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Pauline Chaumont-Olive, Jorge Sánchez-Quesada, Ana María Collado Pérez, Janine Cossy. Synthetic approaches to the damascone and damascenone isomers. *Tetrahedron*, 2021, 82, pp.131932. 10.1016/j.tet.2021.131932 . hal-03407603

HAL Id: hal-03407603

<https://hal.science/hal-03407603v1>

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Synthetic approaches to the Damascone and Damascenone isomers

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ARTICLE INFO

Article history:

Received
Received in revised form
Accepted
Available online

Keywords:

Damask rose
Damascones
Damascenones
Organoleptic compounds
Fragrance

ABSTRACT

This review covers the synthesis of damascones and damascenones from their early discovery to nowadays starting from ionones, cyclic or linear starting materials. Gram-scale syntheses are highlighted.

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1. Introduction

The essence of the Bulgarian rose, the Damask rose (*Rosa Damascena mill.*), has been one of the oldest essence explored as it contains different organoleptic compounds with a large diversity of flavors and fragrances.¹⁻⁹ With a low threshold concentration, some of these constituents stand for an important source of odors for flavor and fragrance companies such as plum, cooked apple-like, rose, tobacco, black tea, wood, honey, etc. This essence **has been used** since the 80's in the composition of fragrances, soaps, cosmetic powders and detergents.^{10,11}

The complex composition of the essential oil of the Bulgarian rose has been elucidated in part by Kováts between 1962 and 1967, who identified 127 constituents using two-dimensional preparative gas chromatography for the isolation and spectroscopic analytical methods, this study being of "enormous economic importance".¹² Since then, the number of identified constituents has **more than doubled**.¹ During these studies, **β -damascenone** has been identified as a 0.1% constituent of the extract of the Bulgarian rose. This compound possesses a powerful floral rose odor, which can be detected at very low concentration and represents 70% of the relative proportion of the rose oil in scent units.

In 1970, the structure and the first synthesis of α -damascone, β -damascone and β -damascenone were reported by Demole *et al.* at *Firmenich* and Kováts from the *Chemical Laboratory, ETH Zürich*.^{13,14} The origin of the names, damascone and damascenone, is damascene coming from the Damask rose "damasc" and "one" or "enone" related to their chemical functionalities, and the α -, β -, δ - and γ -nomenclature of damascones is related to ionones as damascones are finally *iso-ionones* (Fig. 1).¹⁵

The biosynthesis of natural products can be highly useful to understand the origin of compounds and to design suitable and efficient synthetic routes. Following the identification of the chemical structure of damascones, in 1973 Ohloff *et al.* in their initial research at *Firmenich* as well as Isoe *et al.*, reported their discoveries on the biosynthesis of these natural products.^{16,17} Based on results published in 1968 on the origin of β -ionone from β -carotene,¹⁸⁻²³ the authors reported that damascones were formed through the same biosynthetic pathway. This metabolic pathway was mainly confirmed by mimicking the *in vivo* degradation of damascones with *in vitro* model reactions applied to β -ionone or other carotenoid metabolites, which lead to

β -damascenone. This work was then completed by numerous experiments affording the complete damascone biosynthetic route, which is finally part of C13-norisoprenoids: a class of volatile carotenoid metabolites.^{8,24-28}

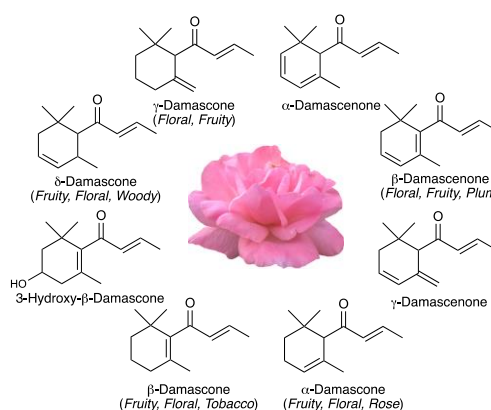
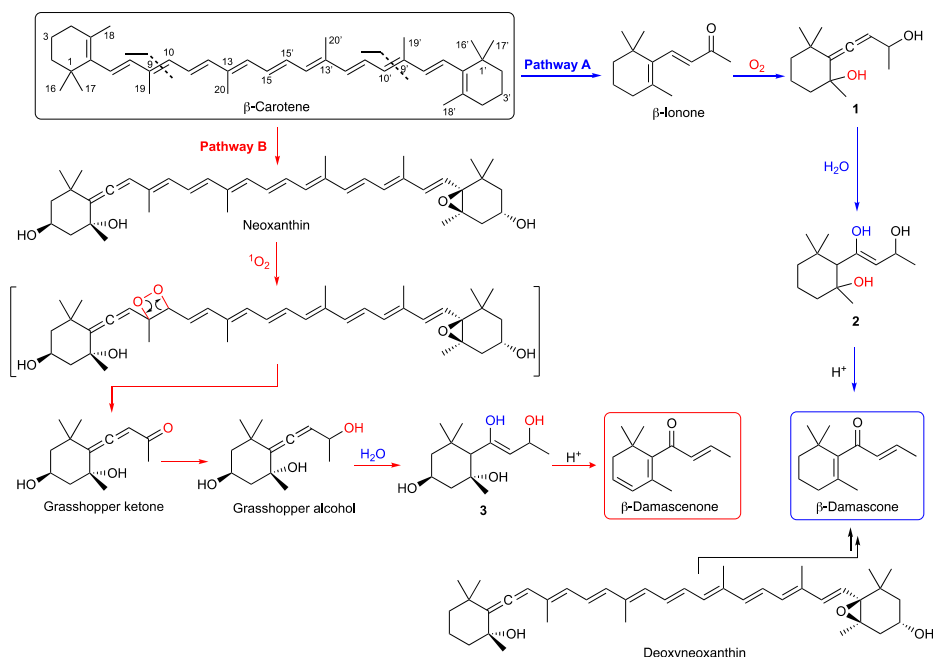


Fig. 1. Damask rose: Structure of damascones and damascenones and their fragrances.

Considering the biosynthetic pathway, allowing the formation of β -ionone from β -carotene, the first step is an enzymatic oxidative bond cleavage of the C9-C10 double bond of β -carotene by β -carotene-dioxygenase. This enzyme produces singlet oxygen, a highly reactive entity towards double bonds. After the oxidative cleavage of β -carotene, the resulting β -ionone undergoes another oxidation step giving the allenic intermediate **1**, followed by a Meyer-Shuster rearrangement to afford intermediate **2**.²⁹ β -Damascone is then formed by dehydration under acidic conditions (**Scheme 1**, Pathway A).

Another biosynthetic pathway to damascones can be considered from β -carotene as this latter can be enzymatically degraded to neoxanthin after several oxidation steps. The cleavage of neoxanthin by carotenoid enzymes, mainly xanthine oxidase, leads to the Grasshopper ketone, an allenic carotenoid. This ketone is then enzymatically reduced to Grasshopper alcohol which undergoes a Meyer-Shuster rearrangement affording the enolized hydroxy ketone **3**. After several dehydration steps under acidic conditions, β -damascenone is produced. It is worth mentioning that this biosynthetic route can also lead to β -damascone *via* deoxyneoxanthin which is also a metabolite issued from the enzymatic oxidation of β -carotene (**Scheme 1**, Pathway B).

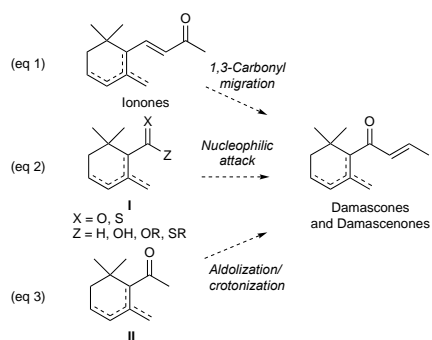


Scheme 1. Biosynthesis of β -damascone and β -damascenone from β -carotene and derivatives.

The biosynthesis of damascones from β -carotene explains the variety of odors and their ubiquitous presence in other natural sources than Damask rose. Their close structure to ionones is also enlightened as the ionones are also issued from β -carotene.³⁰⁻⁴⁰

Since their early discovery, damascones and damascenones are of high interest for fragrance companies. Due to the number of reported syntheses,^{4,41} we will only focus on the most important syntheses. Three main strategies have been used to access damascones and damascenones:

- From ionones by 1,3-carbonyl migration (**Scheme 2**, eq 1).
- From or *via* cyclohexenyl aldehydes, esters and acids, such as **I**, by attack of a nucleophile on the carbonyl group. To access the cyclohexenyl derivatives, from linear starting materials, the cyclization step can be at early or at late stage (**Scheme 2**, eq 2).
- From cyclohexenyl methylketones, such as **II**, by using an aldolization/crotonization sequence (**Scheme 2**, eq 3).



Scheme 2. General synthetic routes to access damascones and damascenones.

In this review, the synthesis of damascones and damascenones will be classified according to the starting cyclic substrates (ionone, cyclocitral, cyclogeranate and cyclohexenyl methylketones) and subdivided according to the starting materials used to produce the cyclic substrate. The multigram scale syntheses will be highlighted by notifying the number of grams or kilograms obtained.

2. α -Damascone

The first syntheses of α -damascone were realized in a racemic form and efforts have been made to access selectively the two enantiomers.

2.1. Racemic syntheses

Syntheses of α -damascone from cheap starting materials were realized. One of the most evident starting material to access α -damascone is α -ionone. As α -damascone possesses the α -ionone carbon skeleton, only a 1,3-carbonyl transposition is necessary to obtain α -damascone.

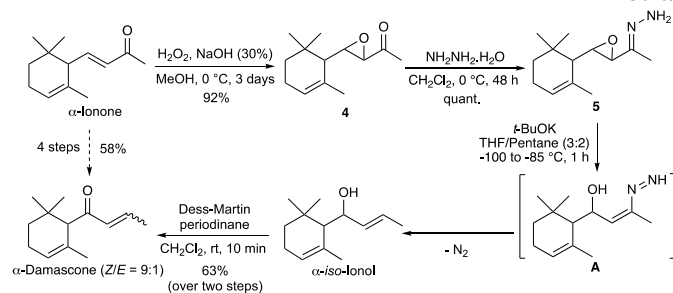
2.1.1. From α -ionone

To realize the 1,3-transposition of the α -ionone carbonyl, several rearrangements were used: a Wharton rearrangement, a Büchi-Veders rearrangement and a Meisenheimer rearrangement.

Wharton rearrangement

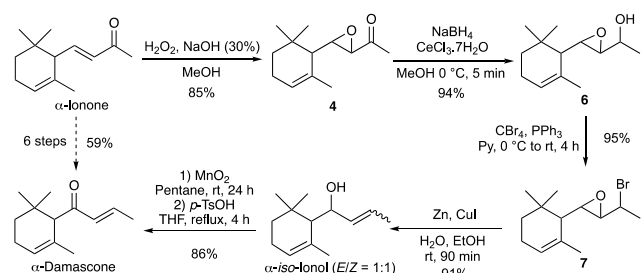
To transform α -ionone to α -damascone, Luche *et al.* applied a Wharton rearrangement to an epoxy-hydrazone.⁴² This compound was obtained from α -ionone (epoxidation/hydrazone formation) *via* epoxy-ionone **4** and, epoxy-hydrazone **5** was converted to α -*iso*-ionol under basic conditions (*t*-BuOK, THF/pentane, -100 °C to -85 °C). It is worth mentioning that the use of *t*-BuOK is necessary to realize the deprotonation of the diazene intermediate **A** to avoid the formation of bicyclic side-products.⁴³ α -*iso*-ionol was then oxidized to α -damascone by using the Dess-Martin periodinane (4 steps, overall yield = 58%) (**Scheme 3**).

We have to mention that an alternative to the Wharton rearrangement was applied to an α -bromo-epoxyde.⁴⁴ Epoxy-ionone **4** was reduced to epoxy-ionol **6** (NaBH₄, CeCl₃, MeOH, 0 °C) and this latter was transformed to the corresponding α -bromo-epoxide **7** (CBr₄, PPh₃, Py). The bromide intermediate underwent a reductive debromination/ring-opening of the epoxide, *via* a radical intermediate or an anion generated by zinc (Zn, CuI, EtOH, H₂O), and α -*iso*-ionol was isolated in high yield (91%) as an equimolar mixture of (*Z*)- and (*E*)-stereoisomers.



Scheme 3. Synthesis of α -damascone using a Wharton rearrangement.

After oxidation of the resulting (*E*)- and (*Z*)-allylic alcohols (MnO_2 , pentane), the isomerization of the double bond to the (*E*)-isomer was achieved under acidic conditions (*p*-TsOH, refluxing THF). α -Damascone was produced in 6 steps from α -ionone with an overall yield similar to the one obtained by applying a Wharton rearrangement to **5** (59% *versus* 58%), however with two more steps (6 steps *versus* 4 steps) (**Scheme 4**).

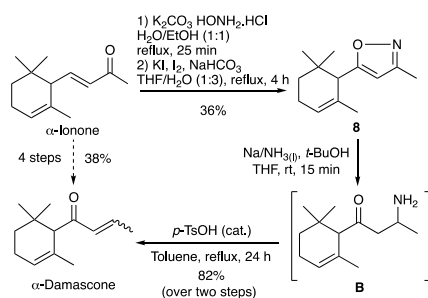


Scheme 4. Synthesis of α -damascone by reductive ring-opening of an α -bromo epoxide.

Büchi-Vederas rearrangement

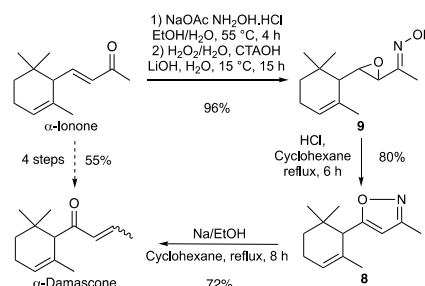
Büchi and Vederas took advantage of the Crabbé *et al.* work⁴⁵ to synthesize α -damascone from α -ionone by rearrangement of an isoxazole.⁴⁶ α -Ionone was treated with hydroxylamine hydrochloride to produce an α -ionone-oxime intermediate, which after an **iodocyclization/elimination** sequence (KI , I_2 , NaHCO_3 , refluxing THF/ H_2O), led to isoxazole **8**. A Birch reduction ($\text{NH}_3(\text{l})$, *t*-BuOH, THF) applied to **8** produced the amino-ketone intermediate **B** which after an acidic treatment (*p*-TsOH, refluxing toluene), was converted to α -damascone. If only 4 steps were necessary to access α -damascone from α -ionone, the overall yield is modest (38%) (**Scheme 5**).

An improvement of the Büchi-Vederas rearrangement was reported by Xu *et al.* via an isoxazole intermediate obtained in 3 steps from α -ionone.⁴⁷ At first, α -ionone was converted to an α -ionone-oxime (NaOAc , $\text{NH}_2\text{OH}\cdot\text{HCl}$, $\text{EtOH}/\text{H}_2\text{O}$) and, after an epoxidation [H_2O_2 , cetyltrimethylammonium hydroperoxide (CTAOH), LiOH , H_2O], the resulting epoxy-oxime **9** was converted to isoxazole **8** under acidic conditions (HCl , refluxing cyclohexane).



Scheme 5. Synthesis of α -damascone from α -ionone using a Büchi-Vederas rearrangement.

The transformation of isoxazole **8** to α -damascone was achieved in one step using sodium in EtOH (refluxing cyclohexane). This straightforward synthesis of α -damascone from α -ionone is competitive with the Luche *et al.* synthesis (4 steps, overall yield = 55%) (**Scheme 6**).



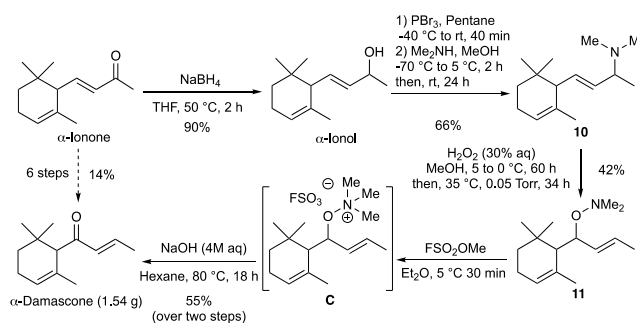
Scheme 6. Synthesis of α -damascone from α -ionone via an epoxy-oxime intermediate.

It is worth mentioning that a less effective Büchi-Vederas rearrangement was reported by Schulte-Elte *et al.*^{48,49}

[2,3]-Meisenheimer rearrangement

Rautenstrauch *et al.* took advantage of the [2,3]-Meisenheimer rearrangement⁵⁰ to synthesize α -damascone.⁵¹ After reduction of α -ionone to α -ionol (NaBH_4 , THF, $50\text{ }^\circ\text{C}$), this latter was transformed to the corresponding bromide (PBr_3 , pentane), which after treatment with *N,N*-dimethylamine, afforded α -*N*-ionyl-*N,N*-dimethylamine **10**. This tertiary amine was oxidized to the key *N*-amine-oxide intermediate which was rearranged to *O*-damascyl-*N,N*-dimethylhydroxylamine **11** according to a Meisenheimer rearrangement ($35\text{ }^\circ\text{C}$, 0.05 Torr). Compound **11** was then *N*-alkylated (FSO_2OMe , Et_2O , $5\text{ }^\circ\text{C}$) to intermediate **C** and, after treatment under basic conditions (NaOH , $80\text{ }^\circ\text{C}$), a Hoffman elimination took place to afford α -damascone (6 steps, overall yield = 14%) (**Scheme 7**).

The two most efficient syntheses of α -damascone from α -ionone were the Luche *et al.* synthesis, using a Wharton rearrangement, and the Xu *et al.* synthesis, using a Büchi-Vederas rearrangement.



Scheme 7. Synthesis of α -damascone from α -ionone using a Meisenheimer rearrangement.

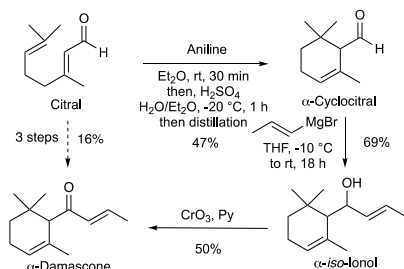
2.1.2. Via α -cyclocitral

The synthesis of α -damascone from different starting materials, precursors of α -cyclocitral, were developed as α -cyclocitral can be transformed easily to α -iso-ionol.

From citral

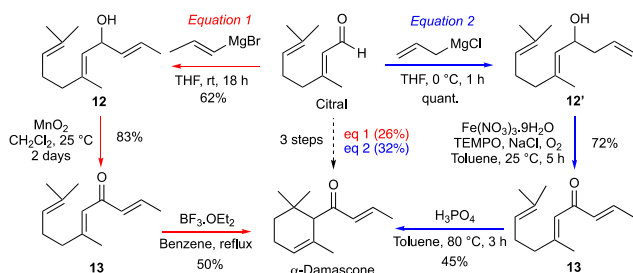
The first synthesis of α -damascone from α -cyclocitral, prepared from citral by an intramolecular cyclization,^{52,53} was reported by Demole *et al.*¹⁴ Treatment of citral with aniline led to the corresponding Schiff base which was cyclized under acidic conditions (H_2SO_4 , $\text{H}_2\text{O}/\text{Et}_2\text{O}$, $-20\text{ }^\circ\text{C}$) to produce a mixture of α - and β -cyclocitral in a ratio of 2 to 1 (70%).^{54,55} These

cyclocitral were separated by distillation yielding α -cyclocitral in 47% yield. Addition of 1-propenyllithium to α -cyclocitral led to the corresponding α -*iso*-ionol which was then oxidized by the Sarrett reagent (CrO_3 , Py) to afford the expected α -damascone (3 steps, overall yield = 16%) (**Scheme 8**).



Scheme 8. Synthesis of α -damascone from citral.

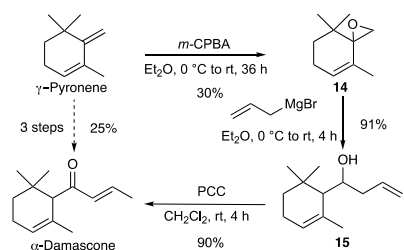
Kováts *et al.* and Ruedenauer *et al.* reported the synthesis of α -damascone from citral with a late stage cyclization.^{56,57,58} Citral was transformed to trienone **13** via the allylic alcohol **12** (propenylMgBr, THF then MnO_2 , CH_2Cl_2) which was then cyclized under acidic conditions ($\text{BF}_3 \cdot \text{OEt}_2$, refluxing benzene) to produce α -damascone with an overall yield of 26% (**Scheme 9**, eq 1). The overall yield of α -damascone was increased to 32% by replacing the vinyl Grignard reagent by the allyl Grignard reagent (**Scheme 9**, eq 2). After oxidation of the obtained homo-allylic alcohol **12'** [$\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$, TEMPO, NaCl, O_2 , toluene], the obtained linear non-conjugated enone **13** was cyclized under acidic conditions (H_3PO_4 , toluene, 80 °C) to produce α -damascone (**Scheme 9**).



Scheme 9. Synthesis of α -damascone from citral.

From γ -pyronene

Another starting material than citral was used by Delmond *et al.* to access α -damascone: the γ -pyronene, a terpenic compound easily accessible by pyrolysis of β -pinene via myrcene.⁵⁹ A chemoselective epoxidation of the *exo* cyclic double bond of γ -pyronene (*m*-CPBA, Et_2O , 0 °C) led to epoxy-pyronene **14** (30%). After treatment with allylmagnesium bromide, epoxy-pyronene **14** was converted to homo-allylic alcohol **15** via α -cyclocitral, formed *in situ* by rearrangement of the epoxide induced by the Grignard reagent acting as a Lewis acid. After a one-pot oxidation/isomerization sequence using PCC (CH_2Cl_2 , rt), α -damascone was isolated (3 steps, overall yield = 25%) (**Scheme 10**).



Scheme 10. Synthesis of α -damascone from γ -pyronene.

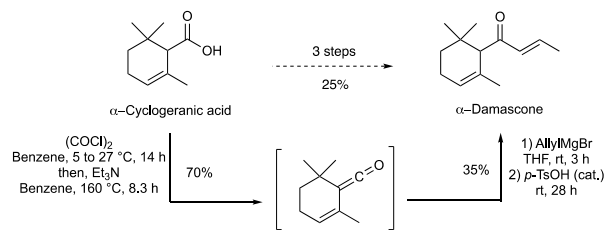
Even if citral or γ -pyronene can be transformed to α -damascone in 3 to 4 steps, the overall yields are always very modest (16% to 32%).

2.1.3. From α -cyclogeranic acid and derivatives

α -Cyclogeranic acid and derivatives were transformed to α -damascone. It is worth mentioning that α -cyclogeranic acid and derivatives can be prepared by cyclization of α -geranic acid.

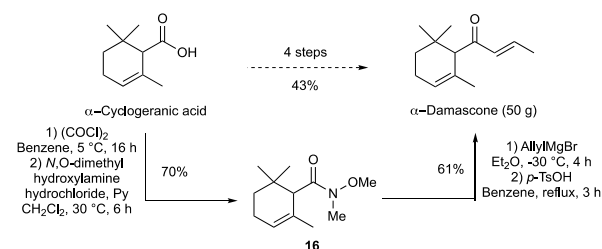
From α -cyclogeranic acid

After the generation of ketene **D** from α -cyclogeranic acid [$(\text{COCl})_2$, benzene, then Et_3N],⁶⁰ the addition of allylmagnesium bromide afforded a non-conjugated enone which was isomerized under acidic conditions (*p*-TsOH, rt, 28 h) to produce α -damascone⁶¹ (3 steps, overall yield = 25%) (**Scheme 11**).



Scheme 11. Synthesis of α -damascone from α -cyclogeranic acid via a ketene intermediate.

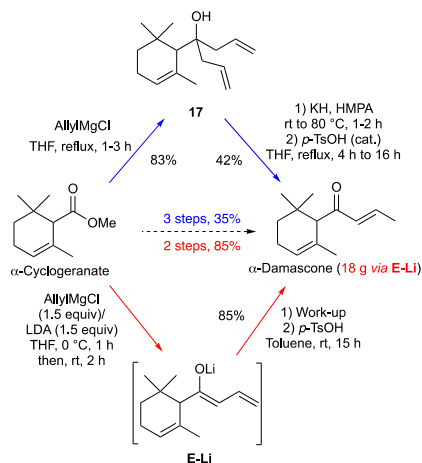
The overall yield in α -damascone was doubled by Chen *et al.* who synthesized the Weinreb amide **16** from cyclogeranic acid. After addition of allylmagnesium bromide to **16** and isomerization of the double bond, α -damascone was isolated (4 steps, overall yield = 43%).⁶² By using this sequence of reactions, the synthesis of 50 g of α -damascone was possible (**Scheme 12**).



Scheme 12. Synthesis of α -damascone from α -cyclogeranic acid via Weinreb amide **16**.

From methyl α -cyclogeranate

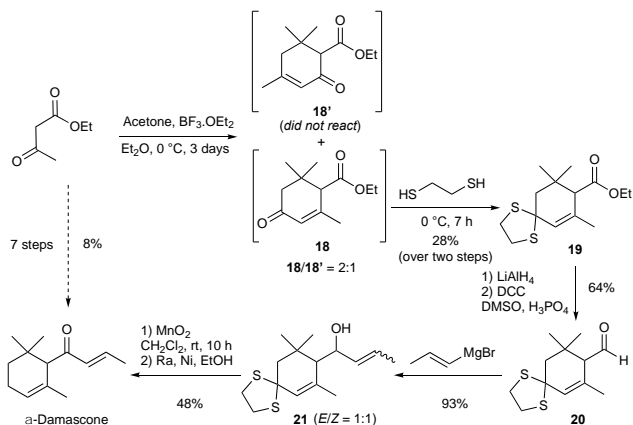
Snowden *et al.*, in collaboration with Schulte-Elte, synthesized α -damascone from methyl α -cyclogeranate.^{63–65} After a double addition of allylmagnesium bromide on methyl cyclogeranate, the obtained tertiary alcohol **17** was deprotonated (KH, HMPA, rt to 80 °C), generating a non-conjugated enone which was then transformed to α -damascone under acidic conditions (*p*-TsOH, refluxing THF) (3 steps, overall yield = 35%). The overall yield in α -damascone was improved to 85% by Fehr *et al.*⁶⁶ The main improvement consists of the treatment of methyl α -cyclogeranate with an equimolar mixture of allylmagnesium bromide and LDA. Under these conditions, the addition of allylmagnesium bromide to the enone intermediate cannot happen as enolate **E-Li** is formed. After workup and acidic treatment, α -damascone was obtained with an excellent yield (85%). Multigram of α -damascone were obtained by generating the **E-Li** intermediate (18 g) (**Scheme 13**).



Scheme 13. Synthesis of α -damascone from α -cyclogeranate.

From a functionalized α -cyclogeranate derivative

α -Damascone was also synthesized from a functionalized α -cyclogeranate derivative obtained from ethyl acetoacetate.⁶⁷ Ethyl acetoacetate was condensed with acetone ($\text{BF}_3 \cdot \text{OEt}_2$, Et_2O) to produce a mixture of two regio-isomers **18** and **18'** in a 2 to 1 ratio. The difficult separation of these two isomers was avoided by treatment of the mixture with 1,2-ethanedithiol, as only isomer **18** was reacting to produce thioketal **19** (28% over two steps). The latter was then converted to allylic alcohol **21** after a reduction/oxidation sequence and treatment with propenyl magnesium bromide. Allylic alcohol **21** was isolated in 93% yield as a mixture of (*E*)- and (*Z*)-isomers in an equimolar ratio. After separation of these two stereoisomers, by preparative thin-layer chromatography on silica, the (*E*)-isomer was isolated and, after a two-step sequence (oxidation/reduction of the thioketal), α -damascone was obtained in a very low overall yield (7 steps, overall yield = 8%) (Scheme 14).



Scheme 14. Synthesis of α -damascone from a functionalized α -cyclogeranate.

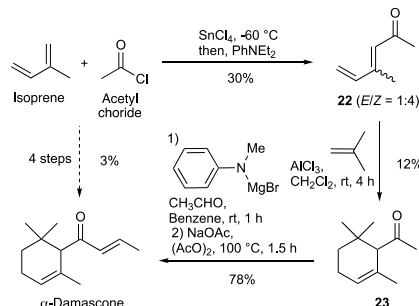
2.1.4. From cyclohexenyl methylketone

Cyclohexenyl methylketones can be prepared by a Diels-Alder reaction and then transformed to α -damascone by an aldolization/crotonization sequence.

From isoprene

Cookson *et al.* reported the synthesis of α -cyclohexenyl methylketone **23** through a Lewis acid-catalyzed inverse electron-demand Diels-Alder reaction.^{68,69} At first, the electron-poor diene, dienone **22**, was synthesized from isoprene and acetyl chloride as a mixture of (*E*)- and (*Z*)-isomers in a 1 to 4 ratio (SnCl_4 , PhNEt_2). This dienone **22** was then involved in an inverse electron-demand Diels-Alder reaction with isobutene (AlCl_3 ,

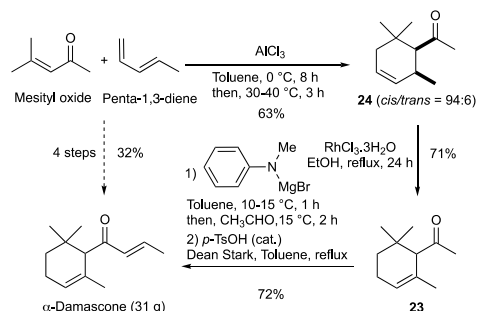
CH_2Cl_2) affording α -cyclohexenyl methylketone **23** in very low yield (12%) due to the formation of numerous side products. However, the transformation of **23** to α -damascone was efficiently achieved by using an aldolization/crotonization sequence under the Zimmerman's conditions [$\text{PhN}(\text{Me})\text{MgBr}$, CH_3CHO , benzene then NaOAc , $(\text{AcO})_2$, 100°C].⁷⁰ It is worth mentioning that the use of *N*-methyl aniline magnesium bromide is very important to obtain a good yield in the aldol product (4 steps, overall yield = 3%) (Scheme 15).



Scheme 15. Synthesis of α -damascone from α -cyclohexene methylketone by an aldolization/crotonization sequence.

From penta-1,3-diene

Yamamoto *et al.* reported an industrial process for the synthesis of α -damascone by replacing the low yielding inverse electron-demand Diels-Alder reaction by a normal electron-demand Diels-Alder reaction between penta-1,3-diene and mesityl oxide, which afforded δ -cyclohexenyl methylketone **24** (63%).⁷¹ The isomerization of the double bond in **24** ($\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$, refluxing EtOH) led to **23**, which was then converted to α -damascone through an aldolization/crotonization sequence [$\text{PhN}(\text{Me})\text{MgBr}$, CH_3CHO , benzene then NaOAc , $(\text{AcO})_2$, 100°C]. According to this sequence of reactions, the synthesis of α -damascone was realized on multigram scale (31 g) with an overall yield of 32% (4 steps). It is worth pointing out that this process was highlighted in *Org. Process Res. Dev.* as "a novel route to useful intermediates that may be cheaper than alternative processes" (Scheme 16).⁷²



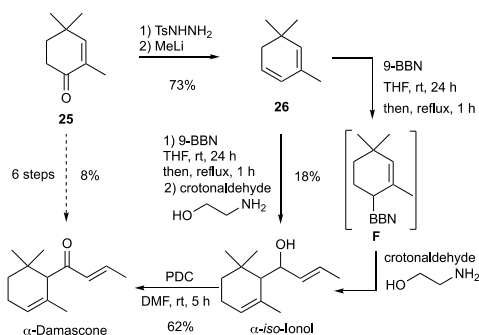
Scheme 16. Synthesis of α -damascone from α -cyclohexenyl methylketone **24**.

2.1.5. Miscellaneous

From cyclohexenyl borane

Another strategy to access α -damascone from cyclohexenyl derivatives was reported by Zaidlewicz *et al.* as these authors used a cyclohexenylborane, prepared from 2,4,4-trimethyl 2-cyclohexenone **25**, to prepare α -damascone.⁷³ Cyclohexenone **25** was transformed to allylborane **F** via diene **26**, using a Shapiro reaction (TsNHNH_2 then MeLi), followed by a regioselective hydroboration (9-BBN, THF, rt then reflux). The allylboration of crotonaldehyde using **F** led to α -iso-ionol which was then oxidized (PDC, DMF, rt) to produce α -damascone,

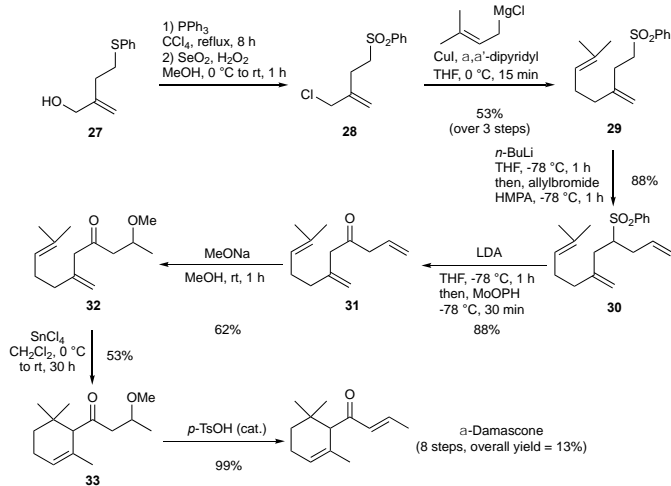
however with a low overall yield (6 steps, overall yield = 8%) (Scheme 17).



Scheme 17. Synthesis of α -damascone by allylboration of crotonaldehyde.

From a δ -hydroxy-sulfide

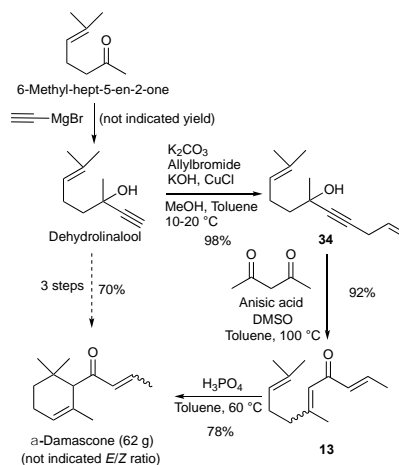
Starting from δ -hydroxy-sulfide **27**, the six-membered ring of α -damascone was built at a late stage.⁷⁴ δ -Hydroxy-sulfide **27** was converted to **32** (6 steps), precursor of the cyclized product **33**. At first, δ -hydroxy-sulfide **27** was transformed to dienic sulfone **28** in 3 steps (chlorination/oxidation/nucleophilic substitution), which was then alkylated with allylbromide (*n*-BuLi, allylbromide, HMPA, -78 °C) to produce sulfone **30**. After conversion of this sulfone to ketone **31** (LDA then MoOPH, -78 °C), an isomerization/1,4-addition of methylate (MeONa, MeOH, rt) sequence led to the methoxy ketone **32**, which was then cyclized to **33** (SnCl₄, CH₂Cl₂, 0 °C to rt). After treatment of **33** under acidic conditions (*p*-TsOH), α -damascone was isolated (8 steps, overall yield = 13%) (Scheme 18).



Scheme 18. Synthesis of α -damascone from a dienic sulfone derivative.

From methyl heptenone

A three-step synthesis of α -damascone was reported by Wei *et al.* from dehydrolinalool with an excellent overall yield (70%).⁷⁵ Dehydrolinalool was obtained from 6-methyl-hept-5-en-2-one and then converted to dienyol **34** by allylation under basic conditions (allylbromide, K₂CO₃, KOH, CuCl, MeOH, toluene). After a Meyer-Schuster rearrangement/ isomerization sequence (pentan-2,4-dione, anisic acid, DMSO/ toluene, 100 °C), trienone **13** was isolated with an excellent yield (92%). α -Damascone was obtained from **13** after treatment under acidic conditions (H₃PO₄, toluene, 60 °C). This synthesis of α -damascone is very efficient and was run on multigram scale (62 g) with an overall yield of 70% (Scheme 19).



Scheme 19. Synthesis of α -damascone from dehydrolinalool.

If the syntheses α -damascone from α -ionone and citral using a rearrangement as a key step are efficient, the most efficient synthesis is the one implying a Meyer-Schuster rearrangement.

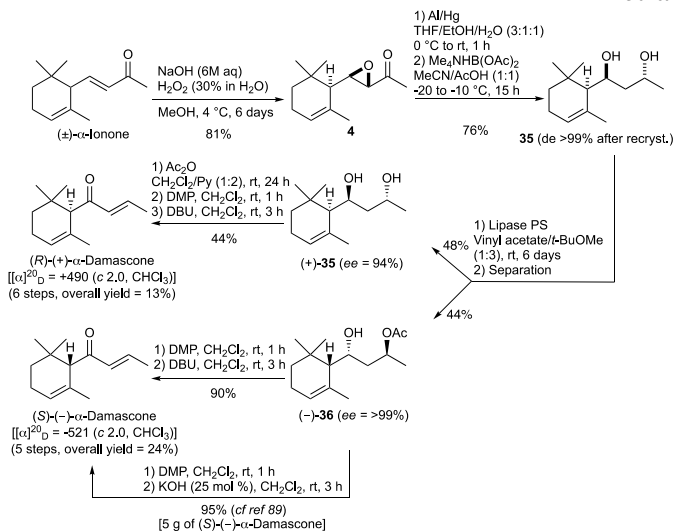
2.2. Enantioselective syntheses

Due to the importance of chirality for organoleptic compounds,⁷⁶⁻⁷⁸ the two enantiomers of α -damascone were separated by chiral chromatography⁷⁹ to evaluate their distinctive odor and olfactive power. As a continuum, the syntheses of these two enantiomers were explored from enantio-enriched starting materials such as ionones, cyclocitral and cyclohexenyl methylketones, or from racemic starting materials by realizing an enantioselective protonation of an enolate, an enantioselective reduction of a ketone, or an enzymatic resolution of a diol.^{80,81}

2.2.1. From α -ionone

From (\pm)- α -ionone by enzymatic resolution of a diol

By using an enzymatic resolution of a 1,3-diol synthesized from (\pm)- α -ionone, (*R*)-(+)- α -damascone and (*S*)-(-)- α -damascone were synthesized by Serra and Fuganti.⁸² At first, (\pm)- α -ionone was transformed to epoxide (\pm)-**4** (NaOH, H₂O₂, MeOH) and this latter was converted to the *anti*-1,3-diol **35** (ring-opening of the epoxide by generating a ketyl radical by Al/Hg, THF/EtOH/H₂O), followed by a diastereoselective reduction of the obtained 1,3-hydroxyketone [Me₄NHB(OAc)₂, MeCN/AcOH, -20 °C to -10 °C]. An enzymatic resolution of this diol (Lipase PS, vinyl acetate/*t*-BuOMe) led to 1,3-diol (+)-**35** (48%, *ee* = 94%) and to hydroxyacetate (-)-**36** (44%, *ee* > 99%). Diol (+)-**35** was transformed to (*R*)-(+)- α -damascone in 3 steps (acetylation/oxidation/elimination) with an overall yield of 13%, and to (*S*)-(-)- α -damascone in 2 steps (oxidation/ elimination) with an overall yield of 24%. The synthesis of (*S*)-(-)- α -damascone was patented by Tianyi *et al.* and it is worth mentioning that the only modification of the procedure developed by Serra *et al.* was the replacement of DBU by KOH to realize the final elimination step.⁸³ Under these conditions, (-)-**36** was transformed to (*S*)-(-)- α -damascone in 95% yield and 5 g of (*S*)-(-)- α -damascone were obtained (Scheme 20).

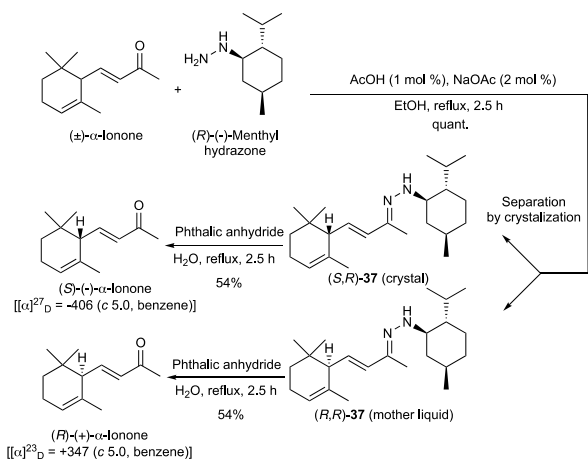


Scheme 20. Synthesis of (*R*)-(+)- and (*S*)-(-)-α-damascone by enzymatic resolution of 1,3-diol.

From (*R*)-(+)-α-ionone by chemical resolution

As (*R*)- and (*S*)-α-ionones can be obtained from (±)-α-ionone by chemical resolution, the (*R*)- and (*S*)-α-damascones were synthesized using the same synthetic scheme than the one used to synthesize (±)-α-damascone.

(±)-α-Ionone was condensed with (*R*)-menthylhydrazone (AcOH cat., NaOAc cat.) to furnish α-ionone-(*R*)-(-)-menthylhydrazone **37**.^{84–86} As in EtOH (*S*)-(-)-α-ionone-(*R*)-(-)-menthylhydrazone (*S,R*)-**37** is crystalline and (*R,R*)-**37** soluble, the two diastereomers were separated. After an acidic treatment (phthalic anhydride, H_2O reflux), (*S*)-(+)-α-ionone and (*R*)-(-)-α-ionone were respectively obtained and converted to enantio-enriched α-damascones (**Scheme 21**).

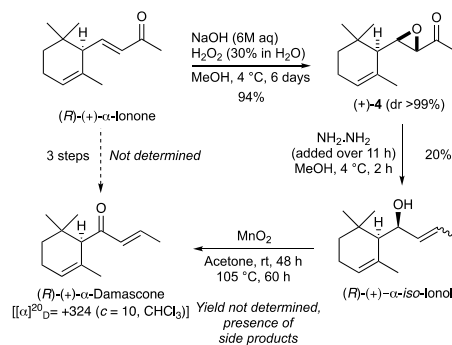


Scheme 21. Resolution of (±)-α-ionone using (*R*)-(-)-menthylhydrazone.

Wharton rearrangement

As for the racemic synthesis, a Wharton rearrangement was used by Ohloff *et al.* to transform (*R*)-(+)-α-ionone to (*R*)-(+)-α-damascone (cf *Scheme 4*) however, the use of slightly different conditions was detrimental to the overall yield of α-damascone.¹³ A highly diastereomeric epoxidation of (*R*)-(+)-α-ionone (NaOH, H_2O_2 , MeOH, 4 °C) was achieved and the Wharton rearrangement was applied to epoxy ketone (+)-**4** without any additional base (NH_2NH_2 , MeOH) affording (*R*)-(+)-α-iso-ionol in low yield (20%). After oxidation (MnO_2 , acetone, rt then 105 °C), (*R*)-(+)-α-damascone was produced. It is worth

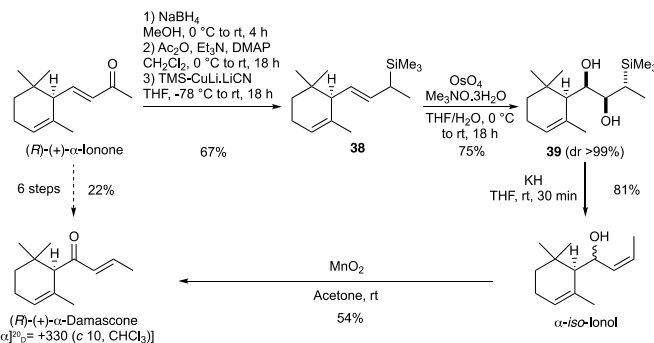
mentioning that the overall yield was not reported as (*R*)-(+)-α-damascone was contaminated by side-products (**Scheme 22**).



Scheme 22. Synthesis of (*R*)-(+)-α-damascone from (*R*)-(+)-α-ionone using a Wharton rearrangement.

Dihydroxylation/Peterson elimination sequence

Taddei *et al.* reported the synthesis of (*R*)-(+)-α-damascone from (*R*)-(+)-α-ionone by using a Peterson elimination as the key step.⁸⁷ (*R*)-(+)-α-Ionone was converted to allylsilane **38** in 3 steps (reduction/acetylation/silylation) and, after a dihydroxylation (OsO_4 , $\text{Me}_3\text{NO}\cdot 3\text{H}_2\text{O}$, THF/ H_2O , 0 °C) and treatment of the resulting silyl diol **39** with KH (THF, rt), α-iso-ionol was formed. After oxidation, (*R*)-(+)-α-damascone (MnO_2 , acetone, rt) was isolated with a low overall yield of 22% (6 steps). It is worth mentioning that the *ee* of the obtained (*R*)-(+)-α-damascone was not reported and only the [α]_D was indicated. Compared to the [α]_D reported by Oloff *et al.*, it seems that by using this sequence of reactions, (*R*)-(+)-damascone is also contaminated by side-products (**Scheme 23**).

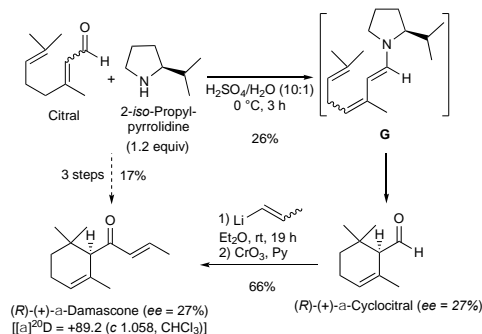


Scheme 23. Synthesis of (*R*)-(+)-α-damascone from (*R*)-(+)-α-ionone using a Peterson elimination.

2.2.2. Via optically active α-cyclocitral

From citral

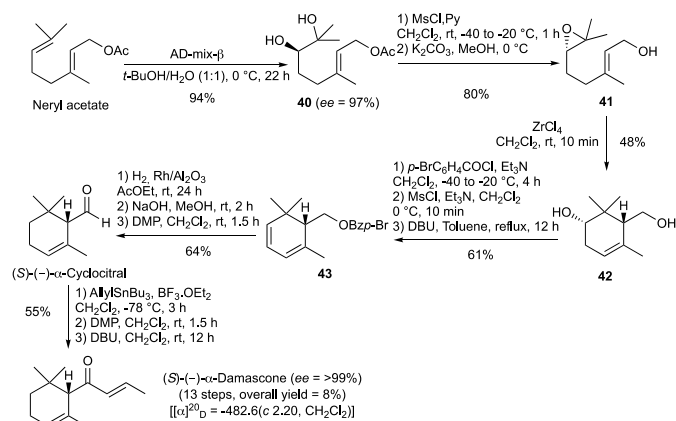
Yamada *et al.* reported a non-efficient synthesis of (*R*)-(+)-α-damascone from citral.⁸⁸ When citral was treated with the optically active 2-isopropylpyrrolidine under acidic conditions (H_2SO_4 , H_2O , 0 °C), the yield in (*R*)-(+)-α-cyclocitral was low (26%) as well as the enantiomeric excess (*ee* = 27%). However, the synthesis of enantio-enriched (*R*)-(+)-α-damascone was completed from the enantio-enriched α-cyclocitral by treatment with 1-propenyllithium (Et_2O , rt) and the resulting allylic alcohol was oxidized to (*R*)-(+)-α-damascone (CrO_3 , Py). Even if a good transfer of chirality from (*R*)-(+)-α-cyclocitral to (*R*)-(+)-α-damascone took place, the enantiomeric excess of (*R*)-(+)-α-damascone is low (*ee* = 27%) as well as the overall yield (3 steps, overall yield = 17%) (**Scheme 24**).



Scheme 24. Synthesis of *(R)*-(+)- α -damascone from citral *via* *(R)*-(+)- α -cyclocitral.

From neryl acetate

Vidari *et al.* achieved the synthesis of *(S)*-(-)- α -damascone from neryl acetate.⁸⁹ Taking advantage of their studies on the regioselective asymmetric Sharpless hydroxylation of non-conjugated dienes using AD-mix- β (*t*-BuOH/H₂O, 0 °C),⁹⁰ the optically active epoxide **41** was synthesized *via* diol **40**, and then transformed to *(S)*-(-)- α -cyclocitral in 7 steps (cyclization/protection/mesylation/elimination/hydrogenation/deprotection/oxidation). It is worth mentioning that the hydrogenation of diene, present in the 6-membered ring of **43**, is chemoselective [H_2 , (Rh/Al₂O₃), AcOEt] and a good transfer of chirality from **40** to *(S)*-(-)- α -cyclocitral was observed (*ee* = 97%). After treatment of *(S)*-(-)- α -cyclocitral with allyltributyltin (AllylSnBu₃, BF₃·OEt₂, CH₂Cl₂), the resulting homo-allylic alcohol was oxidized (DMP, CH₂Cl₂, rt) and the non-conjugated enone was isomerized to *(S)*-(-)- α -damascone (DBU, CH₂Cl₂, rt). If the *ee* is excellent (99%), the overall yield of the synthesis is low (8%). Noting that the Sharpless dihydroxylation could also produce the *(R)*-(+)- α -damascone from neryl acetate using AD-mix- α (**Scheme 25**).



Scheme 25. Synthesis of *(S)*-(-)- α -damascone from neryl acetate *via* *(S)*-(-)- α -cyclocitral.

2.2.3. From (\pm)-cyclogeranic acid by enantioselective protonation

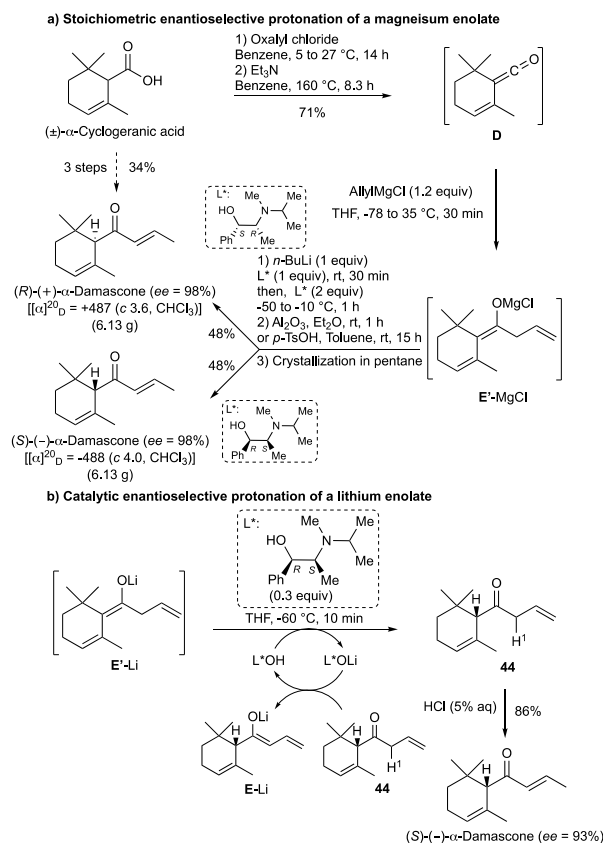
The enantio-enriched *(R)*-(+)- and *(S)*-(-)- α -damascones were efficiently obtained by the enantioselective protonation of enolates. In 1988, Fehr *et al.* reported the enantioselective protonation of enolates to access optically active ketones, esters and thio-esters,^{91–96} and this method was applied to the synthesis of optically active damascones.

Protonation of a keto-enolate

The nucleophilic attack of ketene **D**, generated from (\pm)- α -cyclogeranic acid, by allylmagnesium bromide led to a magnesium enolate intermediate **E'**-MgCl which was then

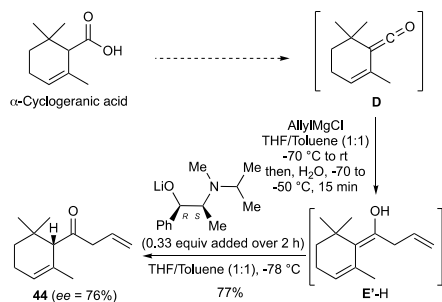
enantioselectively protonated by *N*-isopropylephedrine to produce either *(R)*-(+)- or *(S)*-(-)- α -damascone.⁹⁷ The best conditions to induce a good enantiomeric excess revealed to be the *in situ* generation of 1 equivalent of lithium *N*-isopropylephedrine alkoxide, as this alkoxide generates an equimolar enolate/alkoxide complex and, after addition of 2 equivalents of *N*-isopropylephedrine, the enantioselective protonation of a mixed lithium-magnesium aggregate took place, affording the expected enantio-enriched non-conjugated enone. After isomerization of the enone (Al₂O₃ or *p*-TsOH, toluene, rt), the expected optically active damascones were isolated. The use of (*S,R*)-*N*-isopropylephedrine led to *(R)*-(+)- α -damascone (34% yield, *ee* = 98% after recrystallization) and the use of (*R,S*)-*N*-isopropylephedrine led to *(S)*-(-)- α -damascone with an identical yield and enantiomeric excess. This enantioselective protonation of the enolate intermediate **E'**-MgCl allowed the preparation of 6 g of each enantiomer of α -damascone (**Scheme 26a**).

A catalytic enantioselective protonation is possible due to the presence of the acidic proton H1 in the non-conjugated enone **44**.⁹⁸ When the lithium enolate **E'**-Li was treated with only 0.3 equivalent of (*R,S*)-*N*-isopropylephedrine, *(S)*-(-)- α -damascone was obtained in 86% yield and 93% *ee*. By performing a control reaction, the authors demonstrated that ketone **44** did not enantioselectively protonate enolate **E'**-Li in the absence of a chiral proton source. It is worth mentioning that, in the case of the lithium enolate, it is not necessary to form an organometallic aggregate to obtain a high *ee* for α -damascone, as in the case of the magnesium enolate (**Scheme 26b**).



Scheme 26. Enantioselective protonation. Synthesis of *(R)*-(+)- and *(S)*-(-)- α -damascones from α -cyclogeranic acid.

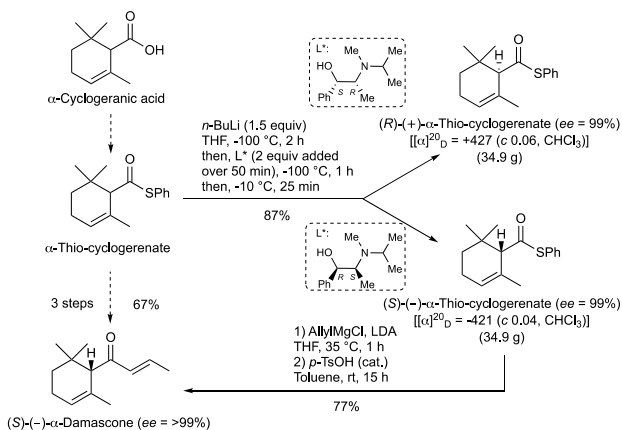
When the enol intermediate **E'**-H, obtained by addition of allylmagnesium bromide on ketene **D**, was deprotonated/reprotonated with a catalytic amount of lithium (*R,S*)-*N*-isopropylephedrine alkoxide (0.33 equiv), ketone **44** was isolated with a good *ee* of 76% and in 77% yield and then converted to α -damascone (**Scheme 27**).⁹⁹



Scheme 27. Catalytic enantioselective protonation.

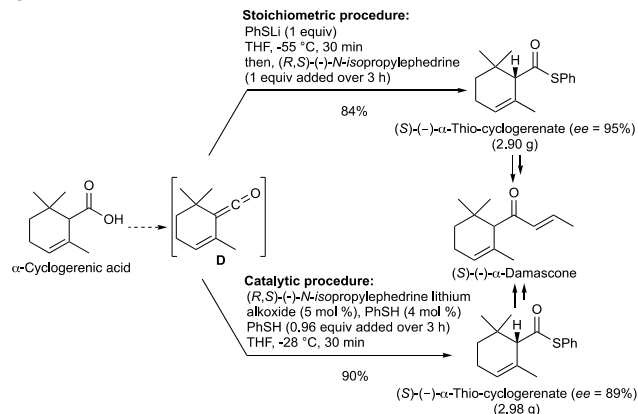
Enantioselective protonation of lithium thio-ester enolate

Fehr *et al.* compared the enantio-discrimination of the protonation of a lithium keto-enolate with a lithium thio-ester enolate using the same chiral inductor: *N*-isopropylephedrine.¹⁰⁰ The lithium thio-ester enolate was generated from (\pm)- α -thio-cyclogeranate (*n*-BuLi, THF, -100 °C), and then protonated either with (*S,R*)-(+)-*N*-isopropylephedrine, leading to (*R*)-(+)- α -thio-cyclogeranate (*ee* = 99%, yield = 87%), or by the (*R,S*)-(-)-*N*-isopropylephedrine, producing (*S*)-(-)- α -thio-cyclogeranate (*ee* = 99%, yield = 87%). By addition of allylmagnesium bromide followed by an acidic treatment, (*S*)-(-)- α -thio-cyclogeranate was transformed to (*S*)-(-)- α -damascone (*ee* = 99%, overall yield = 67%) and 27 g of this compound were prepared (**Scheme 28**).



Scheme 28. Synthesis of (*S*)-(-)- α -damascone from α -cyclogeranic acid via α -thio-cyclogeranate enolate.

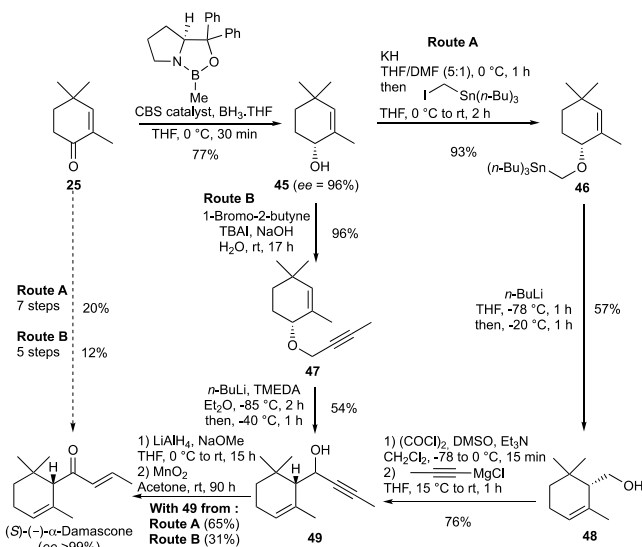
The optically active (*S*)-(-)- α -thio-cyclogeranate was generated from ketene **D**, obtained from α -cyclogeranic acid, by addition of lithium thiophenolate followed by an enantioselective protonation of the enolate, using 1 equivalent of (*R,S*)-(-)-*N*-isopropylephedrine. (*S*)-(-)- α -Thio-cyclogeranate was isolated with a high *ee* (*ee* = 95%, yield = 84%) (**Scheme 29**).¹⁰¹ A catalytic procedure was also set up, consisting of the treatment of ketene **D** with a catalytic amount of lithium (*R,S*)-(-)-*N*-isopropylephedrine alkoxide (5 mol %) in the presence of 4 mol % of thiophenol, followed by a slow addition of 0.96 equivalent of thiophenol at -28 °C. **This second procedure led to (*S*)-(-)- α -thio-cyclogeranate with an *ee* of 89%.** These transformations were achieved on gram scale (around 3 g). (*S*)-(-)- α -Thio-cyclogeranate was then converted to the corresponding enantio-enriched (*S*)-(-)- α -damascone (3 steps, overall yield = 67%) (**Scheme 29**).



Scheme 29. Synthesis of enantio-enriched (*S*)-(-)- α -thio-cyclogeranate from ketene intermediate.

2.2.4. From a cyclohexenone derivative by an enantioselective rearrangement

Mori *et al.* achieved the synthesis of (*S*)-(-)- α -damascone by using a [2,3]-Wittig rearrangement.¹⁰² To access the precursors of the Wittig rearrangement, 2,4,4-trimethylcyclohex-2-en-1-one **25** was enantioselectively reduced (BH₃.THF, CBS, *ee* = 96%) and the resulting alcohol **45** was converted either to stannyl ether **46** or to propargyl ether **47**. Both of these ethers were rearranged to propargyl alcohol **49** (*n*-BuLi with or without TMEDA, -85 °C, -78 °C) and then transformed to (*S*)-(-)- α -damascone after a reduction/oxidation sequence (LiAlH₄, NaOMe, THF then MnO₂, acetone, rt). It is worth mentioning that the access to (*S*)-(-)- α -damascone from propargylic ester **47** is more straightforward than from stannyl ether **46**. **However, the yield in (*S*)-(-)- α -damascone from **49** depends on the synthetic route used to produce this latter intermediate. The synthesis of **49** by Route B affords by-products during the Wittig rearrangement, which could not be separated from **49**, and dramatically affects the yield of (*S*)-(-)- α -damascone during the last reduction/oxidation sequence (**Scheme 30**).**

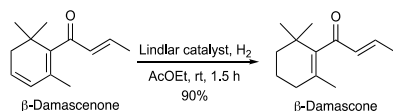


Scheme 30. Synthesis of (*S*)-(-)- α -damascone by a [2,3]-Wittig rearrangement.

Among all the reported methods to access the optically (*R*)-(+)- and (*S*)-(-)- α -damascones, the asymmetric protonation of a lithium thio-enolate synthesized from (\pm)- α -cyclogeranic acid, reported by Fehr *et al.*, seems to be the most powerful method in terms of enantioselectivity. In addition, (\pm)- α -cyclogeranic acid, is a cheap and commercially available compound and the enantioselective protonation can be performed on gram scale.

3. β -Damascone

β -Damascone was synthesized from β -ionone, β -cyclocitral and β -cyclogeranates using the strategies developed to produce α -damascone. However, some more specific strategies were developed to produce β -damascone by using, for example, an Overman rearrangement. It is worth pointing out that β -damascone can also be synthesized in good yield by selective hydrogenation of β -damascenone (Lindlar cat., H_2 , AcOEt, 90%) (Scheme 31).^{103,104}

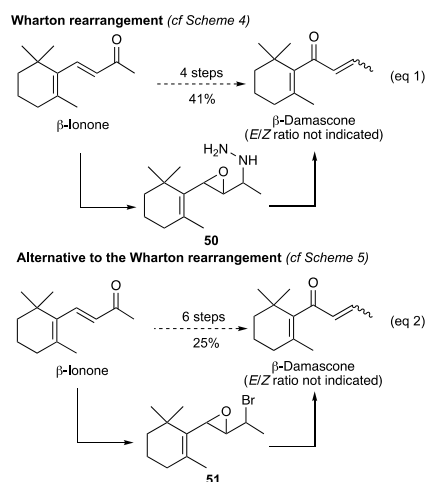


Scheme 31. Synthesis of β -damascone from β -damascenone.

3.1. From β -ionone

Wharton rearrangement

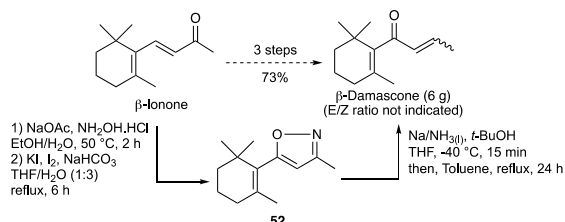
As for the formation of α -ionone to α -damascone by using a Wharton rearrangement, β -ionone was transformed to β -damascone by using also a Wharton rearrangement⁴² applied to an epoxy-hydrazone or an epoxy-bromide intermediate⁴⁴ (Scheme 32, eq 1-2).



Scheme 32. Synthesis of β -damascone from β -ionone using a Wharton rearrangement.

Büchi-Vederas rearrangement

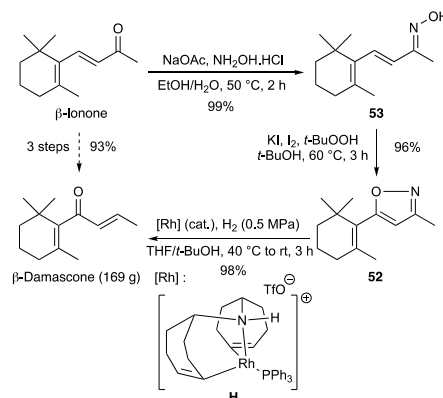
Similarly to the transformation of α -ionone to α -damascone (cf Scheme 6 and Scheme 7), β -ionone was transformed to β -damascone by using a Büchi-Vederas rearrangement.^{46,47} This rearrangement allowed the synthesis of 6 g of β -damascone (Scheme 33).¹⁰⁵



Scheme 33. Synthesis of β -damascone from β -ionone via a Büchi-Vederas rearrangement.

The most efficient synthesis of β -damascone from β -ionone is the synthesis reported in 2019 by Guanqun *et al.*, allowing the synthesis of 169 g of β -damascone.¹⁰⁶ Treatment of β -ionone-oxime **53** with a mixture of iodine and *tert*-butyl hydroperoxide led to β -isoxazole **52**, which was converted to β -damascone in a

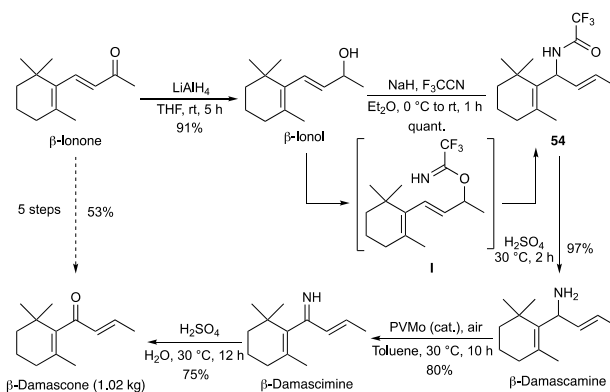
one-step process using the rhodium catalyst **H** under an atmosphere of hydrogen (Scheme 34).



Scheme 34. Synthesis of β -damascone from β -ionone oxime on multi-gram scale using a the Büchi-Vederas rearrangement.

Overman rearrangement

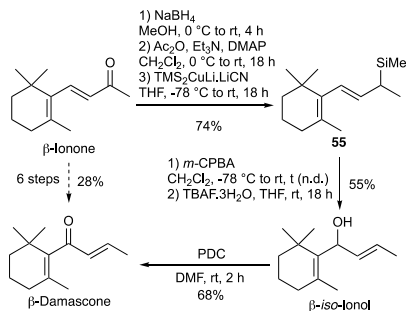
An efficient synthesis of β -damascone was realized from β -ionone by Zhixun *et al.* using an Overman rearrangement as the key step.¹⁰⁷ β -ionone was reduced to β -ionol ($LiAlH_4$, THF), and then transformed to imidate **I** (NaH , CF_3CN , Et_2O , 0 °C) which rearranged to allyl amide **54** according to an Overman rearrangement. After deprotection of the amine under acidic conditions (H_2SO_4 , 30 °C), **54** was transformed to β -damascamine and then to β -damascimine by oxidation [Keggin-type heteropolyacids 11-molybdo-vanado-phosphoric acid $H_4[PVMO_{11}O_{40}].13H_2O$ catalyst (PVMo), air]. After hydrolysis of the imine (H_2SO_4 , H_2O , 30 °C), β -damascone was isolated (5 steps, overall yield = 53%) and 1.02 kg of β -damascone was produced from β -ionone by using this rearrangement (Scheme 35).



Scheme 35. Synthesis of β -damascimine on a kg scale using an Overman rearrangement.

Epoxidation/ring-opening

Similarly to their synthesis of enantio-enriched α -damascone (cf Scheme 20), Taddei *et al.* have synthesized β -damascone from β -ionone via an epoxy-silane intermediate.⁸⁷ Starting from β -ionone, the enone was selectively reduced to the corresponding allylic alcohol. After acylation (Ac_2O , Et_3N , DMAP) and a S_N2 reaction using $TMS_2CuLi.LiCN$, the silyl derivative **55** was isolated. Epoxidation of the double bond of the allylic silane was achieved (*m*-CPBA, CH_2Cl_2), and the resulting epoxy-silane was opened by treatment with tetra-*n*-butylammonium fluoride (TBAF, THF, rt), due to the generation of an anion α to the epoxide which induces the epoxide ring-opening. The obtained β -iso-ionol was oxidized (PDC, DMF, rt) to β -damascone (6 steps, overall yield = 28%) (Scheme 36).

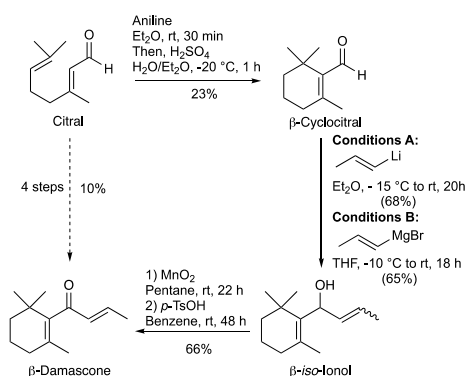


Scheme 36. Synthesis of β -damascone and β -damasconone from β -ionone via an allylsilane.

3.2. via Cyclocitral

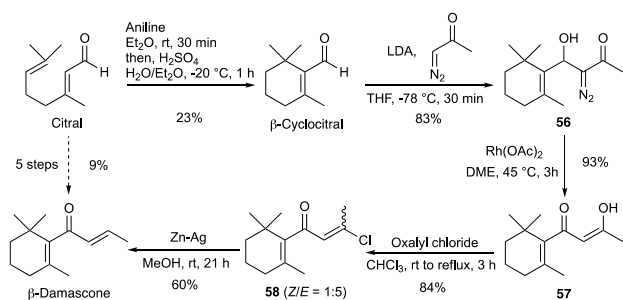
From citral

As reported previously, β -cyclocitral can be synthesized from citral by condensation with aniline followed by an acidic treatment and distillation to separate β -cyclocitral from α -cyclocitral. β -Cyclocitral was then converted to β -*iso*-ionol in similar yields by addition of either 1-propenyllithium or 1-propenylmagnesium bromide (68%-65%). After oxidation of β -*iso*-ionol (MnO_2 , pentane) followed by an acidic treatment (*p*-TsOH, benzene, rt), β -damascone was isolated with a very low overall yield (4 steps, overall yield = 10%) (**Scheme 37**).¹⁴



Scheme 37. Synthesis of β -damascone from β -cyclocitral.

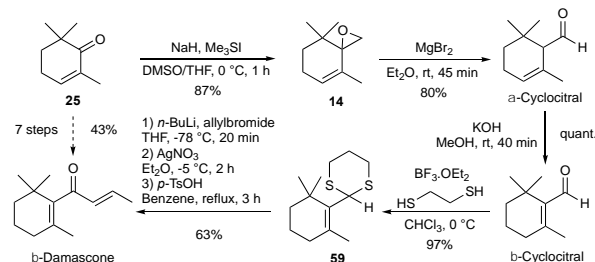
Pellicciari *et al.* used another nucleophile than **prop-1-enyllithium** or magnesium bromide to introduce the enone side chain of β -damascone, *i.e.* the lithium anion of diazoacetone.^{108,109} Addition of 1-diazo-1-lithioacetone, generated *in situ*, to β -cyclocitral afforded diazo hydroxy-ketone **56** and, the metallacarbene generated with the rhodium(II) catalyst $\text{Rh}(\text{OAc})_2$ (DME, 45 °C), led to the enolized 1,3-diketone **57**. After treatment with oxalyl chloride (CHCl_3 , rt to reflux), chloro-enone **58** was isolated as a 1:5 mixture of (*Z*)- and (*E*)-isomers. After separation by chromatography of these two stereoisomers and treatment of the (*E*)-isomer with a Zn-Ag (MeOH, rt), β -damascone was isolated with a low overall yield (5 steps, overall yield = 9%) (**Scheme 38**).



Scheme 38. Synthesis of β -damascone from β -cyclocitral via diazo hydroxy-ketone **56**.

From a cyclohexenone derivative

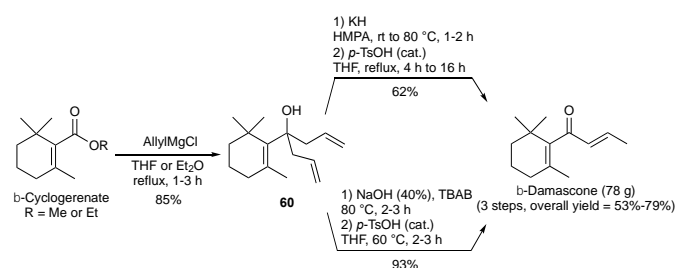
An umpolung reactivity of β -cyclocitral, due to its conversion to an thioacetal, allowed the access to β -damascone.¹¹⁰ Thioacetal **59** was synthesized from 2,6,6-trimethyl-cyclohexen-2-one **25** in 4 steps. After epoxidation of **25** (NaH , Me_3Si , DMSO/THF , 0 °C) to **14** and rearrangement to α -cyclocitral under Lewis acidic conditions (MgBr_2 , Et_2O), α -cyclocitral was quantitatively isomerized to β -cyclocitral under basic conditions (KOH , MeOH) and then converted to thioacetal **59** (1,2-ethanedithiol, $\text{BF}_3 \cdot \text{OEt}_2$). β -Cyclocitral thioacetal **59** was then converted to β -damascone by an allylation/thioacetal cleavage/isomerization sequence (7 steps, overall yield = 43%) (**Scheme 39**).



Scheme 39. Synthesis of β -damascone from 2,6,6-trimethyl-cyclohexen-2-one **25**.

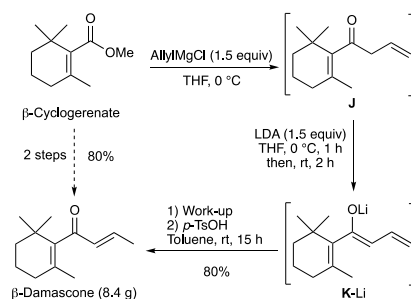
3.3. From methyl β -cyclogeranate

Similarly to α -damascone (*cf* **Scheme 13**), β -damascone was synthesized from β -cyclogeranate by Snowden *et al.* by double allylation using allylmagnesium bromide followed by a fragmentation under basic conditions (KH , HMPA) and an isomerization of the resulting non-conjugated enone which produces β -damascone (3 steps, overall yield = 53%).⁶³⁻⁶⁵ This process was improved by Ximin *et al.* by replacing KH by NaOH , and the authors were able to obtain 78 g of β -damascone (3 steps, overall yield = 79%) (**Scheme 40**).¹¹¹



Scheme 40. Synthesis of β -damascone from methyl and ethyl β -cyclogeranates.

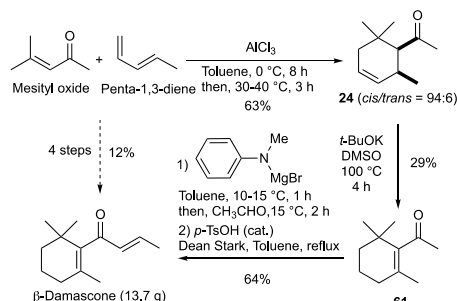
Fehr *et al.*, by using the conditions that they **had developed** for the synthesis of α -damascone from α -cyclogeranate (allylmagnesium bromide/LDA) (*cf* **Scheme 13**), were able to produce 8 g β -damascone from β -cyclogeranate in 2 steps (2 steps, overall yield = 80%) (**Scheme 41**).⁶⁶



Scheme 41. Synthesis of β -damascone from methyl β -cyclogeranate.

3.4. From cyclohexenyl methylketone

As previously reported for the synthesis of α -damascone (cf **Scheme 16**), Yamamoto *et al.* synthesized β -damascone from mesityl oxide.⁷¹ A normal Diels-Alder reaction followed by an isomerization of the obtained cyclic methylketone under basic conditions (*t*-BuOK, DMSO, 100 °C) and an aldolization/crotonization sequence, produced β -damascone. This sequence of reactions allowed the preparation of 13.7 g of β -damascone (4 steps, overall yield = 12%) (**Scheme 42**).



Scheme 42. Synthesis of β -damascone from cyclohexenyl methylketone.

The most efficient synthesis of β -damascone was achieved by Guanqun *et al.* from β -ionone by using a Büchi-Vederas rearrangement, which allowed the preparation of 169 g of β -damascone with an overall yield of 93%.

4. γ -Damascone

As γ -ionone, γ -cyclocitral and γ -cyclogeranates are accessible, γ -damascone was synthesized from these compounds by using similar strategies and conditions to the ones used to produce α - and β -damascones.

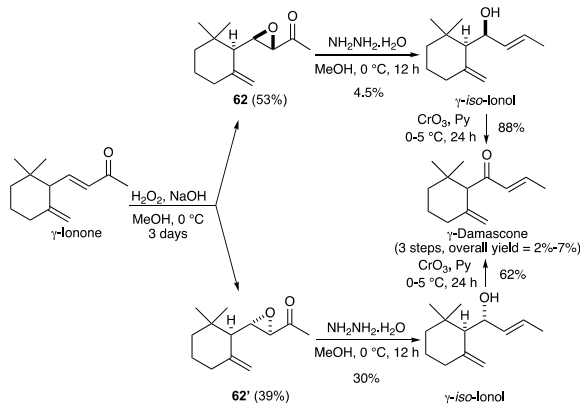
4.1. Racemic syntheses of γ -damascone

4.1.1. From γ -ionone

The two rearrangements previously reported, e.g. the Wharton and the Büchi-Vederas rearrangements, were used to synthesize γ -damascone from γ -ionone.

Wharton rearrangement

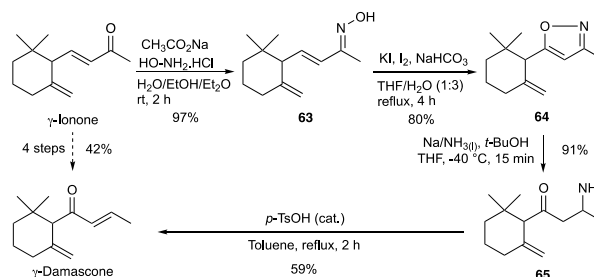
When the Wharton rearrangement was applied to γ -ionone epoxides **62** and **62'**, the yield in γ -*iso*-ionone was very low from **62** (4.5%) and very modest from **62'** (30%) (**Scheme 43**).⁴³ Thus, the overall yield of γ -damascone from γ -ionone is very low (2-7%).



Scheme 43. Synthesis of γ -damascone using the Wharton rearrangement.

Büchi-Vederas rearrangement

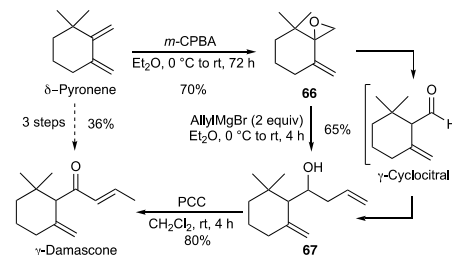
γ -Damascone was also synthesized by Schulte-Elte *et al.* from γ -ionone using a Büchi-Vederas rearrangement (4 steps, overall yield = 42%) (**Scheme 44**).^{48,49}



Scheme 44. Synthesis of γ -damascone from γ -ionone through the Büchi-Vederas rearrangement.

4.1.2. Via γ -cyclocitral

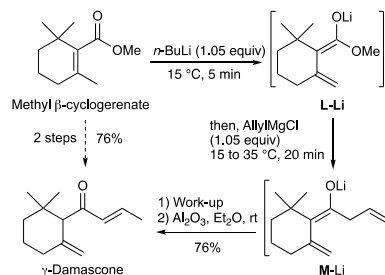
Epoxidation of δ -pyronene by epoxidation (*m*-CPBA, Et₂O, 0 °C) and rearrangement of the obtained epoxide **66** by allylmagnesium bromide, acting as a Lewis acid, led to γ -cyclocitral which reacts with a second equivalent of allylmagnesium bromide to form the non-conjugated alcohol **67**. After oxidation by PCC (CH₂Cl₂, rt), γ -damascone was isolated in 80% yield (3 steps, overall yield = 36%) (**Scheme 45**).⁵⁹



Scheme 45. Synthesis of γ -damascone from δ -pyronene.

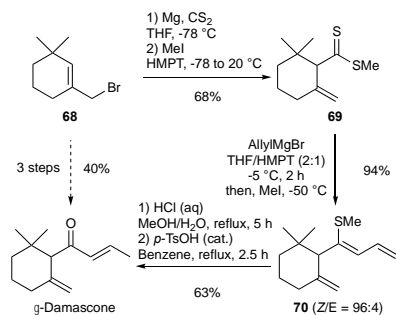
4.1.3. From cyclogeranate

In a one-pot reaction, by treatment of methyl β -cyclogeranate with *n*-BuLi followed by the addition of allylmagnesium bromide to enolate **L**-Li, the non-conjugated dienol **M**-Li was formed and, after work-up and a basic treatment (Al₂O₃, Et₂O), γ -damascone was produced with an overall yield of 76% (2 steps) (**Scheme 46**).¹¹²



Scheme 46. Synthesis of γ -damascone from methyl β -cyclogeranate.

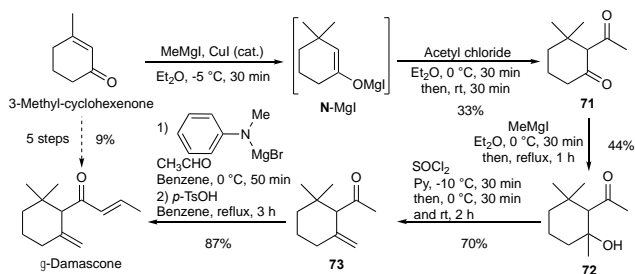
γ -Methyl di-thio-cyclogeranate **69**, prepared from allylic bromide **68**,¹¹³ was transformed to γ -damascone in three steps.^{114,115} After addition of allylmagnesium bromide (THF/HMPT then MeI), the conjugated thio-enol **70** (*Z/E* = 96:4) was obtained and transformed to γ -damascone by two consecutive acidic treatments (HCl, H₂O/MeOH then *p*-TsOH, refluxing benzene) (3 steps, overall yield = 40%) (**Scheme 47**).



Scheme 47. Synthesis of γ -damascone from γ -methyl thio-cyclogeranate **69**.

4.1.4. Via cyclohexenyl methylketone derivative

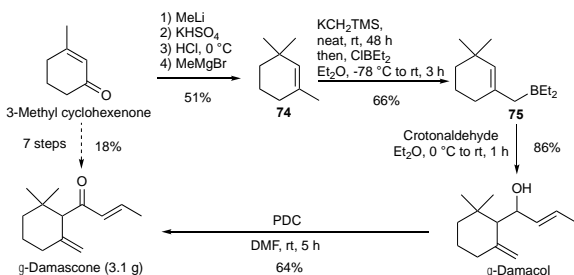
Starting from 3-methyl cyclohexen-2-one, 4 steps (1,4-addition/acetylation/1,2-addition/dehydration) were necessary to synthesize the non-conjugated enone **73**, precursor of γ -damascone.¹¹⁶ When methylketone **73** was submitted to an aldolization/crotonization sequence [PhN(Me)MgBr, CH₃CHO then *p*-TsOH], γ -damascone was isolated with a low overall yield of 9% (5 steps) (**Scheme 48**).



Scheme 48. Synthesis of γ -damascone from 3-methyl cyclohexen-2-one.

4.1.5. Miscellaneous

As for the synthesis of α -damascone (*cf* **Scheme 17**), the allylboration of crotonaldehyde with **75** led to γ -damascol, which after oxidation (PDC, DMF), furnished 3.1 g of γ -damascone (7 steps, overall yield = 18%) (**Scheme 49**).⁷³



Scheme 49. Synthesis of γ -damascone from 3-methyl 2-cyclohexenone.

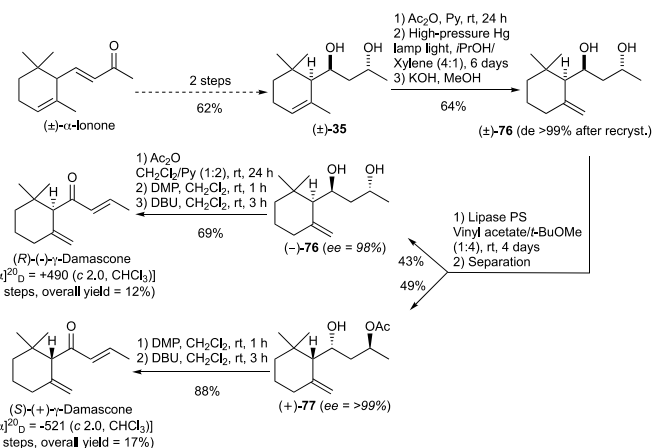
4.2. Enantioselective syntheses of γ -damascone

Similarly to the synthesis of optically active α -damascone, enantio-enriched (*R*)-(-) and (*S*)-(+)- γ -damascones were synthesized either from (\pm)- α -ionone using either an enzymatic resolution as the key step, or an enantioselective protonation of an enolate.

4.2.1. From (\pm)- α -ionone by an enzymatic resolution of a diol

The synthesis of (*R*)-(-) and (*S*)-(+)- γ -damascones was realized from (\pm)- γ -ionone.⁸² At first, (\pm)- α -ionone was converted to 1,3-diol (\pm)-**35**, as previously reported for the synthesis of enantio-enriched α -damascones (*cf* **Scheme 20**). After an

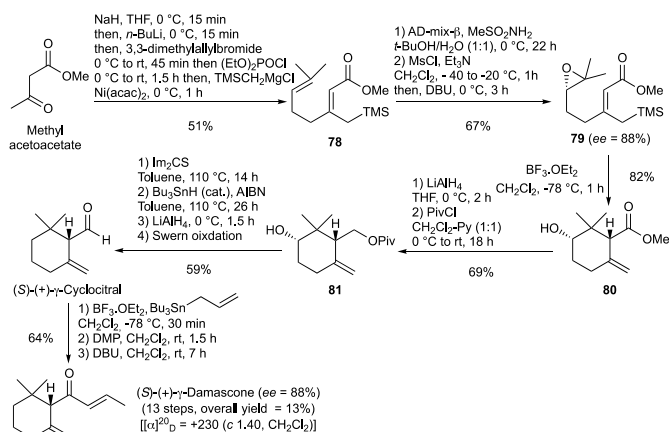
acetylation (Ac₂O, Py), a photochemical isomerization of the *endo* cyclic double bond to the *exo* cyclic double (hv, high pressure mercury lamp, *i*PrOH/xylene) and a saponification (KOH, MeOH), diol **76** was obtained. An enzymatic resolution of **76** using Lipase PS (*Pseudomonas cepacia*) followed by a separation, afforded diol (-)-**76** (43% yield, *ee* = 98%) and hydroxy-acetate (+)-**77** (49% yield, *ee* >99%). Diol (-)-**76** was converted to (*R*)-(-)- γ -damascone in three steps (regioselective acylation/oxidation/elimination) and hydroxyl-acetate (+)-**77** was converted to (*S*)-(+)- γ -damascone in 2 steps (oxidation/elimination). The two enantiomers were obtained with high *ees* (>99%) but with low overall yields (9 steps, overall yield for (*R*)-(-)- γ -damascone = 12%; 8 steps, overall yield for (*S*)-(+)- γ -damascone = 17%) (**Scheme 50**).



Scheme 50. Synthesis of (*R*)-(-) and (*S*)-(+)- γ -damascones involving an enzymatic resolution.

4.2.2. Via enantio-enriched γ -cyclocitral

Similarly to the synthesis of enantio-enriched α -damascones (*cf* **Scheme 25**), Vidari *et al.* synthesized (*S*)-(+)- γ -damascone from methyl acetoacetate *via* (*S*)-(+)- γ -cyclocitral.¹¹⁷ Methyl acetoacetate was converted to the non-conjugated diene **78** in a three-step one-pot sequence (alkylation/enol phosphorylation/cross-coupling). Diene **78** was then subjected to a Sharpless dihydroxylation (AD-mix- β , MeSO₂NH₂, *t*-BuOH/H₂O) and the 1,2-diol was transformed to epoxide **79** (mesylation/S_Ni). After cyclization of **79** to **80** (BF₃·OEt₂, CH₂Cl₂), 6 steps were necessary to transform **80** to (*S*)-(+)- γ -cyclocitral (reduction/protection/thio-esterification/Barton deoxygenation/deprotection/oxidation). (*S*)-(+)- γ -Cyclocitral was then involved in an alkylation/oxidation/isomerization sequence to produce γ -damascone (*ee* = 88%, 13 steps, overall yield = 7%) (**Scheme 51**).

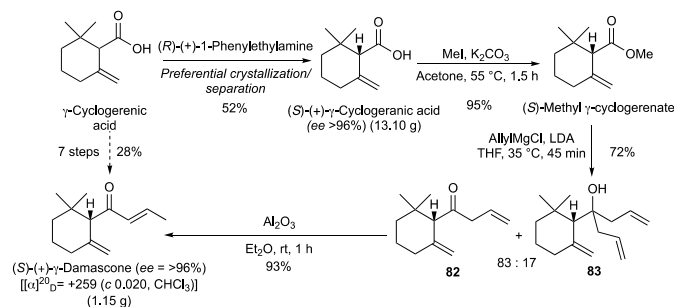


Scheme 51. Synthesis of (*S*)-(+)- γ -damascone from methyl acetoacetate *via* (*S*)-(+)- γ -cyclocitral.

4.2.3. From γ -cyclogeranic acid and derivatives

By chemical resolution of γ -cyclogeranic acid

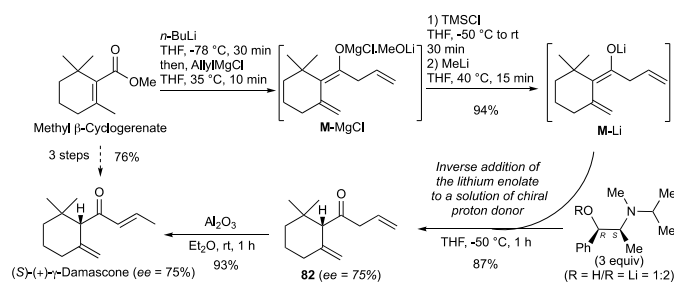
Fehr *et al.* have explored the synthesis of optically active γ -damascone from (\pm)- γ -cyclogeranic acid after separation of the two enantiomers by preferential crystallization with (*R*)-phenylethylamine.¹¹⁸ (*S*)-(+)- γ -Cyclogeranic acid was recovered in 52% yield with a high *ee* (>96%) and, after esterification (K_2CO_3 , MeI), (*S*)-(+)-methyl- γ -cyclogeranate was converted to (*S*)-(+)- γ -damascone in a two-step sequence (allylation/isomerization) with an *ee* of 96% (4 steps, overall yield = 28%). Around 1 g of (*S*)-(+)- γ -damascone was obtained (**Scheme 52**).



Scheme 52. Synthesis of (*S*)-(+)- γ -damascone by resolution of (\pm)- γ -cyclogeranic acid using (*R*)-(+)-1-phenylethylamine.

By enantioselective protonation of enolates

Enantioselective protonation of an enolate was also used to access (*S*)-(+)- γ -damascone from methyl β -cyclogeranate.¹¹⁸ The non-conjugated magnesium enolate **M**-MgCl was generated from methyl β -cyclogeranate (*n*-BuLi, allylMgCl) and then transformed to lithium enolate **M**-Li in 2 steps (TMSCl then MeLi). An inverse addition of lithium enolate **M**-Li to a 1:2 mixture of (*R,S*)-(-)-*N*-isopropylphedrine/(*R,S*)-(-)-*N*-isopropylphedrine lithium alkoxide, led to the non-conjugated enone **82** with an *ee* of 75% (87% yield). After isomerization of the double bond (Al_2O_3 , Et_2O), (*S*)-(+)- γ -damascone was isolated (3 steps, overall yield = 76%) (**Scheme 53**).

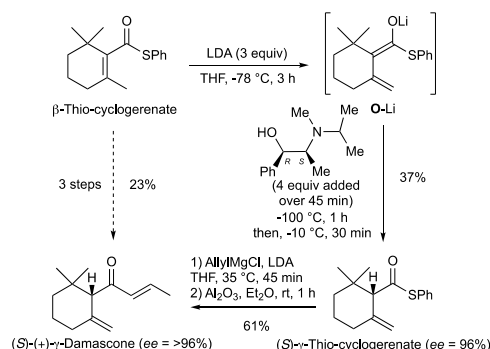


Scheme 53. Synthesis of (*S*)-(+)- γ -damascone from methyl β -cyclogeranate by enantioselective protonation of an enolate.

Based on an enantioselective protonation of lithium thio-enolate **O**-Li, the synthesis of (*S*)-(+)- γ -damascone was realized from β -thio-cyclogeranate prepared from methyl β -cyclogeranate.¹¹⁸ By treating β -thio-cyclogeranate with LDA, the lithium thio-enolate intermediate **O**-Li was generated and, after addition of 4 equivalents of (*R,S*)-*N*-isopropylphedrine, an enantioselective protonation occurred to produce the expected (*S*)- γ -thio-cyclogeranate with a good enantiomeric excess (*ee* = >96%) however with a low yield (37%). After addition of allylmagnesium bromide in the presence of LDA, the obtained homo-allylic ketone was isomerized to (*S*)-(+)- γ -damascone (Al_2O_3 , Et_2O , rt) (*ee* = >96%, 3 steps, overall yield = 23%) (**Scheme 54**).

The most efficient synthesis of (\pm)- γ -damascone was realized by Fehr *et al.* starting from (\pm)-methyl β -cyclogeranate and by

adding allylmagnesium bromide to a lithium ester (*cf* **Scheme 46**). This method was also the best method to synthesize 1 g (*S*)-(+)- γ -damascone with an *ee* of 96% starting from (\pm)- γ -cyclogeranic acid (*cf* **Scheme 52**).¹¹⁸



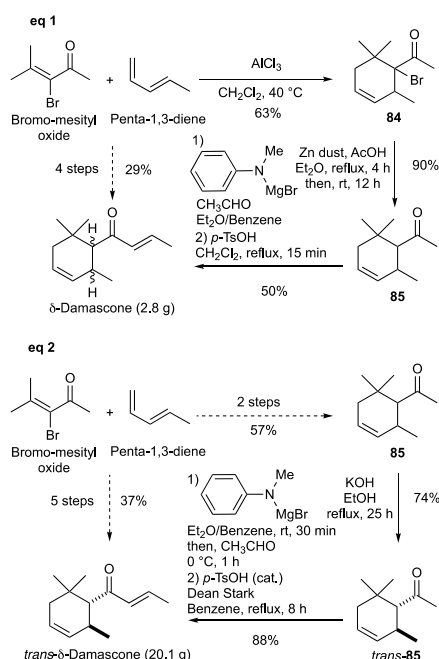
Scheme 54. Synthesis of (*S*)-(+)- γ -damascone from β -thio-cyclogeranate.

5. δ -Damascone

Two main strategies were reported to synthesize δ -damascone: one starting from a cyclohexenyl methylketone and the other one from Meldrum's acid.

5.1. From δ -cyclohexenyl methylketone

To synthesize δ -cyclohexenyl methylketone **85**, a normal Diels-Alder reaction between bromo-mesityl oxide and penta-1,3-diene ($AlCl_3$, CH_2Cl_2 , 40 °C) was achieved by Cookson *et al.* followed by a dehalogenation (Zn dust, AcOH, Et_2O) (2 steps, overall yield = 57%).^{119,120} After an aldolization/crotonization sequence [$PhN(Me)MgBr$, CH_3CHO then *p*-TsOH], δ -cyclohexenyl methylketone **85** was converted to a mixture of *cis*- and *trans*- δ -damascones in 2.8 g quantity (4 steps, overall yield = 29%) (**Scheme 55**, eq 1).



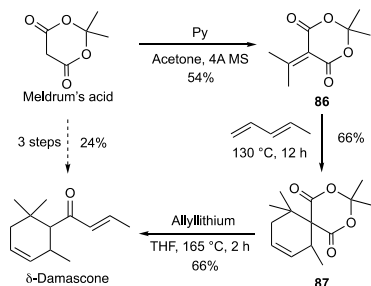
Scheme 55. Synthesis of δ -damascone and *trans*- δ -damascone from bromo-mesityl oxide using a Diels-Alder reaction.

Mookherjee *et al.* improved the yield of the conversion of cyclohexenyl methylketone **85** to δ -damascone from 50% to 88% by realizing the crotonization step over 8 h, instead of 15 min, in refluxing benzene as an azeotrope to remove the formed water instead of refluxing CH_2Cl_2 .¹²¹ In addition, they submitted

δ -cyclohexenyl methylketone **85** to a diastereo-convergent epimerization under basic conditions (KOH, EtOH) to obtain only the *trans*- δ -cyclohexenyl methylketone **85**. The authors were able to obtain 20.1 g of *trans*- δ -damascone (5 steps, overall yield = 37%) (Scheme 55, eq 2).

5.2. From Meldrum's acid

A cheap commercially available starting material, Meldrum's acid (synthesized from malonic acid in 50% yield),¹²² was considered by Dauben *et al.* to access δ -damascone.¹²³ Meldrum's acid was condensed with acetone (Knoevenagel condensation) to produce dienophile **86** and this latter was then engaged in a Diels-Alder reaction with penta-1,3-diene to afford the spirocyclic derivative **87**. After treatment with allyllithium, the keto-acid intermediate was decarboxylated by heating at 165 °C to produce δ -damascone (3 steps, overall yield = 24%) (Scheme 56).

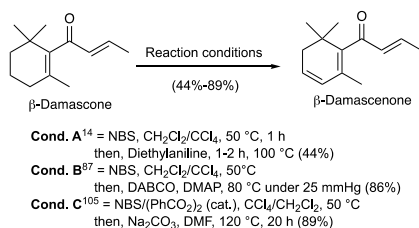


Scheme 56. Synthesis of δ -damascone from Meldrum's acid.

The best synthesis of δ -damascone was reported by Mookherjee *et al.* from mesityl oxide and penta-1,3-diene to form δ -cyclohexenyl methylketone by a Diels-Alder reaction and then 3 steps were necessary to obtain the *trans*- δ -damascone (epimerization/aldolization/crotonization sequence, overall yield = 37%) (cf Scheme 55).^{119,120,121}

6. Damascones

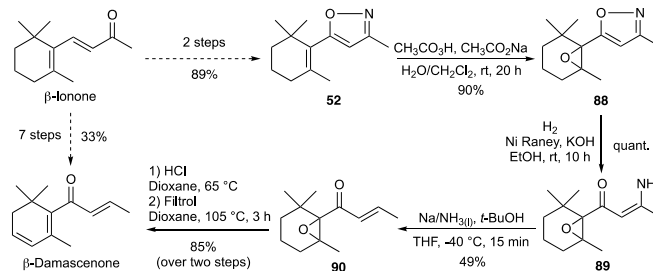
Different syntheses of β -damasconone were reported. As there is only one synthesis of α -damasconone and one synthesis of γ -damasconone, their synthesis will be concomitantly described. It is worth mentioning that β -damasconone can be transformed to β -damasconone in two steps *e.g.* by an allylic bromination followed by an elimination. Depending on the conditions, the overall yield varies from 44% to 88% (Scheme 57).^{14,87,105}



Scheme 57. Synthesis of β -damasconone from β -damascone.

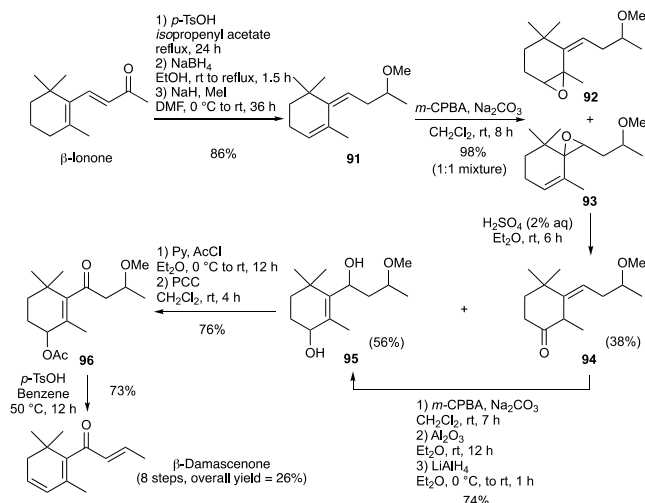
6.1. From β -ionone (β -damasconone)

β -Damasconone was synthesized from β -ionone *via* isoxazole **52** prepared in two steps from β -ionone.⁴⁸ Isoxazole **52** was treated with peracetic acid ($\text{CH}_3\text{CO}_3\text{H}$, $\text{CH}_3\text{CO}_2\text{Na}$, $\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$) to produce epoxy-isoxazole **88**, which after hydrogenolysis under hydrogen pressure (H_2 , Raney Ni, KOH), was transformed to epoxy enamino-ketone **89**. After a Birch reduction ($\text{Na}/\text{NH}_3(l)$, *t*-BuOH), the resulting epoxy dihydro β -damasconone **90**, was treated under acidic conditions (HCl then fittrol, dioxane, 105 °C), to produce β -damasconone (7 steps, overall yield = 33%) (Scheme 58).



Scheme 58. Synthesis of β -damasconone from β -ionone *via* an epoxy-isoxazole.

Another strategy was developed by Campagnole *et al.* to synthesize β -damasconone from β -ionone *via* a methoxy-ionol derivative **91** synthesized in 3 steps (deconjugation/reduction/methylation).¹²⁴ After epoxidation of **91** (*m*-CPBA, Na_2CO_3 , CH_2Cl_2), treatment of the obtained epoxides **92** and **93** under acidic conditions (H_2SO_4) led to **94** and **95**. Fortunately, **94** could be transformed to **95** (3 steps) and, after a selective acylation of the allylic alcohol and oxidation (AcCl, Py then PCC, CH_2Cl_2), **96** was produced and converted to β -damasconone under acidic conditions (*p*-TsOH, benzene, 50 °C) (8 steps, overall yield = 26%) (Scheme 59).

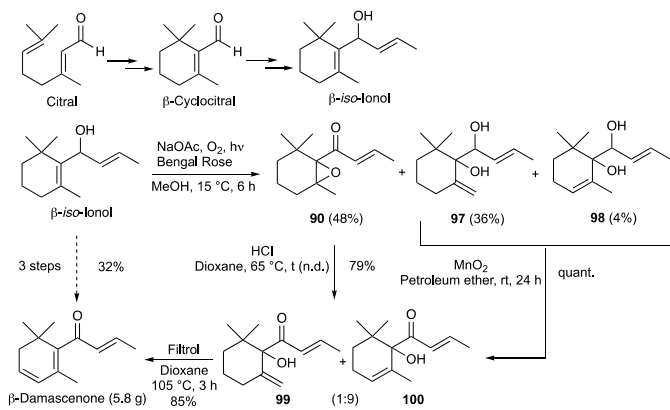


Scheme 59. Synthesis of β -damasconone from β -ionone *via* a methoxy-ionol derivative **91**.

6.2. *via* Cyclocitral and functionalized cyclocitral

6.2.1. From citral (β -damasconone)

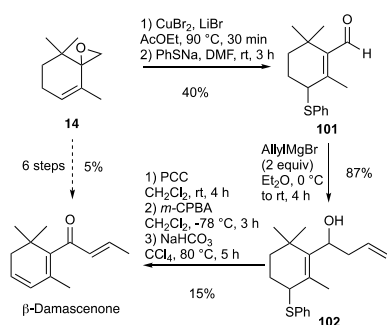
β -Cyclocitral was transformed to β -damasconone *via* β -isoiionol.¹²⁵ β -*iso*-ionol was photo-oxidized (NaOAc , O_2 , Bengal rose, hv) to produce the key epoxy-ketone **90** and the unsaturated 1,2-diols **97** and **98** (**90/97/98** = 55:40:5). After separation of keto-epoxide **90** from **97** and **98**, the epoxide was opened under acidic conditions (HCl, dioxane, 65 °C) affording a 1:9 mixture of hydroxy-ketones **99** and **100**, which were not separated but transformed to β -damasconone after treatment with fittrol (acidic clay, dioxane, 105 °C). It is worth mentioning that the unsaturated 1,2-diols **97** and **98**, obtained during the photo-oxidation, were also transformed to β -damasconone (oxidation with MnO_2 and acidic treatment with fittrol, 85% yield). β -Damasconone was obtained on multi-gram scale (5.8 g) in 3 steps from β -*iso*-ionol with an overall yield of 32% (Scheme 60). The synthesis of β -damasconone from β -cyclocitral was patented in 1976 and 1980.^{56,57}



Scheme 60. Synthesis of β -damascenone by photo-oxidation of β -iso-ionol.

6.2.2. From pyronene (β -damascenone)

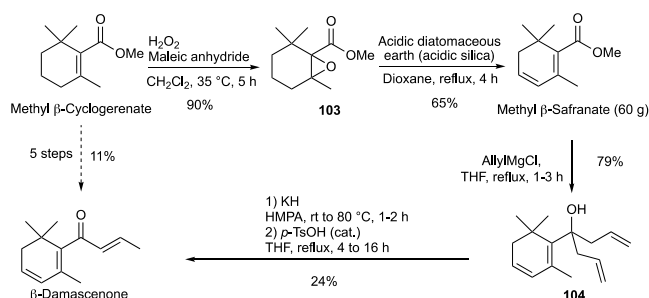
β -Damascenone was synthesized from γ -epoxy-pyronene **14** via cyclocitral derivative **101**, however with a poor overall yield (6 steps, overall yield = 5%) (**Scheme 61**).⁵⁹



Scheme 61. Synthesis of β -damascenone from γ -epoxy-pyronene **14**.

6.2.3. From cyclogeranate/safranate (α -, β - and γ -damascenones)

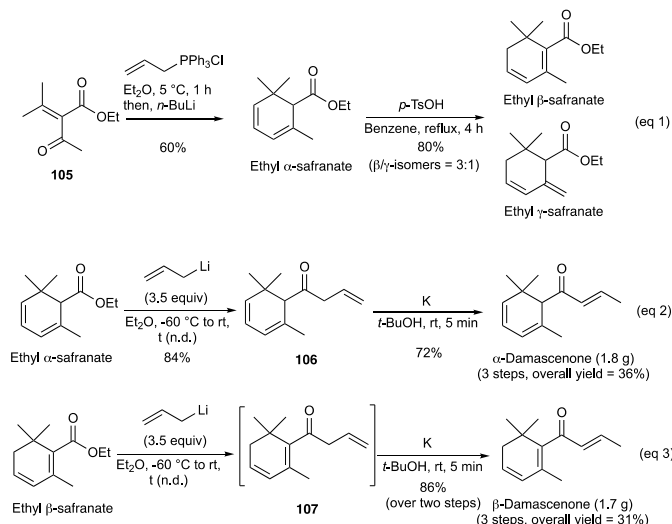
Methyl β -cyclogeranate was transformed to β -damascenone in 5 steps via methyl β -safranate.^{63–65} After epoxidation of methyl β -cyclogeranate (H_2O_2 , maleic anhydride, CH_2Cl_2) and treatment of the resulting epoxide **103** with acidic silica (refluxing dioxane). Methyl β -safranate was obtained and transformed to β -damascenone by a double addition of allylmagnesium bromide to the ester, followed by a fragmentation (KH, HMPA) and an isomerization (*p*-TsOH, THF, reflux) (5 steps, overall yield = 11%) (**Scheme 62**).



Scheme 62. Synthesis of β -damascenone from methyl β -cyclogeranate via methyl β -safranate.

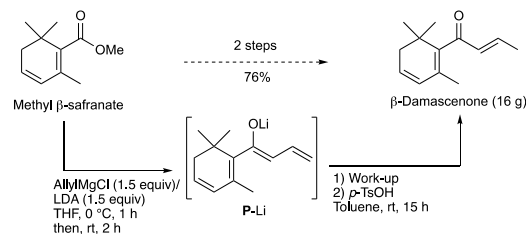
Ethyl β -safranate can be synthesized from keto-ester **105** via ethyl α -safranate by using a Wittig reaction followed by an acidic treatment (*p*-TsOH, refluxing benzene) (**Scheme 63**, eq 1).^{103,104} It is worth mentioning that a mixture of ethyl β - and γ -safranates were isolated and converted to α - and β -damascenones

respectively (**Scheme 63**, eq 2 and 3).^{103,104} At first, ethyl α - and β -safranates were respectively transformed to the corresponding damascenone derivatives **106** and **107** by addition of allyllithium and, after treatment under basic conditions (K, *t*-BuOH), 1.8 g and 1.7 g of α - and β -damascenones were respectively obtained (overall yield from **105** = 36% and 31%, respectively). It is worth mentioning that the use of allyllithium at -60 °C is sufficient to prevent the second addition of allyllithium to **106** and **107**.



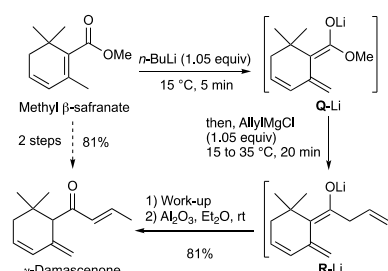
Scheme 63. Synthesis of α - and β -damascenones from keto-ester **102** via ethyl α - and β -safranates.

Fehr *et al.* applied their cooperative process between LDA and allylmagnesium bromide (*cf* **Scheme 13**) to synthesize β -damascenone on a multi-gram scale from methyl β -safranate (76% overall yield) (**Scheme 64**).⁶⁶



Scheme 64. Synthesis of β -damascenone from methyl β -cyclogeranate.

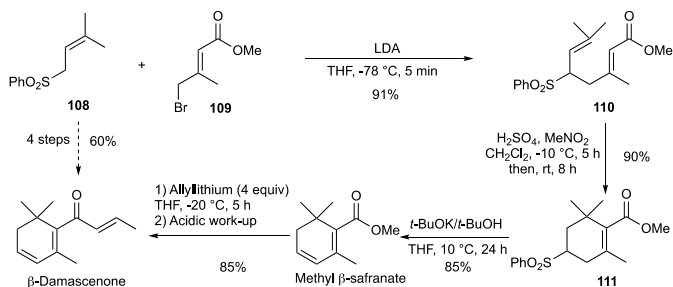
According to the Fehr *et al.* procedure (*cf* **Scheme 46**), when methyl β -safranate was treated with 1 equivalent of *n*-BuLi followed by the addition of allylmagnesium bromide, lithium enolate **R-Li** was formed and, after an acidic work-up and an isomerization (Al_2O_3 , Et_2O), γ -damascenone was isolated (2 steps, overall yield = 81%) (**Scheme 65**).¹¹²



Scheme 65. Synthesis of γ -damascenone from methyl β -cyclogeranate.

A linear starting material, the allylic sulfone **108**, was transformed to β -methyl safranate in 3 steps (alkylation with

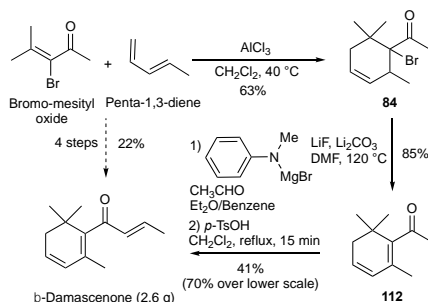
109/cyclization/elimination).¹²⁶ After addition of allyllithium (4 equiv, at -20 °C, THF) to methyl β -safranate and isomerization of the non-conjugated double-bond of the obtained enone, β -damascenone was synthesized (4 steps, overall yield = 60%) (**Scheme 66**).



Scheme 66. Synthesis of β -damascenone from allylic sulfone derivative *via* methyl β -safranate.

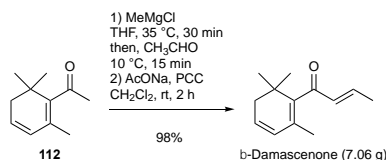
6.2.4. *Via cyclohexadienyl methylketone (β -damascenone)*

A normal Diels-Alder reaction between bromo-mesityl oxide and penta-1,3-diene was realized by Cookson *et al.* leading to bromo-cyclohexenyl methylketone **84** (as reported for δ -damascenone, *cf* **Scheme 55**). After dehalogenation (LiF, Li₂CO₃, DMF, 120 °C), the resulting dienyl methylketone **112** was submitted to an aldolization/crotonization sequence producing β -damascenone with an overall yield of 22% (4 steps) (**Scheme 67**).^{119,120}



Scheme 67. Synthesis of β -damascenone *via* bromo-cyclohexadienyl methylketone **112**.

An improvement of the aldolization/crotonization sequence was realized by Mookherjee *et al.* by using methylmagnesium bromide to generate the enolate which reacted with acetaldehyde and after an oxidation/crotonization sequence induced by PCC (PCC, NaOAc, CH₂Cl₂) β -damascenone was isolated (7 g were obtained by using this method) (**Scheme 68**).¹²⁷



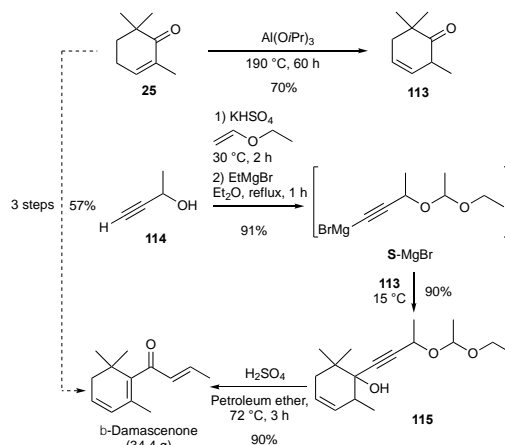
Scheme 68. Synthesis of β -damascenone *via* β -cyclohexadiene methylketone.

6.3. Miscellaneous

6.3.1. *From 2,6,6-trimethyl-cyclohexen-2-one (β -damascenone)*

2,6,6-Trimethyl-cyclohexen-2-one **25** was used to efficiently produce β -damascenone using a Meyer-Shuster rearrangement.^{128,129} 2,6,6-Trimethyl-cyclohexen-2-one **25** was deconjugated to enone **113** [(AlO*i*Pr)₄, 190 °C] and then treated with propargylic magnesium bromide **S-MgBr** (prepared in 2 steps from the corresponding propargylic alcohol **114**). The

resulting tertiary propargylic alcohol **115** was rearranged to β -damascenone under acidic conditions (H₂SO₄, petroleum ether), according to the Meyer-Shuster rearrangement, with an excellent yield of 90%. By using this rearrangement, 34 g of β -damascenone were prepared (3 steps, overall yield = 57%) (**Scheme 69**).

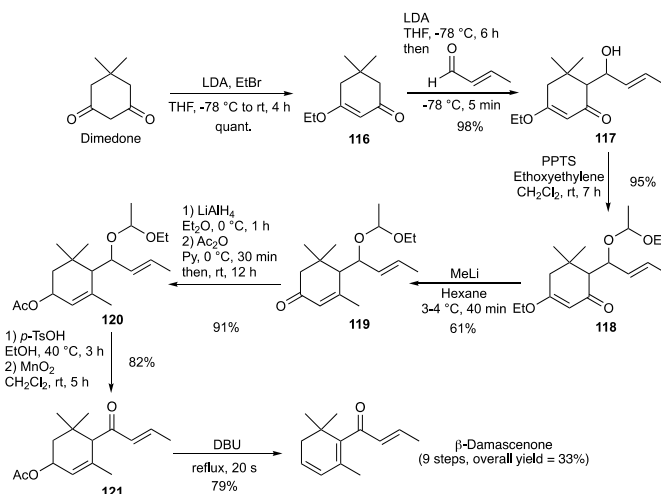


Scheme 69. Synthesis of β -damascenone from 2,6,6-trimethyl-cyclohexen-2-one.

6.3.2. *From dimedone (β -damascenone)*

Torri *et al.* reported the synthesis of β -damascenone from dimedone using an aldolization as the key step.^{130,131} After the mono protection of dimedone (LDA, EtBr), **116** was involved in an aldol condensation with crotonaldehyde (LDA) and the resulting aldol product **117** was protected to produce **118** (PPTS, ethoxyethylene) which was then converted to enone **119** (MeLi, hexane, 3–4 °C). After a 4-step sequence (reduction/acetylation/deprotection/oxidation), enone **121** was isolated and treated with DBU (reflux, 20 s) to produce β -damascenone (9 steps, overall yield = 33%) (**Scheme 70**).

Even though the syntheses of α -, β - and γ -damascenones from safranate are efficient (2 steps, overall yields = 61% to 81%, **Scheme 62** to **66**), the synthesis of β -damascenone from 2,6,6-trimethyl-cyclohexen-2-one, involving a Meyer-Shuster rearrangement, is also efficient and can produce 34 g of β -damascenone (3 steps, overall yield = 57%) (*cf* **Scheme 69**).^{128,129} It is worth mentioning that to the best of our knowledge, no enantio-enriched synthesis of α - and γ -damascenones were reported.



Scheme 70. Synthesis of β -damascenone from dimedone.

7. Conclusion

Due to the highly powerful organoleptic properties of damascenes and damascenones and their importance for fragrance companies, many syntheses of the isomers and enantiomers of damascenes, as well as the different isomers of damascenones, were developed since their discovery. Starting from academic syntheses, the syntheses were improved for industry to access efficient and low-cost synthetic routes which can be performed on gram and even kilogram scale.

Acknowledgments

IFF is acknowledged for financial support

References

- Ohloff, G.; Demole, E. *J. Chrom.* **1987**, *406*, 181–183.
- Frater, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* **1998**, *54*, 7633–7703.
- Kraft, P.; Bajgrowicz, J. A.; Denis, C.; Frater, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 2980–3010.
- Williams, A. *Perfum. Flavor.* **2002**, *27*, 18–31.
- Fortineau, A.-D. *J. Chem. Educ.* **2004**, *81*, 45–50.
- Natural Raw Materials in the Flavor and Fragrance Industry. In *Common Fragrance and Flavor Materials*; Wiley-VCH Verlag GmbH & Co. KGaA, 2006; pp 177–238.
- Mannschreck, A.; von Angerer, E. *J. Chem. Educ.* **2011**, *88*, 1501–1506.
- Schaefer, B. Flavours and Fragrances. In *Natural Products in the Chemical Industry*; Springer Berlin Heidelberg: Berlin, Heidelberg, 2014; pp 45–168.
- Dunkel, A.; Steinhaus, M.; Kotthoff, M.; Nowak, B.; Krautwurst, D.; Schieberle, P.; Hofmann, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 7124–7143.
- Schmitt, F. L. U.S. Patent 4225444A, 1980.
- Schulte-Elite, K. H.; Kastner, D. U.S. Patent 4411829A, 1983.
- Kovats, E. *J. Chrom.* **1987**, *406*, 185–222.
- Ohloff, G.; Uhde, G. *Helv. Chim. Acta* **1970**, *53*, 531–541.
- Demole, E.; Enggist, P.; Säuberli, U.; Stoll, M.; Sz. Kováts, E. *Helv. Chim. Acta* **1970**, *53*, 541–551.
- Kraft, P. Designing Damascene-and Ionone-like Odorants. In *Advances in Flavours and Fragrances*; Swift, K. A. D., Ed.; Royal Society of Chemistry: Cambridge, 2002; pp 138–146.
- Ohloff, G.; Rautenstrauch, V.; Schulte-Elite, K. H. *Helv. Chim. Acta* **1973**, *56*, 1503–1513.
- Isoe, S.; Katsumura, S.; Sakan, T. *Helv. Chim. Acta* **1973**, *56*, 1514–1516.
- Foote, C. S.; Brenner, M. *Tetrahedron Lett.* **1968**, 6041–6044.
- Meinwald, J.; Erickson, K.; Hartshorn, M.; Meinwald, Y. C.; Elsner, T. *Tetrahedron Lett.* **1968**, 2959–2962.
- Moussaron-Can, M.; Dalle, J.-P.; Mani, J.-C. *Tetrahedron Lett.* **1968**, 6037–6040.
- Hyeon, B. *Tetrahedron Lett.* **1969**, 279–281.
- Russell, S. W.; Weedon, B. C. L. *Chem. Commun.* **1969**, 85–86.
- Isoe, S.; Katsumura, S.; Hyeon, S. B.; Sakau, T. *Tetrahedron Lett.* **1971**, 1089–1092.
- Fleischmann, P.; Lutz-Röder, A.; Winterhalter, P.; Watanabe, N. Carotenoid Cleavage Enzymes in Animals and Plants. In *Carotenoid-Derived Aroma Compounds*; Winterhalter, P., Rouseff, R. L., Eds.; American Chemical Society: Washington, DC, 2001; Vol. 802, pp 76–88.
- Suzuki, M.; Matsumoto, S.; Fleischmann, H.-P.; Shimada, H.; Yamano, Y.; Ito, M.; Watanabe, N. Identification of β -Damascenone Progenitors and Their Biogenesis in Rose Flowers (*Rosa Damascena* Mill.). In *Carotenoid-Derived Aroma Compounds*; Winterhalter, P., Rouseff, R. L., Eds.; American Chemical Society: Washington, DC, 2001; Vol. 802, pp 89–101.
- Waché, Y.; Bossier-De Ratuld, A.; Belin, J.-M. Production of Aroma Compounds by Enzymatic Cooxidation of Carotenoids. In *Carotenoid-Derived Aroma Compounds*; Winterhalter, P., Rouseff, R. L., Eds.; American Chemical Society: Washington, DC, 2001; Vol. 802, pp 102–113.
- Bezman, Y.; Bilkis, I.; Winterhalter, P.; Fleischmann, P.; Rouseff, R. L.; Baldermann, S.; Naim, M. *J. Agric. Food Chem.* **2005**, *53*, 9199–9206.
- Álvarez, R.; Vaz, B.; Gronemeyer, H.; de Lera, Á. R. *Chem. Rev.* **2014**, *114*, 1–125.
- Edens, M.; Boerner, D.; Chase, C. R.; Nass, D.; Schiavelli, M. D. *J. Org. Chem.* **1977**, *42*, 3403–3408.
- Demole, E.; Berthet, D. *Helv. Chim. Acta* **1971**, *54*, 681–682.
- Winter, M.; Enggist, P. *Helv. Chim. Acta* **1971**, *54*, 1891–1898.
- Kaneko, H.; Harada, M. *Agr. Biol. Chem.* **1972**, *36*, 168–171.
- Renold, W.; Näf-Müller, R.; Keller, U.; Willhalm, B.; Ohloff, G. *Helv. Chim. Acta* **1974**, *57*, 1301–1308.
- Tokitomo, Y.; Kobayashi, A.; Yamanishi, T.; Muraki, S. *Proc. Jpn. Acad., Ser. B* **1980**, *56*, 452–456.
- Roberts, D. D.; Acree, T. E. Developments in the Isolation and Characterization of β -Damascenone Precursors from Apples. In *Fruit Flavors*; Rouseff, R. L., Leahy, M. M., Eds.; American Chemical Society, 1995; Vol. 596, pp 190–199.
- Skouroumounis, G. K.; Sefton, M. A. The Formation of β -Damascenone in Wine. In *Carotenoid-Derived Aroma Compounds*; Winterhalter, P., Rouseff, R. L., Eds.; American Chemical Society: Washington, DC, 2001; Vol. 802, pp 241–254.
- Winterhalter, P.; Rouseff, R. Carotenoid-Derived Aroma Compounds: An Introduction. In *Carotenoid-Derived Aroma Compounds*; Winterhalter, P., Rouseff, R. L., Eds.; American Chemical Society: Washington, DC, 2001; Vol. 802, pp 1–17.
- Crupi, P.; Coletta, A.; Antonacci, D. *J. Agric. Food Chem.* **2010**, *58*, 9647–9656.
- Sefton, M. A.; Skouroumounis, G. K.; Elsey, G. M.; Taylor, D. K. *J. Agric. Food Chem.* **2011**, *59*, 9717–9746.
- Uselmann, V.; Schieberle, P. *J. Agric. Food Chem.* **2015**, *63*, 1948–1956.
- Serra, S. *Molecules* **2015**, *20*, 12817–12840.
- Dupuy, C.; Luche, J. L. *Tetrahedron* **1989**, *45*, 3437–3444.
- Schulte-Elite, K. H.; Rautenstrauch, V.; Ohloff, G. *Helv. Chim. Acta* **1971**, *54*, 1805–1812.
- Sarandeses, L. A.; Luche, J. L. *J. Org. Chem.* **1992**, *57*, 2757–2760.
- Kaufmann, S.; Tokes, L.; Murphy, J. W.; Crabbe, P. *J. Org. Chem.* **1969**, *34*, 1618–1621.
- Büchi, G.; Vederas, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 9128–9132.
- Hu, J.; Guo, A.; Xu, Y.; Pan, C.; Wei, X.; Wang, L.; Xiao, G. *Polish Journal of Chemical Technology* **2019**, *21*, 50–51.
- Schulte-Elite, K. H.; Müller, B. L.; Ohloff, G. *Helv. Chim. Acta* **1973**, *56*, 310–320.
- Schulte-Elite, K.-H. Patent 3,968,161, 1976.
- Bamberger, Eug.; Landau, A. *Ber. dtsh. Chem. Ges.* **1919**, *52*, 1093–1110.
- Rautenstrauch, V. *Helv. Chim. Acta* **1973**, *56*, 2492–2508.
- Colombi, L.; Bosshard, A.; Schinz, H.; Seidel, C. F. Cyclocitral, *Helv. Chim. Acta* **1951**, *34*, 265–273.
- Henbest, H. B.; Shaw, L. B.; Woods, G. *J. Chem. Soc.* **1954**, 1154–1159.
- Zhanyi, H.; Feng, H.; Zhenggang, Q.; Jihong, P.; Changzheng, Z. Patent CN106496004A, 2017.
- Watanabe, W. Patent JP4304811B2, 2009.
- Kovats, E.; Demole, E.; Ohloff, G.; Stoll, M. U.S. Patent 3931326A, 1976.
- Kovats, E.; Demole, E.; Ohloff, G.; Stoll, M.; Stoll, S. U.S. Patent 4226892, 1980.
- Ruedenauer, S.; Fenlon, T.; Hindalekar, S.; Pansare, N.; Abhijeet Amiyakumar, R.; Swaminathan, V. Patent WO2017029313A1, 2017.
- Boulin, B.; Taran, M.; Arreguy- San Miguel, B.; Delmond, B. *Synthetic Commun.* **2007**, *37*, 2579–2591.
- Wuest, J. D.; Madonik, A. M.; Gordon, D. C. *J. Org. Chem.* **1977**, *42*, 2111–2113.
- Näf, F.; Decorzant, R. *Tetrahedron* **1986**, *42*, 3245–3250.
- Chen, E.; Jin, T. Patent CN102336636A, 2012.
- Snowden, Roger L.; Muller, B. L.; Shulte-Elite, K. H. *Tetrahedron Lett.* **1982**, *23*, 335–338.
- Snowden, R. L.; Linder, S. M.; Muller, B. L.; Schulte-Elite, K. H. *Helv. Chim. Acta* **1987**, *70*, 1858–1878.
- Snowden, R. L.; Linder, S. M. *Helv. Chim. Acta* **1988**, *71*, 1587–1597.
- Fehr, C.; Galindo, J. *Helv. Chim. Acta* **1986**, *69*, 228–235.

67. Liu, H. J.; Hung, H. X.; Mhehe, G. L. *Tetrahedron Lett.* **1976**, *17*, 4129–4132.
68. Cookson, R. C.; Tuddenham, R. M. *J. Chem. Soc., Chem. Commun.* **1973**, 742–742.
69. Cookson, R. C.; Tuddenham, R. M. *J. Chem. Soc., Perkin Trans. 1* **1978**, 678–680.
70. Nielsen, A. T.; Gibbons, C.; Zimmerman, C. A. *J. Am. Chem. Soc.* **1951**, *73*, 4696–4701.
71. Watanabe, S.; Ujihara, H.; Yamamoto, T.; Hagiwara, T. U.S. Patent 6822121B2, 2004.
72. Turner, K. *Org. Process Res. Dev.* **2005**, *9*, 235–243.
73. Zaidlewicz, M. *Tetrahedron Lett.* **1986**, *27*, 5135–5138.
74. Mandai, T.; Mizobuchi, K.; Kawada, M.; Otera, J. *J. Org. Chem.* **1984**, *49*, 3403–3406.
75. Wei, L.; Xiaomeng, L.; Yuqin, J.; Weiwei, Z.; Baoqi, R.; Longfei, M.; Zhu, L.; Qianqian, H.; Wentao, Z.; Guiqing, X. Patent CN103058841A, 2015.
76. Pickenhagen, W. Enantioselectivity in Odor Perception. In *Flavor Chemistry*; Teranishi, R., Buttery, R. G., Shahidi, F., Eds.; American Chemical Society: Washington, DC, 1989; Vol. 388, pp 151–157.
77. Wetzel, C. H.; Oles, M.; Wellerdieck, C.; Kuczowski, M.; Gisselmann, G.; Hatt, H. *J. Neurosci.* **1999**, *19*, 7426–7433.
78. de March, C. A.; Ryu, S.; Sicard, G.; Moon, C.; Golebiowski, J. *Flavour Fragr. J.* **2015**, *30*, 342–361.
79. König, W. A.; Evers, P.; Krebber, R.; Schulz, S.; Fehr, C.; Ohloff, G. *Tetrahedron* **1989**, *45*, 7003–7006.
80. Pickenhagen, W. Synthetic Approaches to Chiral Flavor Components. In *Aroma Active Compounds in Foods*; Takeoka, G. R., Güntert, M., Engel, K.-H., Eds.; American Chemical Society: Washington, DC, 2001; Vol. 794, pp 151–166.
81. Brenna, E.; Fuganti, C.; Serra, S. *Tetrahedron: Asymmetry* **2003**, *14*, 1–42.
82. Serra, S.; Fuganti, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1573–1580.
83. Tianyi, W.; Minfu, W.; Jinlong, D.; Jilong, X.; Yang, W. Patent CN104630289A, 2015.
84. Woodward, R. B.; Kohman, T. P.; Harris, G. C. *J. Am. Chem. Soc.* **1941**, *63*, 120–124.
85. Sobotka, H.; Bloch, E.; Cahnmann, H.; Feldbau, E.; Rosen, E. *J. Amer. Chem. Soc.* **1943**, *65*, 2061–2062.
86. Naves, Y.-R. *Helv. Chim. Acta* **1947**, *30*, 769–774.
87. Azzari, E.; Faggi, C.; Gelsomini, N.; Taddei, M. *J. Org. Chem.* **1990**, *55*, 1106–1108.
88. Yamada, S.-I.; Shibasaki, M.; Terashima, S. *Tetrahedron Lett.* **1973**, *14*, 381–384.
89. Bovolenta, M.; Castronovo, F.; Vadalà, A.; Zanoni, G.; Vidari, G. *J. Org. Chem.* **2004**, *69*, 8959–8962.
90. Vidari, G.; Dapiaggi, A.; Znnoni, G.; Garhschelli, L. *Tetrahedron Lett.* **1993**, *34*, 6485–6488.
91. Fehr, C. *Chimia* **1991**, *45*, 253–261.
92. Fehr, C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2567–2587.
93. Girard, C.; Kagan, H. B. *Angew. Chem. Int. Ed.* **1998**, *37*, 2922–2959.
94. Chapuis, C.; Jacoby, D. *Applied Catalysis A: General* **2001**, *221*, 93–117.
95. Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748.
96. Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653–3691.
97. Fehr, C.; Galindo, J. *J. Am. Chem. Soc.* **1988**, *110*, 6909–6911.
98. Fehr, C.; Galindo, J. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1888–1889.
99. Fehr, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 7119–7121.
100. Fehr, C.; Stempf, I.; Galindo, J. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1042–1044.
101. Fehr, C.; Stempf, I.; Galindo, J. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1044–1046.
102. Mori, K.; Amaike, M.; Itou, M. *Tetrahedron* **1993**, *49*, 1871–1878.
103. Büchi, G.; Wüest, H. *Helv. Chim. Acta* **1971**, *54*, 1767–1776.
104. Büchi, G. H.; Wüest, H. U.S. Patent 4028278A, 1977.
105. Cheng, Y.-Y.; Ren, T.-L.; Xu, B.-H.; Tao, H.-S.; Zhang, S.-J. *Flavour Fragr. J.* **2016**, *31*, 420–428.
106. Guanqun, Z. Patent CN110002979, 2019.
107. Zhixun, W. Patent CN105859532A, 2016.
108. Pellicciari, R.; Sisani, E.; Fringuelli, R. *Tetrahedron Lett.* **1980**, *21*, 4039–4042.
109. Pellicciari, R.; Fringuelli, R.; Sisani, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2566–2569.
110. Unnikrishnan, P. A. *OPPI* **1993**, *25*, 687–689.
111. Ximin, H.; Xing, L.; Yawen, Y.; Qiong, L. Patent CN101698636A, 2013.
112. Fehr, C.; Galindo, J. *J. Org. Chem.* **1988**, *53*, 1828–1830.
113. Gosselin, P. *Synthesis* **1987**, 267–270.
114. Gosselin, P. *Tetrahedron Lett.* **1986**, *27*, 5495–5496.
115. Gosselin, P. *Tetrahedron* **1988**, *44*, 1979–1990.
116. Näf, F.; Decorzant, R. *Helv. Chim. Acta* **1974**, *57*, 1317–1327.
117. Beszant, S.; Giannini, E.; Zanoni, G.; Vidari, G. *Tetrahedron: Asymmetry* **2002**, *12*, 1245–1255.
118. Fehr, C.; Galindo, J. *Helv. Chim. Acta* **1995**, *78*, 539–552.
119. Ayyar, K. S.; Cookson, R. C.; Kagi, D. A. *J. Chem. Soc., Chem. Commun.* **1973**, 161–161.
120. Ayyar, K. S.; Cookson, R. C.; Kagi, D. A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1727–1736.
121. Mookherjee, B. D.; Trenkle, R. W.; Wilson, R. A.; Schmitt, F. L.; Vock, M. H.; Granda, E. J.; Vinals, J.; Kiwala, J.; Schreiber, W. L. U.S. Patent 4334098A, 1982.
122. Davidson, D.; Berhardt, S. A. *J. Amer. Chem. Soc.* **1948**, *70*, 3426–3428.
123. Dauben, W. G.; Kozikowski, A. P.; Zimmerman, W. T. *Tetrahedron Lett.* **1975**, *16*, 515–517.
124. Campagnole, M.; Delmond, B. *Synthetic Commun.* **2007**, *37*, 1077–1090.
125. Schulte-Elte, K. H.; Müller, B. L.; Ohloff, G. *Helv. Chim. Acta* **1971**, *54*, 1899–1910.
126. Torii, S.; Uneyama, K.; Ichimura, H. *J. Org. Chem.* **1979**, *44*, 2292–2294.
127. Mookherjee, B. D.; Wilson, R. A.; Schmitt, F. L.; Vinals, J.; Kiwala, J. US4157351A, 1979.
128. Fankhauser, P. U.S. Patent 4324729, 1982.
129. Fankhauser, P. U.S. Patent 4453013, 1984.
130. Torii, S.; Inokuchi, T.; Ogawa, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1233–1234.
131. Torii, S.; Inokuchi, T.; Ogawa, H. *J. Org. Chem.* **1979**, *44*, 3412–3414.



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