-stereochemistry of their side chain at C7, but have presently little economic value, and unnatural ones such as allethrolone 3d (Schemes 20, 22, 26, 52, 53, 22, 24, 22, 23, 24, 23, 24, 23, 24) and parallethrolone 3d' (Scheme 24), 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, 21, 23, 20, 22, 26, 52, 53, 21, 23, 24. The strategy used in the “acyclicenic 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 “acyclicenic 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 a3). Amongst the different routes to metal β ketocarboxylates 54Mg, the one involving the carboxylation of ketone 6 by MMC is the most straightforward (Scheme 16, route a3). 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.\textsuperscript{47} The reaction carried out at reflux in DMF that is continuously distilled out of the medium (0.5 h),\textsuperscript{2} exclusively takes place on the methyl group and provides only the monocarboxylated ketone through a magnesium chelate\textsuperscript{2} (54Mg, Schemes 16, 18, 19).\textsuperscript{2} This chelate does not however react with pyruvaldehyde, such a highly electrophilic aldehyde and aldolization requires the exchange of magnesium in 54bMg for potassium in 54bK.\textsuperscript{2} This has been effectively achieved after acidification of 54Mg by 2 N aq. HCl at low temperature (0-5 °C) followed by titration of the resulting carboxylic acid 56H with aqueous potassium hydroxide.\textsuperscript{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.\textsuperscript{2}](image)

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).\textsuperscript{48} It contrasts with the lengthier approach disclosed in Scheme 18, entry a,\textsuperscript{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\textsuperscript{2} to build the olefinic side chain (Scheme 18, entry a, compared to the shorter approach Scheme 18, entry b).\textsuperscript{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 enyne, (ii) the efficient separation of the desired Z-isomer 30az from small amounts of the undesired E-isomer 30ae 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 jasmonolone 3c, achieved² 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 from ketones 6 and diethyl carbonate 57 (Scheme 16 entry azb). 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 conditions⁴⁷ 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.\textsuperscript{22,26,52,53}

\[
\begin{align*}
\text{Scheme 21. Synthesis of cinerolone involving an acetylenic intermediate.}\textsuperscript{26,47}
\end{align*}
\]

5.1.2.3 Synthesis of rethrolones 5 involving acyl chlorides 60 and ethyl acetylacetonate 59 (Scheme 16 entry a\textsubscript{2c}). Another synthesis of alkyl β-ketocarboxylates 54 also uses ethyl acetooacetate 59 (Schemes 22, 23)\textsuperscript{24,25} but differs from the previous ones since it involves its acylation (Schemes 22, 23)\textsuperscript{24,25} rather than its alkylation (Scheme 17, 19-21). It produces ethyl 2-acetyl-3-ketooc-7-enoate 58 that on further reaction with metal alcohohates 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)\textsuperscript{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\textsuperscript{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).\textsuperscript{24} Carbonation of the Grignard reagent derived from the related 1-bromo-3Z-pentene 86b produces, after protonation and reaction with thionyl chloride, the acid chloride 60b.\textsuperscript{2}
Scheme 22. Synthesis of allethrolone from 2-hydroxymethyltetrahydrofuran.\textsuperscript{25}

Scheme 23. Synthesis of cinerolone involving an unsaturated β-keto acid.\textsuperscript{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\textsuperscript{54} from the readily available citric acid 88, that is efficiently alkylated with allyl\textsuperscript{49} or propargyl\textsuperscript{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)\textsuperscript{22,49} and prallethrolone 3d’ (Scheme 25)\textsuperscript{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\textsuperscript{49} or propargyl dimethyl 3-oxoglutarate 67d’\textsuperscript{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\textsuperscript{49} albeit in modest yield (32%, Scheme 24) and the 2,5-dioxo-3-hydroxy-8-nonyne 5d’\textsuperscript{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'. The important difference in yields (32 and 80%) has been attributed to the larger electron withdrawing effect of the 2-propynyl group present on 67d' favoring the preferential regioselective decarboxylation at C₇ (Scheme 25). However careful investigations could suggest another explanation, since the procedures and the processes disclosed by the two groups (compare the proposed intermediates 66dNa and 65d, Scheme 24 to 66d', Scheme 25) are quite different.

Scheme 24. Synthesis of allethrolone from citric acid.

We would suggest, if either of the syntheses has to be repeated, that the procedure of the Sumitomo Company 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 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 C₇-C₈ 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, which are easily
isomerized to rethrolones 3, to involve two different strategies in which the C₄ 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 10ᵧ as starting material (Scheme 26, entry i),³⁴ to take advantage of the aptitude of the furan ring to be (i) easily metallated²⁹,⁵⁹ at C-2 (C₆ or C₇) then alkylated or formylated or (ii) formylated at C-2 in a straightforward way using the Vilsmeier-Haack reaction.⁶³,⁶⁴

\[
\text{Scheme 26. Retrosyntheses of rethrolones involving furans.} ^{30,33-35,45,61}
\]

Accordingly, the R group present at C₇ has been introduced either as an electrophilic entity at C₈ on 2-metallofurans (Scheme 26, entry c)²⁹,⁵⁹ or as nucleophilic species³³ such as a Grignard reagent on the C₇ 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 8ₓ produced under smooth conditions, are prone to produce a carbocycle (3, 7 or 4₄; Scheme 26) and not their E-isomers 8ₑ that are produced (i) on strong acid hydrolysis³⁰ for example from the dimethoxy
derivative 92 or (ii) on oxidation 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 8\(E\) to 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 \(\gamma\)-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 (Cb) 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 (Cb) such as 32 (Scheme 26, entry g).\(^{33}\)

Efficient protocols to transform peroxides 89, enediones 8 and \(\gamma\)-hydroxycyclopent-2-enones 7 to rethrolones 3 are outlined in Scheme 13.

The synthesis of \(\gamma\)-hydroxycyclopent-2-enones (rethrolones) 3 from the peroxides 89, the enediones 8 and \(\gamma\)-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.\(^{34,35}\)

\[\begin{align*}
\text{O} & \quad \text{d: } R= \text{allyl; } d': R= \text{propargyl} \\
\text{c} & \quad \text{HO} \\
\text{a} & \quad \text{R} \\
7d & 7d' \\
a & \text{Al}_2\text{O}_3, \text{toluene-ether (1/1), 30°C, 24h} \\
b & \text{5% eq. NaHCO}_3, \text{100°C, 1h} \\
c & \text{1 eq. MgCl}_2.6\text{H}_2\text{O}, 0.05\text{M aqueous, pH 7.3, 4h} \\
d & \text{1 eq. ZnCl}_2, 0.05\text{M aqueous, pH 7.3, 15h} \\
e & \text{Autoclave, aqueous, 180°C, 6h} \\
3d & 3d' \\
3d' & \text{63%}\text{, 70%}\text{, 75%}\text{, 87%}, 77\%, 80\%, 95\% \\
\end{align*}\]

\textbf{Scheme 27.} Isomerization of iso-rethrolones to rethrolones: syntheses of allethrolone and prallethrolone \textsuperscript{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 metatation 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.\textsuperscript{29}

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

Rationale for the slightly modified process that uses dimethyl sulfide as a reducing agent is shown in Scheme 28, entry d.\textsuperscript{29} Thus, the hydroperoxy intermediate 90 resulting from singlet oxygen cycloaddition rearranges to the hemiperoxyketal 91 precursor of the enedione 8dz 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.\textsuperscript{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\textsuperscript{30}

Scheme 29. Synthesis of allethrolone by electrochemical oxidation of 2,5-dialkylfurans.\textsuperscript{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).\textsuperscript{30}

\begin{center}
\textbf{Scheme 30.} Controlling the nature of the products on reaction of a 2,5-dimethoxydihydofuran in acidic media.\textsuperscript{30}
\end{center}

It was found\textsuperscript{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).\textsuperscript{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.\textsuperscript{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 82 cyclize to hydroxy-cyclopentanones (Scheme 30 entry b) and not their E-isomers (E)-8 (Scheme 30 entry c).\textsuperscript{29,30} Therefore, the discovery\textsuperscript{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,\textsuperscript{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).\textsuperscript{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\textsuperscript{30} and bases\textsuperscript{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 8d2 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).\textsuperscript{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 reaction63,64 and its allylation using allyl metals33,35,36,77 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 C4 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 C3 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 C5 (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).\textsuperscript{35} It has also been found\textsuperscript{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.\textsuperscript{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).\textsuperscript{32,33} Alternatively the transformation of the furfuryl carbinol 32d to the allethrolone 3d has been achieved by Saito\textsuperscript{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).\textsuperscript{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).\textsuperscript{77}
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 to achieve the synthesis of allethrolone (Scheme 34) and prallethrolone (Scheme 35) from 2-formylfuran 10y readily available from natural D-xylose.

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

Scheme 34. Synthesis of allethrolone from D-xylose.
Compared to the approach disclosed above (Sub-section 5.2.2.1.1.), the 2-formylfuran 10y misses the C₃ 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 C₃ methyl group at C₅ 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 C₅ (Scheme 36, entry a) 66 or one of its protected forms (Scheme 36, entries b,c) and implies the formation of the C₅-C₆ bond (Scheme 1, entry c). 57,69

It allows the construction of its carbon framework through a convergent strategy that involves an aldol reaction generating at the same time the C₅-C₆ single bond and the hydroxyl at C₆. Depending upon the case the tetra-substituted C₅=C₆ 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 C₆=C₅ double bond, present in 3d, proceeds through an elimination reaction that implies a leaving group present at C₆ in the first approach (Scheme 36, entry a) 66 and at C₅ 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 C₅C₆.
Scheme 36. Syntheses of allethrolone involving an intramolecular aldol condensation with a methyl ketone bearing a formyl group in β-position.\textsuperscript{66,67,69}

5.3.2 Selected examples. The approach described\textsuperscript{66} in Scheme 37 employs the easily accessible methylthioacetone 100. The methylthio group is involved in (i) the regioselective metalation at the C\textsubscript{f} carbon, that allows the addition of the resulting enolate across the C=C double bond of the monooxidized ketene thioacetals derivative 102 (ii) the subsequent allylation at C\textsubscript{f} with allyl iodide that leads to the highly functionalized 103\textsubscript{d} and (iii) the formation of the C\textsubscript{f}=C\textsubscript{b} double bond by playing sequentially the role of a leaving group, at a last stage leading finally to allethrolone 3\textsubscript{d} (Scheme 37).\textsuperscript{66} It is noteworthy that (i) that deprotection of 103\textsubscript{d} in acidic media generates 104\textsubscript{d} 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 3\textsubscript{b} in 75\% overall yield when using cis-1-iodo-2-butene in place of allyl iodide.\textsuperscript{66}

However, it was very recently reported\textsuperscript{77} (reference 33 therein) that the authors were unable to extend on 100', the phenylthio analog of 100, the transformation leading originally to 103\textsubscript{d}, nor to carry out the carbocyclization of 104\textsubscript{c}, the phenylthio analog of 104\textsubscript{d}, expected to produce 3\textsubscript{c} (Scheme 37, entry a).\textsuperscript{66} The latter reaction (104\textsubscript{c} to 3\textsubscript{c}) 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).\textsuperscript{77}

In order to bypass the difficulties reported above, and following the same strategy, the authors\textsuperscript{77} have trapped the 3-sodio-3-(phenylthio)oct-5-en-2-one with 1-nitropropene 102\textsubscript{c}\textsuperscript{77} in place of a 1-methylthio-1-methylsulfinyl-propene (Scheme 37, compare entry d to entry a).\textsuperscript{66} The next steps to jasmololone 3\textsubscript{c} have been adapted accordingly. The transformation of the nitroalkyl group to the corresponding aldehyde involves the Nef reaction\textsuperscript{77,131,132,133} that produces the dimethoxytetrahydrofuran intermediate. The latter delivers almost quantitatively the γ-ketoaldehyde 104\textsubscript{c} on acidic treatment that has been successfully cyclized to jasmololone 3\textsubscript{c}, as reported above, on reaction with sodium ethoxide in ethanol (Scheme 37, entry d).\textsuperscript{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 dichloromethyllithium68 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-toluenesulfonylic 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
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.

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

5.3.2.3. The synthesis 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 114 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 56dK 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). 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).

Scheme 39. Synthesis of allethrolone involving two consecutive aldol condensations.

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 Cc 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-
The 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\(_1\) carbon present on the side chain in 33c inserted into the five membered of jasmone 12c, but also the oxygen of the carbonyl carbon is no longer attached to C\(_6\) (in 33c) but to C\(_6\) (in 12c) (Scheme 41, entry a),\(^{42}\) or (ii) the C\(_5\)C\(_6\) double bond present on the five-membered ring of 121c migrates to the C\(_6\)C\(_7\) 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), the latter, at least formally, involves the migration of a C=C double bond (Scheme 41, entries b,c) 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) 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 Stork83 (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=Cd double bond” from 120c to 121c is achieved through a retro Diels-Alder reaction83,86,87 that involves flash thermolysis (600°C). This method does not favor the migration of the resulting C=C double bond from Cc,Cd in 121c to Cb,Cf 12c that effectively takes place at much lower temperature (100 °C) or under different experimental conditions (Scheme 41, entry b).83

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 on the 2-phenylseleno cyclopent-2-ene 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 eliminate88,89,90 with a hydrogen located on a β-carbon (Cb) in the suitable syn-relationship to produce the required C=Cb 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 exocyclic 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 Cd (Scheme 41, entry c).84 The latter on oxidation with hydrogen

Scheme 41. Retrosynthetic routes to jasmone involving a preformed cyclopentane ring.42,83,84
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 Cc,Cd to the more stable Cb,Cf 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 Cd an endocyclic allylic position. Such transformation that has been first carried out on cinerone 12c" that bears a saturated side chain at Cf, has been achieved using the three-step sequence that involves allylic bromination71 at Cd 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](image)

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 Cr such as on pyrethrolone and cinerolone failed.52,72,73 It was for example reported73 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 Cc.73

In fact, rethrones possess several potential reactive sites shown on Scheme 43, entry a, that involve either their Cb=Ct or the Cn=Ci double bonds (Scheme 43, entry b) or their allylic positions at Ca, Cc, Ci and Cg that is bi-allylic (Scheme 43, entries c,d). The Ce=O carbonyl group is susceptible of 1,2-addition of nucleophilic species and favors at the same time the 1,4-addition at Cb and the enolization at Cd, Cc and Ca. The Z-stereochemistry of the exocyclic Cn=Ci double bond confers a higher reactivity than its E-isomer, tending to favor electrophilic addition reactions or reaction at Cj and Cg 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 Cc has been discovered, in Chrysanthemum cinerariifolium Nature has achieved it both regio- and stereo-selectively.1,94

![Scheme 43](image)

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) 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 C₈=C₉ double bond, especially when the oxidation is performed in the presence of 5% catalyst 126 (Scheme 44, entry b). 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). Note that in such a case the reaction proceeds differently on the two C=C double bonds, producing a diol on C₈,C₉ and an epoxide on C₉,C₁₀.

\begin{align*}
\text{a} & \quad \text{5 HBr (48%), DMSO} \\
& \quad \text{20°C, 24h} \\
& \quad \text{H₂O₂, Fe(bpmen)(OTf)₂} \\
& \quad \text{AcOH, MeCN, 20°C} \\
& \quad \text{b} & \quad \text{5% Fe(bpmen)(OTf)₂ 126} \\
& \quad \text{c} & \quad \text{15% Fe(bpmen)(OTf)₂ 126} \\
\end{align*}

**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), 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.

\begin{align*}
\text{a} & \quad \text{O₂, Pd(OAc)₂, AcOH} \\
& \quad \text{0.2 p-benzoquinone,} \\
& \quad \text{50°C, 3h} \\
& \quad \text{b} & \quad \text{O₂, 5% PdCl₂, DMA} \\
& \quad \text{20 % H₂O, 20°C, 24h,} \\
& \quad \text{10 atm, 99%} \\
\end{align*}

**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). 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). 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.

5.4.2.3 Bioreagents. Bio-reagents, especially those present in C. cinerariifolium, 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. 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 monoxygenase 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 Cα methyl group (Scheme 46, entry a), and although jasmololone 3c is produced 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). Related results have been obtained by reacting other fungal strains such as Penicillium, Absidia, Syncephalastrum, Botrytis, Aspergillus, Cunninghamella, Chaetomium, and Didymosphaeria. 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 representative bio-reagents.

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).

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 retrolone 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 retrolone 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\textsuperscript{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,\textsuperscript{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 vinylogous), 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.\textsuperscript{102}

![Scheme 49. Synthesis of allethrolone by regioselective reduction of a cyclopentenedione.\textsuperscript{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).\textsuperscript{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 jasmolone 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 \textit{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).\textsuperscript{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). It was achieved, but in very poor overall yield (13%), from the acetate 1dAc via a two-step sequence that involves (i) its “reductive ozonolysis” [(i) O₃, CH₂Cl₂, -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 1aAc (Scheme 50, entry a). Results proved even worse when 19d is generated from 1dAc by the two step one pot sequence involving osmium tetroxide/periodate methods instead (NaIO₄ aq., OsO₄ THF, 20 °C, 24 h, 58% yield) since the aldehyde, formed in reasonably good yield, decomposes on attempt at purification. The authors also tried unsuccessfully on a model 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, but that apparently works only with “non-conjugated ylides”.

Scheme 50. Synthesis of pyrethrolone from allethrolone by modification of the side chain.

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). 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 3aZ from the E+Z mixture that uses chromatography on silver nitrate impregnated support.

Otherwise, the stereoisomeric mixture of d,l-3a resulting from deprotection of 141 (Scheme 34 entry b) was esterified with d-trans-chrysanthemic acid chloride 2aCl (Scheme 51) and the pyrethrin 1aZ possessing a Z-allelthronyl moiety was isolated as shown.
Scheme 51. Synthesis of pyrethrin from a cis/trans mixture of pyrethrolone.  

Purification of the pyrethrin 1az was successfully achieved after reacting the resulting mixture with tetracyanoethylene 28a that exclusively reacts on the undesired pyrethrin 1ae 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 1ae free from 1az.

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 ethyldiene 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 rithrolones, 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, possessing the homoallyl iodide group on its side chain (Scheme 52 entry b). 12 Esterification with chrysanthemoyl chloride 2aCl leads to the ester 1a, 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
**5.8. Stereoselective synthesis of rethrolone side-chains from prallethrolone**

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

The syntheses 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 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 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. 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, Pd(0) in the presence of copper iodide as catalyst and a tertiary amine such as Et₃N or i-Pr₂NEt as a base (Scheme 53, entry b), but did not proved suitable for the alkylation of (S)-3d’ leading finally to cinerolone 3b and jasmololone 3c.

It was however found that the conditions of the modified Sonogashira reaction reported by Fu 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 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).

\[ \text{Scheme 53. Synthesis of allethrolone, cinerolone, jasmololone and pyrethrolone, from prallethrolone.} \]

5.8.2 Hydrogenation of the C≡C triple bond of 3d′ and 144. The last step of the process requires the chemoselective 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 already been 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-CaCO₃ poisoned by Pb(OAc)₂].

These conditions do not apply to the chemoselective dihydrogenation of the C≡C triple bond of the eneyne (S)-144d. Related conditions that involve the use of Pd-catalysts poisoned by quinoline, manganese chloride in the absence or presence of quinoline, 5% Pd-BaSO₄-(6 eq.)-quinoline or NaBH₄-BF₃-Et₂O 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.

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), a reaction previously used to reduce the triple bonds to Z=C=C double bonds in long chain conjugated fatty acids (Section 4.2).

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 involves the reaction of racemic allethrolone 3d with d-(R,R)-trans-chrysanthemic acid chloride (R,R)-2ac 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 145s (Scheme 54). 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 146s intermediate, leads to the isolation of the d-(S)-allethrolone enantiomer 3ds in quite good overall yield and recovery of the d-(R,R)-trans-chrysanthemic acid 1a that can be isolated for reuse (Scheme 54).

The partially resolved allethrin semicarbazone remaining after separation of d-allethrolone does not allow the extraction of pure l-allethrolone. The latter can however be isolated in pure form by resolution of allethrolone 3d with d-(S,S)-trans-chrysanthemoyl chloride (S,S)-2ac instead (Scheme 54, framed).

Scheme 54. Resolution of allethrolone using 1R-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\textsuperscript{105,106} or phthalic anhydride 146b\textsuperscript{107} and resolution of the resulting esters with a enantiopure amine such as (d)-ephedrine 149a with the succinate 148d (Scheme 55)\textsuperscript{105,106} and α-methyl benzylamine\textsuperscript{107} or α-phenyl- or α-p-tolyl-ethyl benzylamine for the phthalate.\textsuperscript{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.

\[ \text{Scheme 55. Resolution of allethrolone using ephedrine.} \textsuperscript{105,106} \]

(ii) on performing an unusual type of acetalization using biocartol 151 as a resolving agent (Scheme 56).\textsuperscript{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.\textsuperscript{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.

\[ \text{Scheme 56. Resolution of allethrolone using biocartol.} \textsuperscript{105} \]
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). The transformation of the alcohol (R)-3d into its tosylate (R)-21a 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)-21da 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). To avoid these side reactions the alcohol (R)-3d has been instead transformed into its mesylate (R)-21db on reaction with the sulfene 156 formed from the reaction of triethylamine with methanesulfonyl chloride (Scheme 58). Its reaction with potassium chrysanthemate 20k occurs with net inversion of configuration and leads to allethrin (R,R,S)-1d (Scheme 57, entry a). 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).

Scheme 57. Unsuccessful outcome of tosylation of allethrolone. To avoid these side reactions the alcohol (R)-3d has been instead transformed into its mesylate (R)-21db on reaction with the sulfene 156 formed from the reaction of triethylamine with methanesulfonyl chloride (Scheme 58). Its reaction with potassium chrysanthemate 20k occurs with net inversion of configuration and leads to allethrin (R,R,S)-1d (Scheme 57, entry a). 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).

Scheme 58. Synthesis of (S)-allethrin and (S)-allethrolone from (R)-allethrolone.
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 (S)-allethrolone, in order to initiate a subsequent resolution step.\textsuperscript{111}

This racemization has been successfully achieved on reaction of allethrolone 3d\textsubscript{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).\textsuperscript{112}

![Scheme 59. Racemization of (R)-allethrolone in a two-step process involving 4-chlorocyclopentenone.\textsuperscript{112}](image)

It was found that the solvent has a profound effect on the stereochemical course of the reaction of (R)-3d with phosphorus trichloride.\textsuperscript{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 a).\textsuperscript{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).\textsuperscript{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.\textsuperscript{113}

Nearly a hundred microorganisms: bacteria (\textit{B. subtilis} IFO-3026), yeasts (\textit{Kloeckera corticis} IFO-0868), actinomycetes (\textit{Streptomyces griseofuscus} IFO-12870), and moulds (\textit{Aspergillus niger} IFO-6342), have been found to hydrolyze, usually enantioselectively, prallethrolonyl- 1d\textsuperscript{′}Ac and allethronyl acetates 1d\textsubscript{Ac}.\textsuperscript{114-116} The (R)-acetates (R)-1d\textsubscript{Ac} are preferentially hydrolysed\textsuperscript{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 \((S)-1dAc\) 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 \((S)-1Ac\) formed by the reaction of the lipase should be either transformed *in situ* into a single alcohol \((S)-3\) or a single acetate \((S)-1Ac\).

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 \((S)-1Ac\) 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 \((S)-1Ac\) 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 1dAc or 1d’Ac or as a single compound have been reacted114,115,116,117 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 reaction114 (Scheme 62) to produce the corresponding prallethrolonyl mesylate (R)-21d’b,109,110,116 -nitrato (R)-21d’c,116 and -borato (R)-21d’d114. Note that all transformations disclosed above, except the one involving the Mitsonobu reaction114 (Scheme 62), do not affect the stereochemistry at the carbon to which the hydroxyl group is attached. The Mitsonobu reaction117 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 prallethrole (S)-3d' with net retention of configuration in acidic aqueous media (Scheme 61, entry c).  

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: Arthrobacter 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). It has been also reported that the rate of hydrolysis increased with chain length from acetate to caprylate but decreased with caprate. 

Scheme 62. Single-pot resolution of prallethronyl acetate and recycling of the unwanted enantiomer using an Arthrobacter lipase and a Mitsonobu reaction.  

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.  

Arthrobacter lipase efficiently performs the enantioselective hydrolysis of racemic allethrolonyl acetate 1dAc (Scheme 63). The reaction is usually carried out at 40 °C and pH 6 and provides (R)-allethrole (R)-3d in good yield (43%–50% maximum) with high enantiomeric excess (98.4%) and recovery of the (S)-allethrolonyl acetate (S)-1dAc (53%) after 17 h.

Reacting the resulting mixture of (S)-allethronyl acetate (S)-1dAc and bio-saponified (R)-allethrole (R)-3d with mesyl chloride or nitric acid then with aqueous calcium carbonate at 85 °C for 4 h allows the formation of enantiopure allethrole (S)-3d by concomitant saponification of the allethrolonyl acetate (S)-1dAc as well as substitution by the hydroxyl ion of the (R)-allethrolonyl mesylate (R)-21dAc or allethrolonyl nitrate (R)-21dAc 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.\textsuperscript{157}

Manipulations of the lipases have been carried out to, \textit{inter alia}, (i) improve their enantioselectivity, their activity, and their reuse and (ii) facilitate the recovery of the products.\textsuperscript{118,119,120,121,122}

Lipases are also able, in the presence of vinyl acetate \textsuperscript{158}, to transform (R)-allethrolone (R)-3d to its acetate (R)-1d\textsubscript{Ac} leaving untouched its (S)-stereoisomer (S)-3d (Scheme 64).\textsuperscript{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 \textsuperscript{158} as both the acyl donor and organic solvent. They lead to the (S)-allethrolone (S)-3d with ee up to 99\%.\textsuperscript{118,120} The \(V_{\text{max}}\) of modified \textit{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 \(K_{\text{m}}\). It allows 40\% conversion in 20 h leading the acetate (S)-1d\textsubscript{Ac} (ee 100\%) with concentration in substrate as high as 1 M and 1.0 mg/ml of coated lipase.\textsuperscript{118}

Immobilization of \textit{Arthrobacter} lipase has been performed by deposition on grafted diatomaceous material,\textsuperscript{120} encapsulation in hydrophobic sol-gel materials,\textsuperscript{121} and onto glutaraldehyde-activated amino-silica gel.\textsuperscript{122} For example the \textit{Arthrobacter} lipase\textsuperscript{120} immobilized on diatomite grafted by methacryloxypropyl-, vinyl-, octyl-, dodecyl-, and \(\gamma\)-(aminopropyl)-glutaraldehyde leads to excellent enantioselective transformations (E\geq400, 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.\textsuperscript{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).

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 C6=C7 double bond (Section 5.1).

The first approach, shown in Scheme 65, 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 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.

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.

Unfortunately however, the cyclization of the last to the cyclopentenolone 3 under the usual conditions (0.1 N aqueous NaOH) is accompanied 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.

Another even more interesting approach involves 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 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 found126 that the modified cinchona alkaloid (DHQD)$_2$PHAL 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

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

The enantiomeric excess is far better128 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 extended128 to aldehydes and cyclic ketones, it does not go well with methyl alkyl ketones that are requested starting materials for the synthesis of rethrolones.
40% aq. \[
\text{O} \\
\text{H}
\] + 5 eq. \[
\text{O} \\
\text{H}
\] 10 mol.% 169, water, 25°C, 12h

\[
\text{O} \\
\text{H}
\]

94%, (ee 90%) 5f

\[
\begin{align*}
\text{N-Tosyl-}\text{(S)-binam-L-prolinamide 169}
\end{align*}
\]

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 an 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.\(^{130}\)

\[
\begin{align*}
\text{Proline}
\end{align*}
\]

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\textsuperscript{136,137} both for building the required skeleton, often through its decarboxylative version,\textsuperscript{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.\textsuperscript{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.

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