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Synthetic approaches to the damascone and damascenone isomers

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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.

Contents

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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 *Firminich* 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 carotenoids 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-*nor*isoprenoids: a class of volatile carotenoid metabolites [8,24–28].

Considering the biosynthetic pathway, allowing the formation of β-ionone from β-carotene, the first step is an enzymatic oxidative

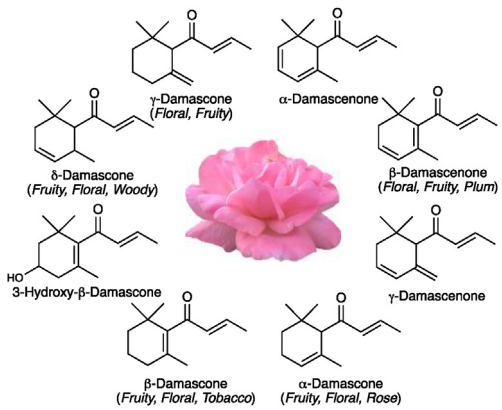
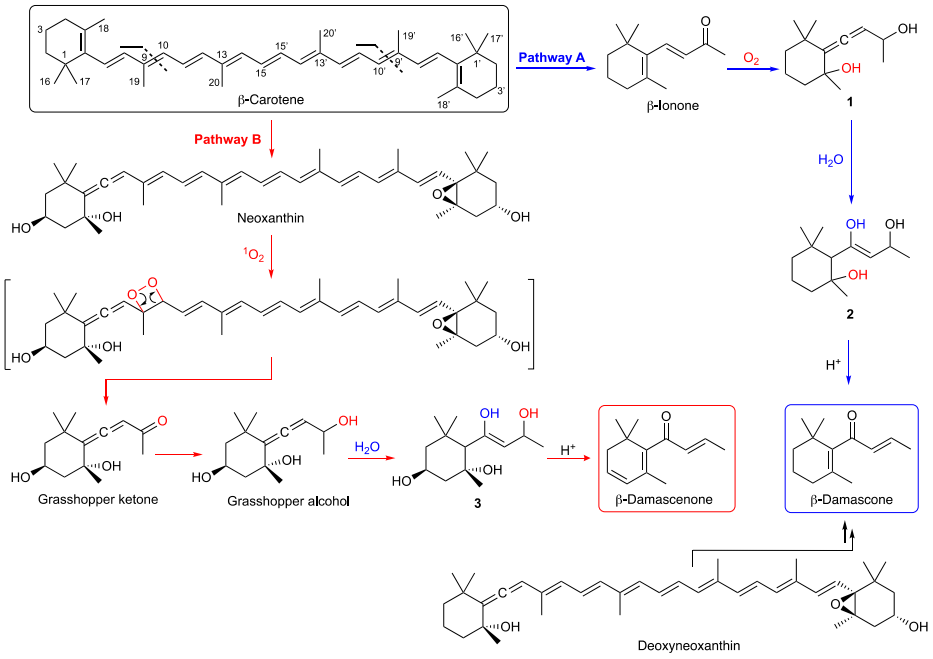


Fig. 1. Damask rose: Structure of damascones and damascenones and their fragrances.



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

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).

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).

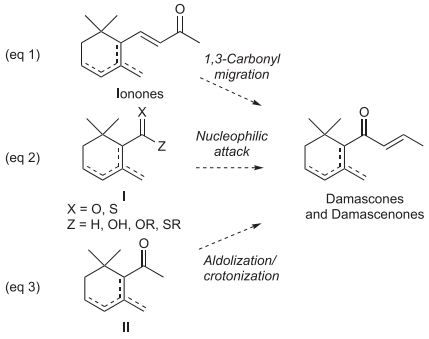
In this review, the synthesis of damascones and damascenones will be classified according to the starting cyclic substrates (ionone, cyclocitral, cyclogeranate and cyclohexenyl methylketones) and subdivided according to the starting materials used to produce the cyclic substrate. The multigram scale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

2. α-Damascone

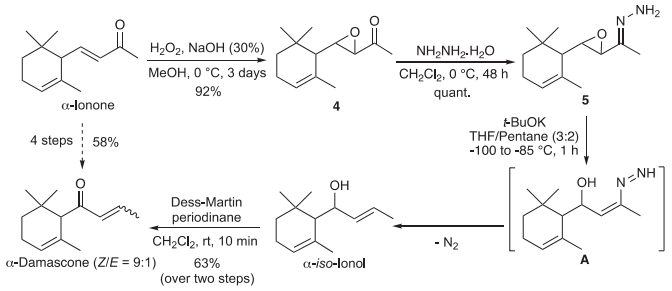
The first syntheses of α-damascone were realized in a racemic form and efforts have been made to access selectively the two enantiomers.

2.1. Racemic syntheses

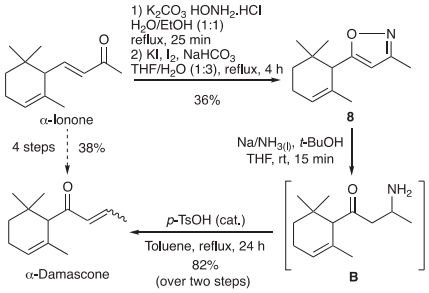
Syntheses of α-damascone from cheap starting materials were realized. One of the most evident starting material to access α-damascone is α-ionone. As α-damascone possesses the α-ionone carbon skeleton, only a 1,3-carbonyl transposition is necessary to obtain α-damascone.



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



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



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

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-Vederas rearrangement and a Meisenheimer rearrangement.

2.1.1.1. 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** ($NaBH_4$, $CeCl_3$, MeOH, 0 °C) and this latter was transformed to the corresponding α-bromo-epoxide **7** (CBr_4, PPh_3, Py). The bromide intermediate underwent a reductive debromination/ring-opening of the epoxide, *via* a radical intermediate or *via* an anion generated by zinc (Zn, CuI, EtOH, H_2O), and α-*iso*-ionol was isolated in high yield (91%) as an equimolar mixture of (*Z*)- and (*E*)-stereoisomers.

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).

2.1.1.2. Büchi-Vederas rearrangement. Büchi and Vederas took advantage of the Crabbé et al. work [45] 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 ($NH_{3(l)}$, *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).

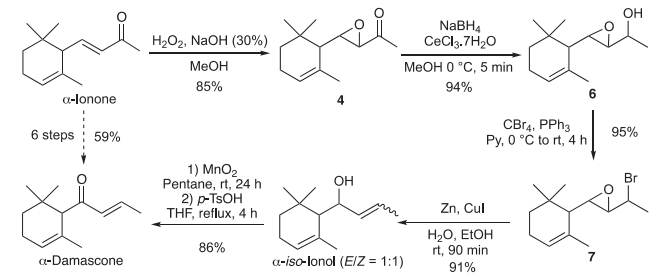
An improvement of the Büchi-Vederas rearrangement was reported by Xu et al. *via* an isoxazole intermediate obtained in 3 steps from α-ionone[47]. At first, α-ionone was converted to an α-ionone-oxime (NaOAc, $NH_2OH{\cdot}HCl$, EtOH/H_2O) and, after an epoxidation [H_2O_2, cetyltrimethylammonium hydroperoxide (CTAOH), LiOH, H_2O], the resulting epoxy-oxime **9** was converted to isoxazole **8** under acidic conditions (HCl, refluxing cyclohexane).

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).

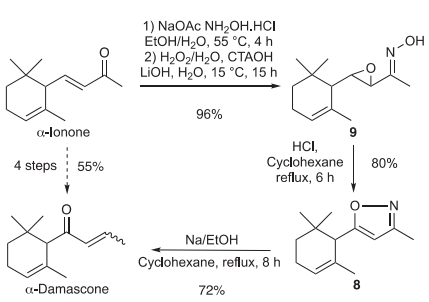
It is worth mentioning that a less effective Büchi-Vederas rearrangement was reported by Schulte-Elte et al. [48,49].

2.1.1.3. [2,3]-Meisenheimer rearrangement. Rautenstrauch et al. took advantage of the [2,3]-Meisenheimer rearrangement [50] to synthetize α-damascone [51]. After reduction of α-ionone to α-ionol ($NaBH_4$, THF, 50 °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*-dimethylhydroxyl-amine **11** according to a Meisenheimer rearrangement (35 °C, 0.05 Torr). Compound **11** was then *N*-alkylated (FSO_2OMe, Et_2O, 5 °C) to intermediate **C** and, after treatment under basic conditions (NaOH, 80 °C), a Hoffman elimination took place to afford α-damascone (6 steps, overall yield = 14%) (Scheme 7).

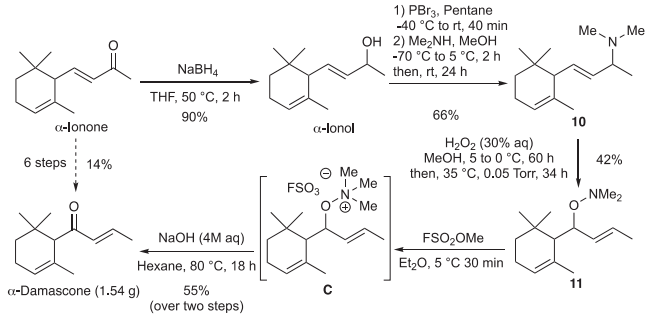
The two most efficient syntheses of α-damascone from α-ionone



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



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



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

were the Luche et al. synthesis, using a Wharton rearrangement, and the Xu et al. synthesis, using a Büchi-Vederas rearrangement.

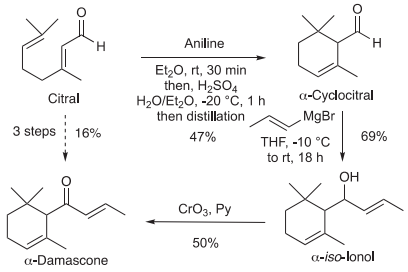
2.1.2. *Via α-cyclocitral*

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.

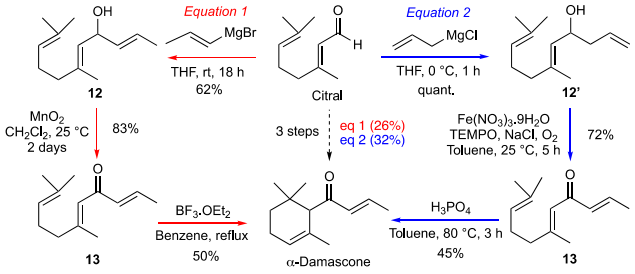
2.1.2.1. From citral. The first synthesis of α-damascone from α-cyclocitral, prepared from citral by an intramolecular cyclization [52,53], was reported by Demole et al.[14]. Treatment of citral with aniline led to the corresponding Schiff base which was cyclized under acidic conditions (H_2SO_4, H_2O/Et_2O, −20 °C) to produce a mixture of α- and β-cyclocitrals in a ratio of 2 to 1 (70%) [54,55]. These cyclocitrals 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).

Kovàts et al. and Ruedenauer et al. reported the synthesis of α-damascone from citral with a late stage cyclization [56–58]. 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 ($BF_3{\cdot}OEt_2$, 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'** [$Fe(NO_3)_3{\cdot}9H_2O$, 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).

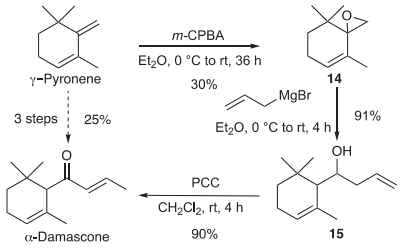
2.1.2.2. From γ-pyronene. Another starting material than citral was used by Delmond et al. to access α-damascone: the γ-pyronene, a terpenic compound easily accessible by pyrolysis of β-pinene *via* myrcene [59]. A chemoselective epoxidation of the *exo* cyclic



Scheme 8. Synthesis of α-damascone from citral.



Scheme 9. Synthesis of α-damascone from citral.



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

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).

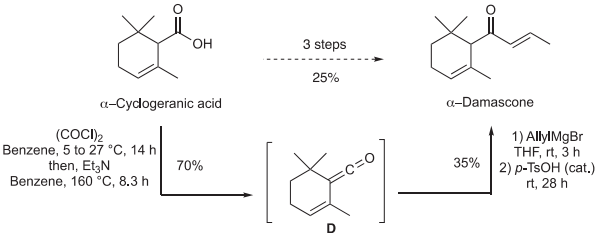
Even if citral or γ-pyronene can be transformed to α-damascone in 3–4 steps, the overall yields are always very modest (16%–32%).

2.1.3. *From α-cyclogeranic acid and derivatives*

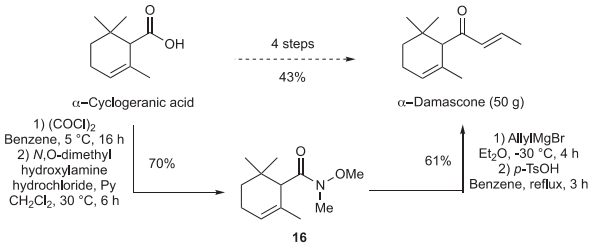
α-Cyclogeranic acid and derivatives were transformed to α-damascone. It is worth mentioning that α-cyclogeranic acid and derivatives can be prepared by cyclization of α-geranic acid.

2.1.3.1. From α-cyclogeranic acid. After the generation of ketene **D** from α-cyclogeranic acid [$(COCl)_2$, 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-damascone [61] (3 steps, overall yield = 25%) (Scheme 11).

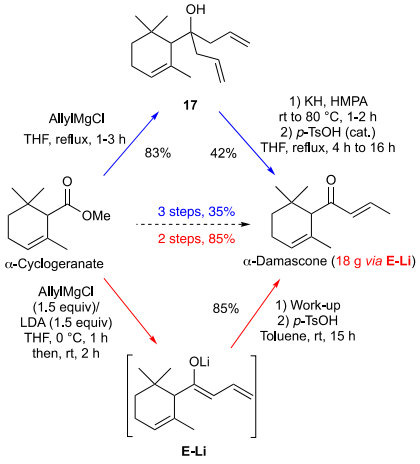
The overall yield in α-damascone was doubled by Chen et al. who synthesized the Weinreb amide **16** from cyclogeranic acid. After addition of allylmagnesium bromide to **16** and isomerization of the double bond, α-damascone was isolated (4 steps, overall yield = 43%) [62]. By using this sequence of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



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



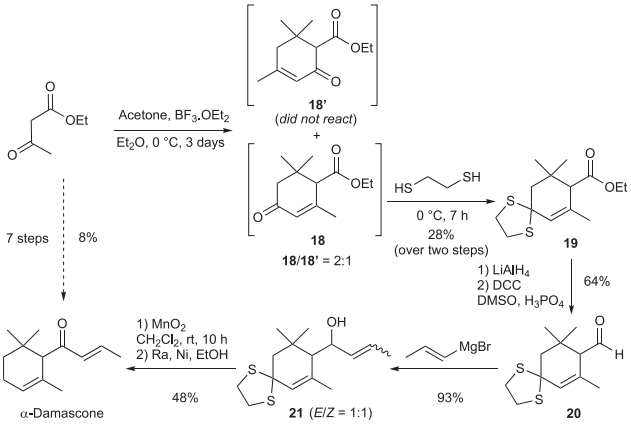
Scheme 12. Synthesis of α-damascone from α-cylogeranic acid *via* Weinreb amide **16.**



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

2.1.3.2. From methyl α-cylogeranate. 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 equimolecular 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).

2.1.3.3. 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 ($BF_3{\cdot}OEt_2$, 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).



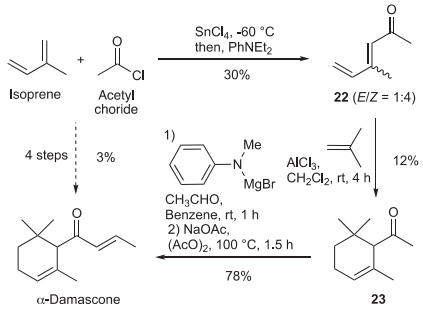
Scheme 14. Synthesis of α-damascone from a functionalized α-cyclogeranate.

2.1.4. From cyclohexenyl methylketone

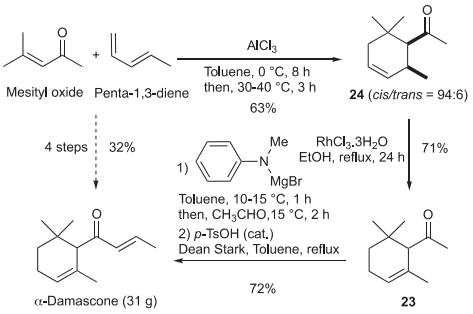
Cyclohexenyl methylketones can be prepared by a Diels-Alder reaction and then transformed to α-damascone by an aldolization/crotonization sequence.

2.1.4.1. 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 [PhN(Me)MgBr, CH_3CHO, benzene then NaOAc, $(AcO)_2$, 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).

2.1.4.2. 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 pentan-1,3-diene and mesityl oxide, which afforded δ-cyclohexenyl methylketone **24** (63%) [71]. The isomerization of the double bond in **24** ($RhCl_3{\cdot}3H_2O$, refluxing EtOH) led to **23**, which was then converted



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



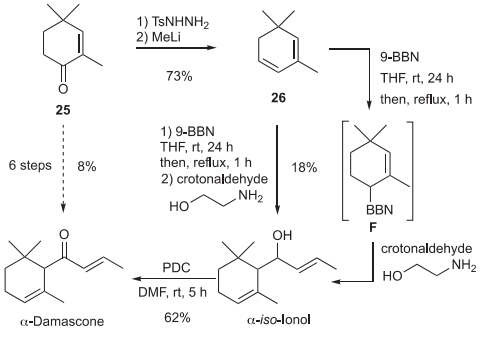
Scheme 16. Synthesis of α-damascone from α-cyclohexenyl methylketone **24**.

to α-damascone through an aldolization/crotonization sequence [PhN(Me)MgBr, CH_3CHO, benzene then NaOAc, $(AcO)_2$, 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].

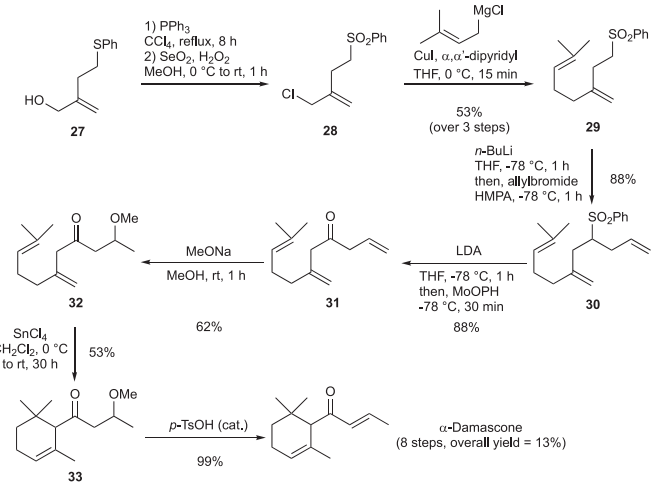
2.1.5. Miscellaneous

2.1.5.1. 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).

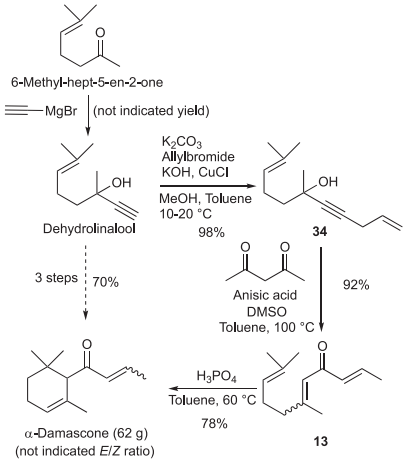
2.1.5.2. From a δ-hydroxy-sulfide. Starting from δ-hydroxy-sulfide **27**, the six-membered ring of α-damascone was built at a late stage [74]. δ-Hydroxy-sulfide **27** was converted to **32** (6 steps), precursor of the cyclized product **33**. At first, δ-hydroxy-sulfide **27** was transformed to dienic 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** ($SnCl_4$, CH_2Cl_2, 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 17. Synthesis of α-damascone by allylboration of crotonaldehyde.



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



Scheme 19. Synthesis of α-damascone from dehydrolinalool.

2.1.5.3. From methyl heptenone. A three-step synthesis of α-damascone was reported by Wei et al. from dehydrolinalool with an a excellent overall yield (70%) [75]. Dehydrolinalool was obtained from 6-methyl-hept-5-en-2-one and then converted to dienylol **34** by allylation under basic conditions (allyl bromide, K_2CO_3, 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 (H_3PO_4, 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).

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 chromatography [79] 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, cyclocitrals and cyclohexenyl methylketones, or

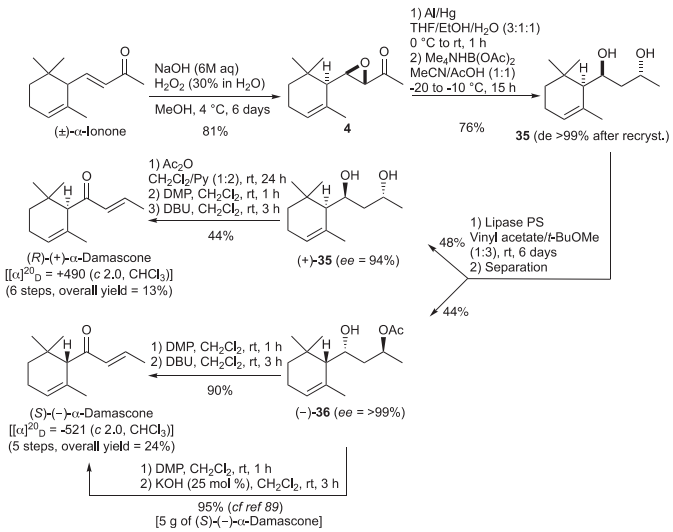
from racemic starting materials by realizing an enantioselective protonation of an enolate, an enantioselective reduction of a ketone, or an enzymatic resolution of a diol [80,81].

2.2.1. From α-ionone

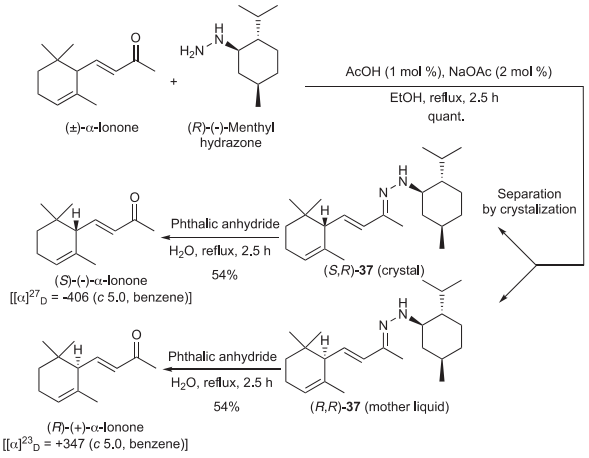
2.2.1.1. From (±)-α-ionone by enzymatic resolution of a diol. By using an enzymatic resolution of a 1,3-diol, synthesized from (±)-α-ionone, (*R*)-(+)-α-damascone and (*S*)-(−)-α-damascone were synthesized by Serra and Fuganti [82]. At first, (±)-α-ionone was transformed to epoxide (±)-**4** (NaOH, H_2O_2, 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/H_2O), followed by a diastereoselective reduction of the obtained 1,3-hydroxyketone [$Me_4NHB(OAc)_2$, 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).

2.2.1.2. 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 syntesize (±)-α-damascone.

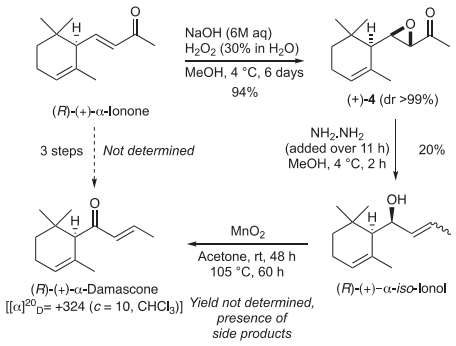
(±)-α-Ionone was condensed with (*R*)-menthylhydrazone (AcOH cat., NaOAc cat.) to furnish α-ionone-(*R*)-(−)-menthylhydrazone **37** [84–86]. As in EtOH (*S*)-(−)-α-ionone-(*R*)-(−)-menthylhydrazone (*S*,*R*)-**37** is crystalline and (*R*,*R*)-**37** soluble, the two diastereomers were separated. After 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 20. Synthesis of (*R*)-(+)- and (*S*)-(−)-α-damascone by enzymatic resolution of 1,3-diol.

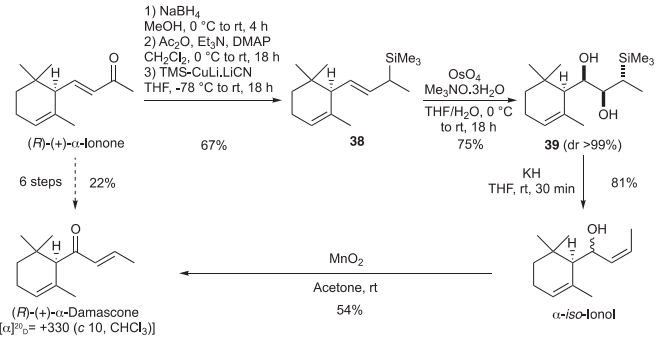


Scheme 21. Resolution of (±)-α-ionone using (*R*)-(−)-menthylhydrazone.



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

2.2.1.3. 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).



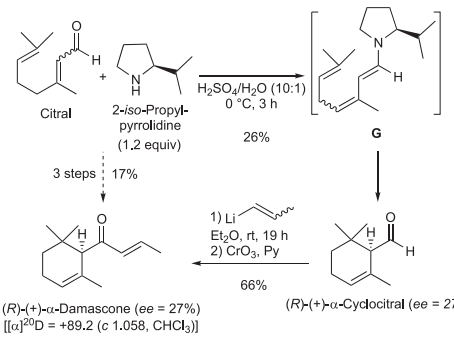
Scheme 23. Synthesis of (*R*)-(+)-α-damascone from (*R*)-(+)-α-ionone using a Peterson elimination.

2.2.1.4. 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/acylation/silylation) and, after a dihydroxylation (OsO_4, $Me_3NO\cdot 3H_2O$, 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 $[\alpha]_D$ was indicated. Compared to the $[\alpha]_D$ reported by Oloff et al., it seems that by using this sequence of reactions, (*R*)-(+)-damascone is also contaminated by side-products (Scheme 23).

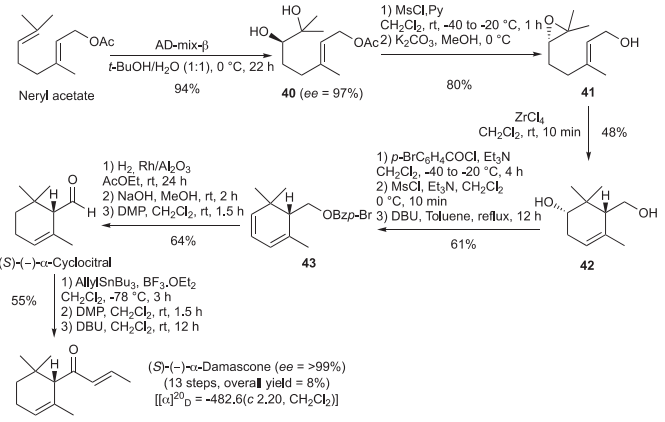
2.2.2. Via optically active α-cyclocitral

2.2.2.1. 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-*iso*propylpyrrolidine 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).

2.2.2.2. 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/H_2O, 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/Al_2O_3), 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 ($AllylSnBu_3$, $BF_3.OEt_2$, CH_2Cl_2), the resulting homoallylic alcohol was oxidized (DMP, CH_2Cl_2, rt) and the non-conjugated enone was isomerized to (*S*)-(−)-α-damascone (DBU, CH_2Cl_2, 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 24. Synthesis of (R)-(+)-α-damascone from citral via (R)-(+)-α-cyclocitral.

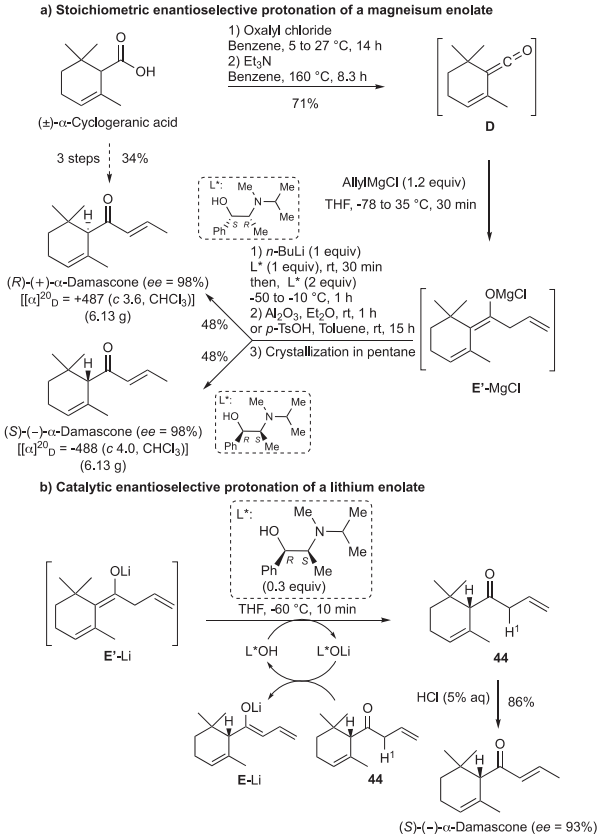


Scheme 25. Synthesis of (*S*)-(−)-α-damascone from neryl acetate *via* (*S*)-(−)-α-cyclocitral.

2.2.3. From (±)-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 thioesters [91–96], and this method was applied to the synthesis of optically active damascones.

2.2.3.1. Protonation of a keto-enolate. The nucleophilic attack of ketene **D**, generated from (±)-α-cyclogeranic acid, by allylmagnesium bromide led to a magnesium enolate intermediate **E′**-MgCl



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

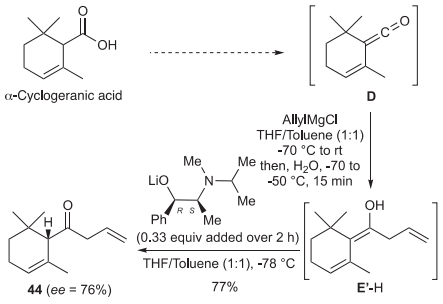
which was then enantioselectively protonated by *N-iso*-propylephedrine to produce either (*R*)-(+)- or (*S*)-(−)-α-damascone [97]. The best conditions to induce a good enantiomeric excess revealed to be the *in situ* generation of 1 equivalent of lithium *N-iso*propyl-ephedrine alkoxide, as this alkoxide generates an equimolar enolate/alkoxide complex and, after addition of 2 equivalents of *N-iso*propyl-ephedrine, the enantioselective protonation of a mixed lithium-magnesium aggregate took place, affording the expected enantio-enriched non-conjugated enone. After isomerization of the enone (Al_2O_3 or *p*-TsOH, toluene, rt), the expected optically active damascones were isolated. The use of (*S*,*R*)-*N-iso*propylephedrine led to (*R*)-(+)-α-damascone (34% yield, *ee* = 98% after recrystallization) and the use of (*R*,*S*)−*N-iso*-propylephedrine 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 equivalents of (*R*,*S*)−*N-iso*propylephedrine, (*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).

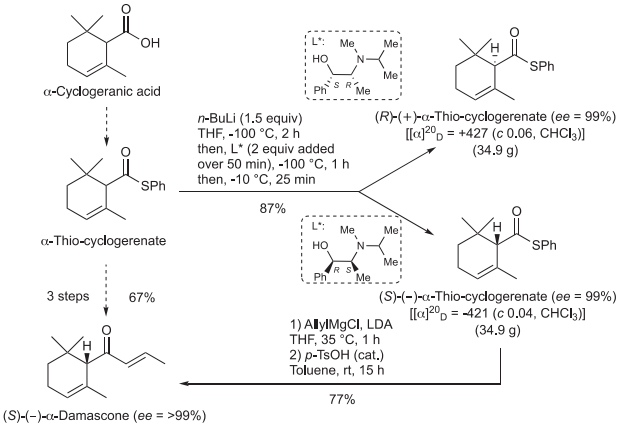
When the enol intermediate **E**′-H, obtained by addition of allylmagnesium bromide on ketene **D**, was deprotonated/reprotonated with a catalytic amount of lithium (*R*,*S*)−*N-iso*propylephedrine alkoxide (0.33 equiv), ketone **44** was isolated with a good ee of 76% and in 77% yield and then converted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

2.2.3.2. 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-iso*propylephedrine [100]. The lithium thio-ester enolate was generated from (±)-α-thio-cyclogeranate (*n*-BuLi, THF, −100 °C), and then protonated either with (*S*,*R*)-(+)-*N-iso*propylephedrine, leading to (*R*)-(+)-α-thio-cyclogeranate (*ee* = 99%, yield = 87%), or by the (*R*,*S*)-(−)-*N-iso*propylephedrine, 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).

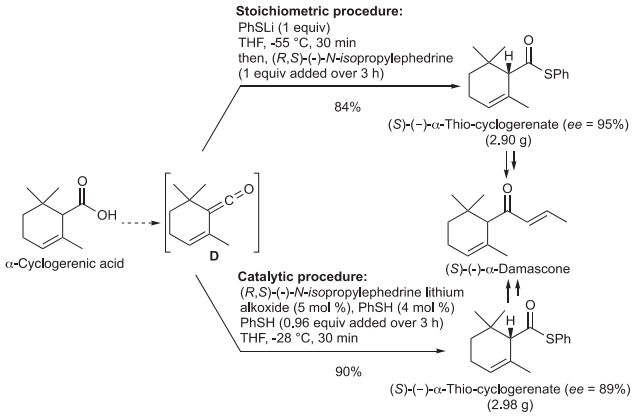
The optically active (*S*)-(−)-α-thio-cyclogeranate was generated from ketene **D**, obtained from α-cyclogeranic acid, by addition of



Scheme 27. Catalytic enantioselective protonation.



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

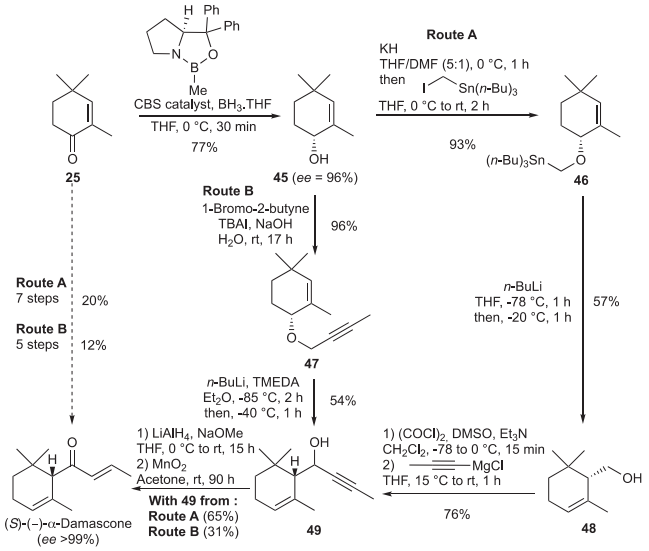


Scheme 29. Synthesis of enantio-enriched (*S*)-(−)-α-thio-cyclogeranate from ketene intermediate.

lithium thiophenolate followed by an enantioselective protonation of the enolate, using 1 equivalent of (*R*,*S*)-(−)-*N-iso*propylephedrine. (*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-iso*propylephedrine alkoxide (5 mol %) in the presence of 4 mol % of thiophenol, followed by a slow addition of 0.96 equivalents 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).

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 (BH_3.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 ($LiAlH_4$, NaOMe, THF then MnO_2, acetone, rt). It is worth mentioning that the access to



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

(*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).

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

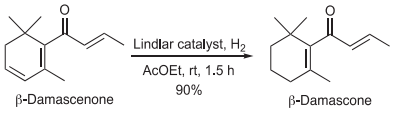
3. β-Damascone

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].

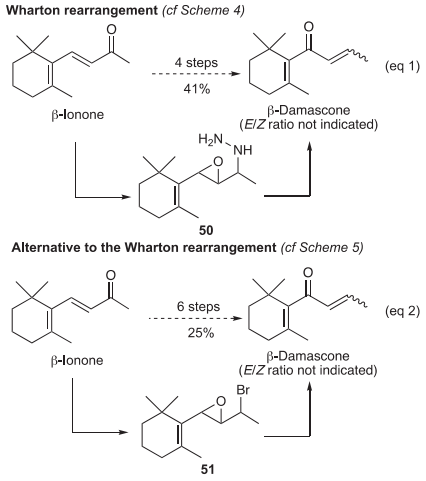
3.1. From β-ionone

3.1.1. Wharton rearrangement

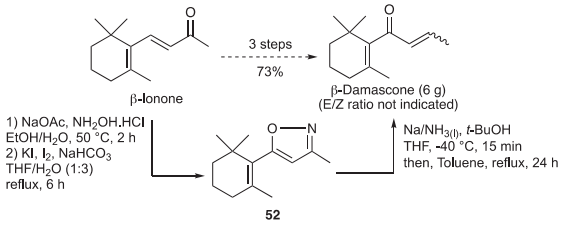
As for the formation of α-ionone to α-damascone by using a Wharton rearrangement, β-ionone was transformed to β-damascone by using also a Wharton rearrangement [42] applied to an epoxy-hydrazone or an epoxy-bromide intermediate [44] (Scheme 32, eq 1-2).



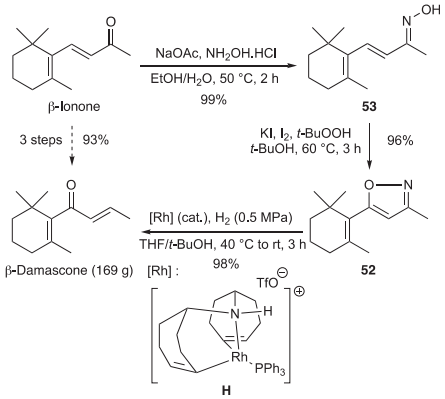
Scheme 31. Synthesis of β-damascone from β-damascenone.



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



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

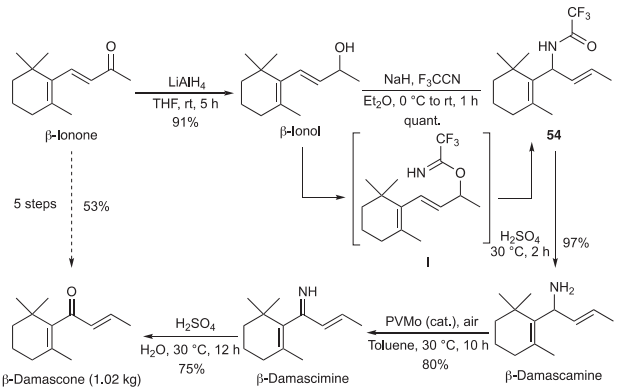


Scheme 34. Synthesis of β-damascone from β-ionone oxime on multi-gram scale using a the Büchi-Vederas rearrangement.

3.1.2. 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].

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).



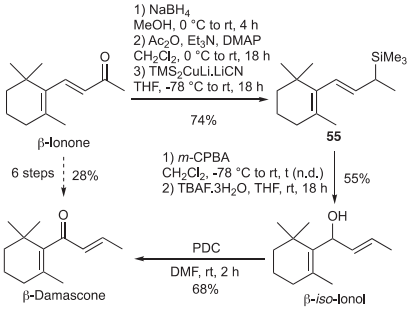
Scheme 35. Synthesis of β-damascone on a kg scale using an Overman rearrangement.

3.1.3. Overman rearrangement

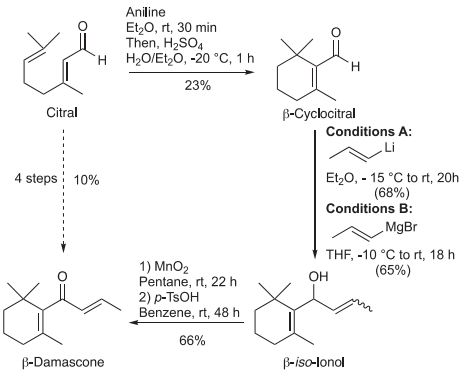
An efficient synthesis of β-damascone was realized from β-ionone by Zhixun et al. using an Overman rearrangement as the key step [107]. β-Ionone was reduced to β-ionol ($LiAlH_4$, THF), and then transformed to imidate **I** (NaH, CF_3CN, Et_2O, 0 °C) which rearranged to allyl amide **54** according to 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 $H_4[PVMo_{11}O_{40}]\cdot 13H_2O$ 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).

3.1.4. 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 $TMS_2CuLi\cdot LiCN$, 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-damascenone from β-ionone *via* an allylsilane.



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

3.2. Via cyclocitral

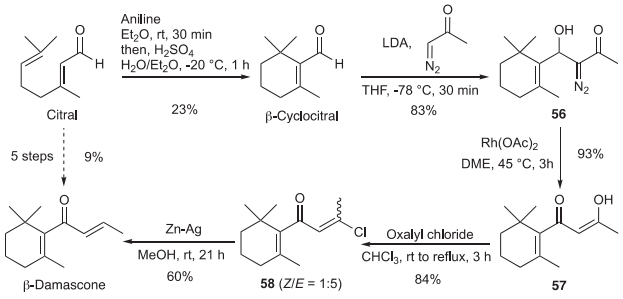
3.2.1. From citral

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].

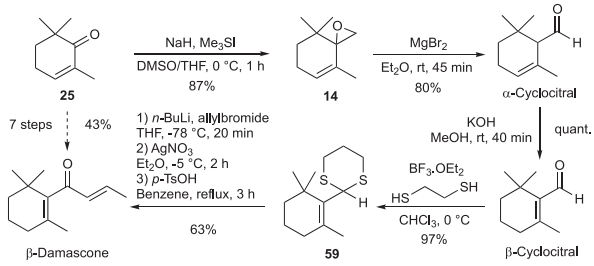
Pelliciari et al. used another nucleophile than prop-1-enyl lihium or magnesium bromide to introduce the enone side chain of β-damascone, i.e. the lithium anion of diazoacetone [108,109]. Addition of 1-diazo-1-lithioacetone, generated *in situ*, to β-cyclocitral afforded diazo hydroxy-ketone **56** and, the metalla-carbene generated with the rhodium(II) catalyst $Rh(OAc)_2$ (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 alloy (MeOH, rt), β-damascone was isolated with a low overall yield (5 steps, overall yield = 9%) (Scheme 38).

3.2.2. From a cyclohexenone derivative

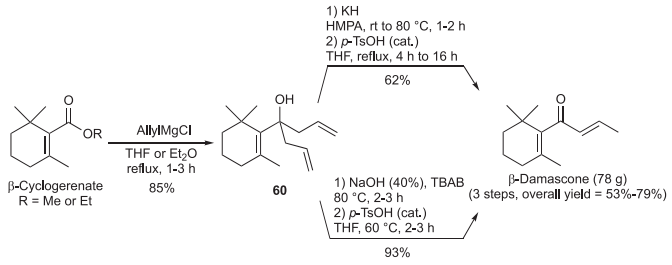
An umpolung reactivity of β-cyclocitral, due to its conversion to an thioacetal, allowed the access to β-damascone [110]. Thioacetal **59** was synthesized from 2,6,6-trimethyl-cyclohexen-2-one **25** in 4 steps. After epoxidation of **25** (NaH, Me_3SI, DMSO/THF, 0 °C) to **14** and rearrangement to 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, $BF_3\cdot OEt_2$). β-Cyclocitral



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



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



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

thioacetal **59** was then converted to β-damascone by an allylation/thioketal cleavage/isomerization sequence (7 steps, overall yield = 43%) (Scheme 39).

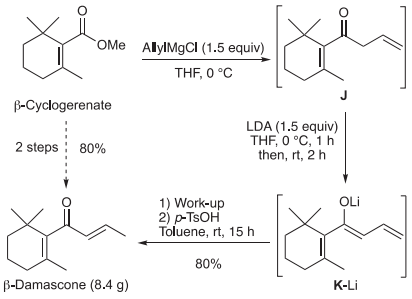
3.3. From methyl β-cyclogeranate

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].

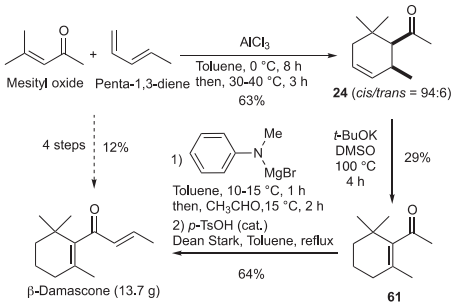
Fehr et al., by using the conditions that they had developed for the synthesis of α-damascone from α-cyclogeranate (allylMgBr/LDA) (*cf* Scheme 13), were able to produced 8 g β-damascone from β-cyclogeranate in 2 steps (2 steps, overall yield = 80%) (Scheme 41) [66].

3.4. From cyclohexenyl methylketone

As previously reported for the synthesis of α-damascone (*cf* Scheme 16), Yamamoto et al. synthesized β-damascone from



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



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

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).

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.

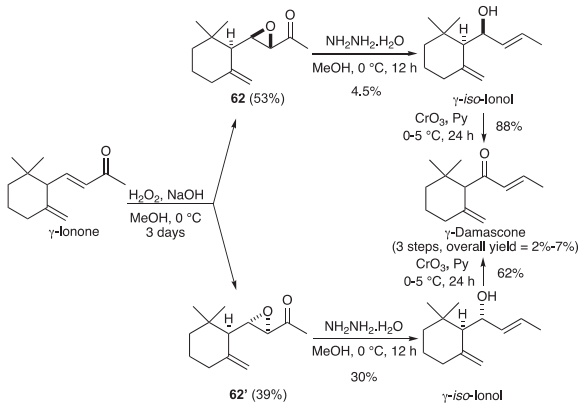
4.1. Racemic syntheses of γ-damascone

4.1.1. From γ-ionone

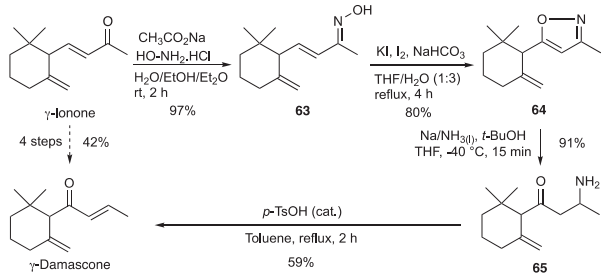
The two rearrangements previously reported, e.g. the Wharton and the Büchi-Vederas rearrangements, were used to synthesize γ-damascone from γ-ionone.

4.1.1.1. 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%).

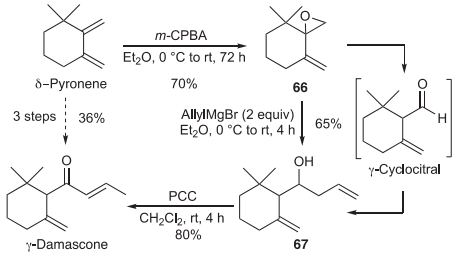
4.1.1.2. Büchi-Vederas rearrangement. γ-Damascone was also



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



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



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

synthesized by Schulte-Elte et al. from γ-ionone using a Büchi-Vederas rearrangement (4 steps, overall yield = 42%) (Scheme 44) [48,49].

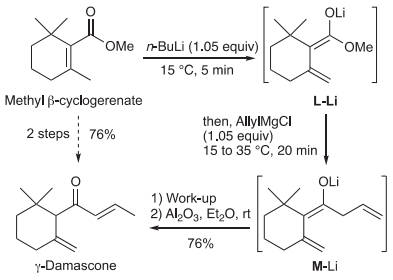
4.1.2. Via γ-cyclocitral

Epoxidation of δ-pyronene by epoxidation (*m*-CPBA, Et_2O, 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 (CH_2Cl_2, rt), γ-damascone was isolated in 80% yield (3 steps, overall yield = 36%) (Scheme 45) [59].

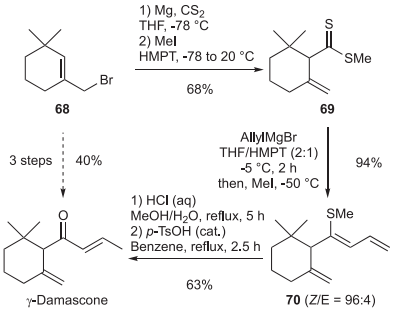
4.1.3. From cyclogeranate

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 (Al_2O_3, Et_2O), γ-damascone was produced with an overall yield of 76% (2 steps) (Scheme 46) [112].

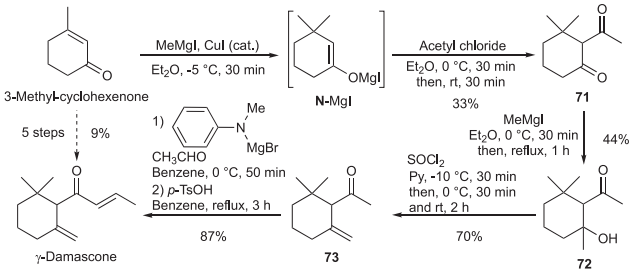
γ-Methyl dithio-cyclogeranate **69**, prepared from allylic bromide **68** [113], was transformed to γ-damascone in three steps [114,115]. After addition of allylmagnesium bromide (THF/HMPT then MeI), the conjugated thio-enol **70** (*Z*/*E* = 96:4) was obtained and transformed to γ-damascone by two consecutive acidic treatments (HCl, H_2O/MeOH then *p*-TsOH, refluxing benzene) (3 steps, overall yield = 40%) (Scheme 47).



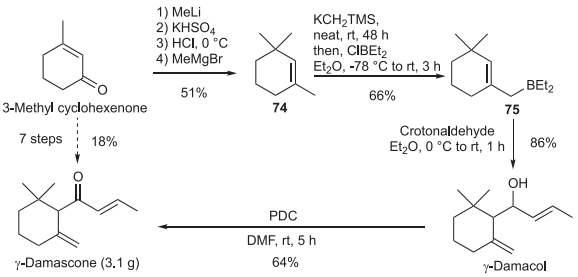
Scheme 46. Synthesis of γ-damascone from methyl β-cyclogeranate.



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



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



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

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, CH_3CHO then *p*-TsOH], γ-damascone was isolated with a low overall yield of 9% (5 steps) (Scheme 48).

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].

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 (±)-α-ionone using either an enzymatic resolution as the key step, or an enantioselective protonation of an enolate.

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

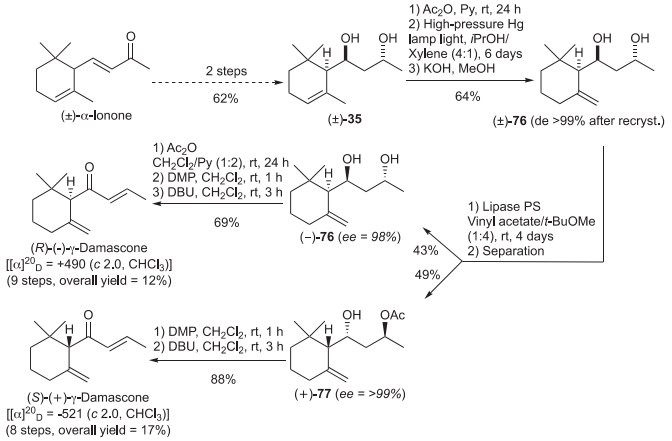
The synthesis of (*R*)-(−)- and (*S*)-(+)-γ-damascones was realized from (±)-γ-ionone [82]. At first, (±)-α-ionone was converted to 1,3-diol (±)-**35**, as previously reported for the synthesis of enantio-enriched α-damascones (*cf* Scheme 20). After an acetylation (Ac_2O, Py), a photochemical isomerization of the *endo* cyclic double bond to the *exo* cyclic double (hν, 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).

4.2.2. Via enantio-enriched γ-cyclocitral

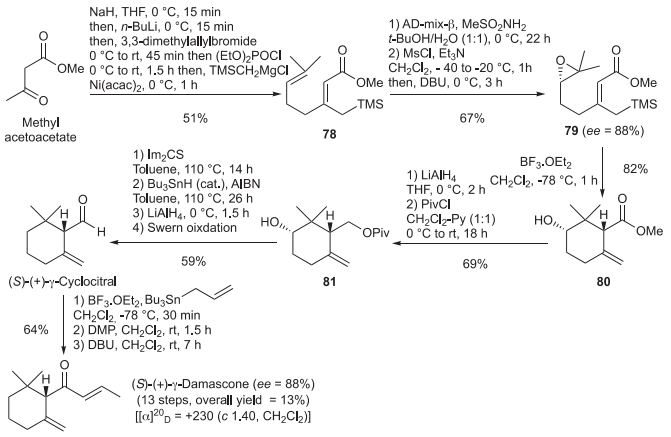
Similarly to the synthesis of enantio-enriched α-damascones (*cf* Scheme 25), Vidari et al. synthesized (*S*)-(+)-γ-damascone from methyl acetoacetate *via* (*S*)-(+)-γ-cyclocitral [117]. Methyl acetoacetate was converted to the non-conjugated diene **78** in a three-step one-pot sequence (alkylation/enol phosphonylation/cross-coupling). Diene **78** was then subjected to a Sharpless dihydroxylation (AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O) and the 1,2-diol was transformed to epoxide **79** (mesylation/S_Ni). After cyclization of **79** to **80** ($BF_3{\cdot}OEt_2$, CH_2Cl_2), 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).

4.2.3. From γ-cyclogeranic acid and derivatives

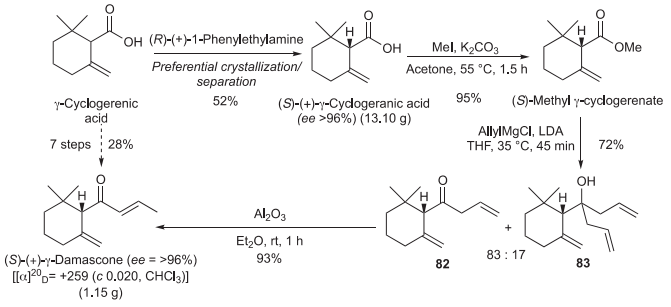
4.2.3.1. By chemical resolution of γ-cyclogeranic acid. Fehr et al. have explored the synthesis of optically active γ-damascones from (±)-γ-cyclogeranic acid after separation of the two enantiomers by preferential crystallization with (*R*)-phenyl-ethylamine [118]. (*S*)-(+)-γ-Cyclogeranic acid was recovered 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).



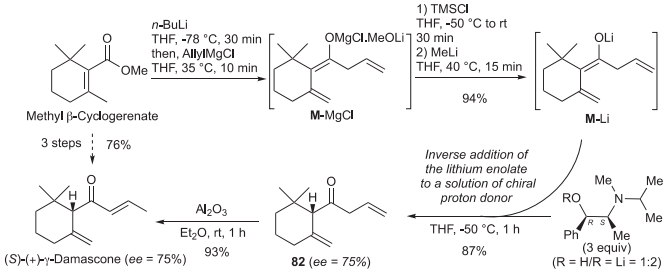
Scheme 50. Synthesis of (*R*)-(−)- and (*S*)-(+)-γ-damascones involving an enzymatic resolution.



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



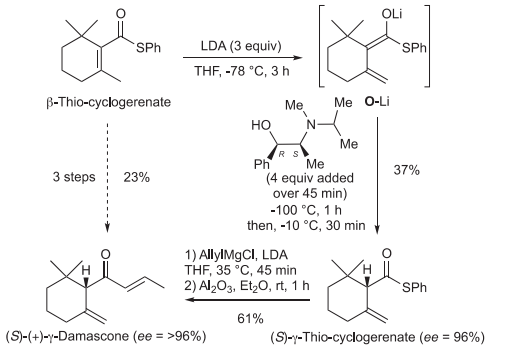
Scheme 52. Synthesis of (*S*)-(+)-γ-damascone by resolution of (±)-γ-cyclogeranic acid using (*R*)-(+)-1-phenylethylamine.



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

4.2.3.2. 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*-*iso*propylephedrine/(*R*,*S*)-(−)-*N*-*iso*propyl-ephedrine 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).

Based on an enantioselective protonation of lithium thio-enolate **O**—Li, the synthesis of (*S*)-(+)-γ-damascone was realized



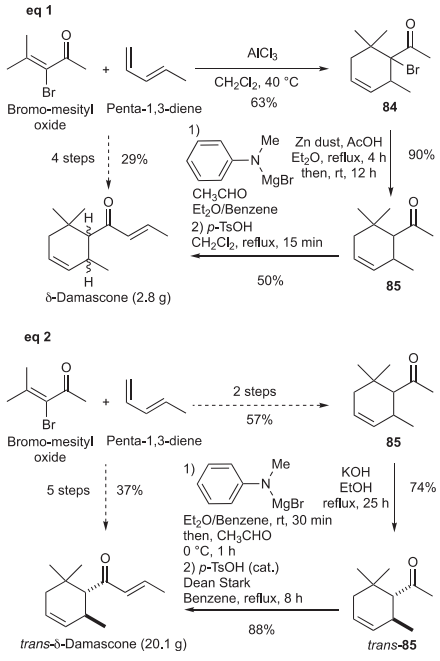
Scheme 54. Synthesis of (*S*)-(+)-γ-damascone from β-thio-cyclogeranate.

from β-thio-cyclogeranate prepared from methyl β-cyclo-geranate [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*-*iso*propylephedrine, an enantioselective protonation occurred to produce the expected (*S*)-γ-thio-cyclo-geranate 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 iso-merized to (*S*)-(+)-γ-damascone (Al_2O_3, Et_2O, rt) (*ee* = >96%, 3 steps, overall yield = 23%) (Scheme 54).

The most efficient synthesis of (±)-γ-damascone was realized by Fehr et al. starting from (±)-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 (±)-γ-cyclogeranic acid (*cf* Scheme 52) [118].

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.



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

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-cyclo-hexenyl methyl-ketone **85** was converted to a mixture of *cis*- and *trans*-δ-dam-ascones in 2.8 g quantity (4 steps, overall yield = 29%) (Scheme 55, eq 1).

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 epimeri-zation 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).

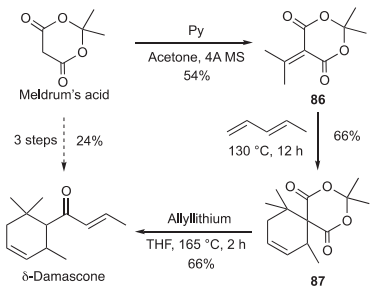
5.2. From Meldrum's acid

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]. Mel-drum's acid was condensed with acetone (Knoevenagel conden-sation) to produce dienophile **86** and this latter was then engaged in a Diels-Alder reaction with penta-1,3-diene to afford the spi-rocyclic 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).

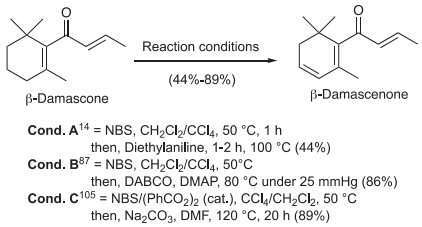
The best synthesis of δ-damascone was reported by Mookherjee et al. from mesityl oxide and penta-1,3-diene to form δ-cyclo-hexenyl methylketone by a Diels-Alder reaction and then 3 steps were necessary to obtained the *trans*-δ-damascone (epimerization/ aldolization/crotonization sequence, overall yield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

6. Damascenones

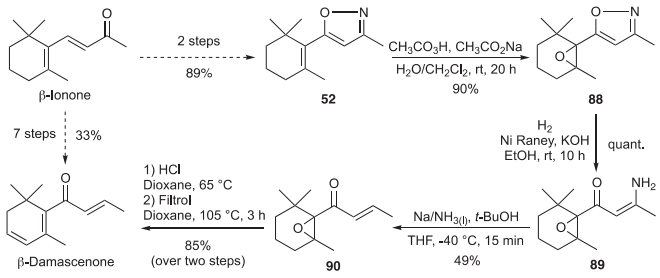
Different syntheses of β-damascenone were reported. As there is only one synthesis of α-damascenone and one synthesis of γ-damascenone, their synthesis will be concomitantly described. It is worth mentioning that β-damascone can be transformed to β-damascenone in two steps e.g. by an allylic bromination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



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



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

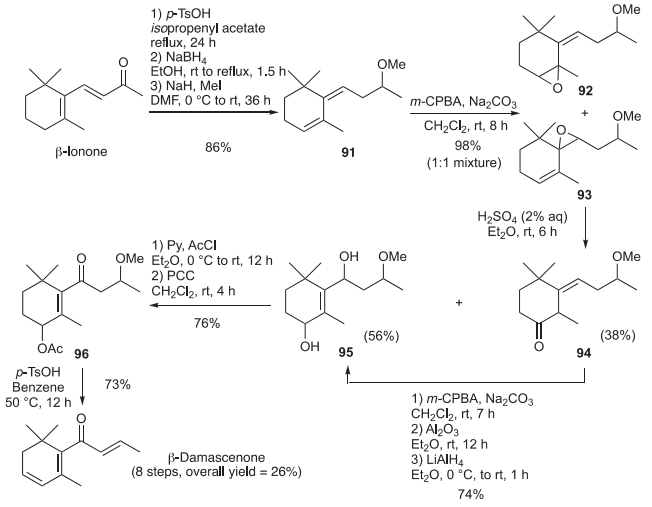


Scheme 58. Synthesis of β-damascenone from β-ionone via an epoxy-isoxazole.

6.1. From β-ionone (β-damascenone)

β-Damascenone was synthesized from β-ionone *via* isoxazole **52** prepared in two steps from β-ionone [48]. Isoxazole **52** was treated with peracetic acid (CH_3CO_3H, CH_3CO_2Na, H_2O/CH_2Cl_2) to produce epoxy-isoxazole **88**, which after hydrogenolysis under hydrogen pressure (H_2, Raney Ni, KOH), was transformed to epoxy enaminoketone **89**. After a Birch reduction ($Na/NH_{3(l)}$, *t*-BuOH), the resulting epoxy dihydro β-damascone **90**, was treated under acidic conditions (HCl then filtrol, dioxane, 105 °C), to produce β-damascenone (7 steps, overall yield = 33%) (Scheme 58).

Another strategy was developed by Campagnole et al. to synthesize β-damascenone 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



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

allylic alcohol and oxidation (AcCl, Py then PCC, CH_2Cl_2), **96** was produced and converted to β-damascenone under acidic conditions (*p*-TsOH, benzene, 50 °C) (8 steps, overall yield = 26%) (Scheme 59).

6.2. Via cyclocitral and functionalized cyclocitral

6.2.1. From citral (β-damascenone)

β-Cyclocitral was transformed to β-damascenone *via* β-iso-ionol [125]. β-iso-Ionol was photo-oxidized (NaOAc, O_2, Bengal rose, hν) 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-damascenone after treatment with filtrol (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-damascenone (oxidation with MnO_2 and acidic treatment with filtrol, 85% yield). β-Damascenone 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-damascenone from β-cyclocitral was patented in 1976 and 1980 [56,57].

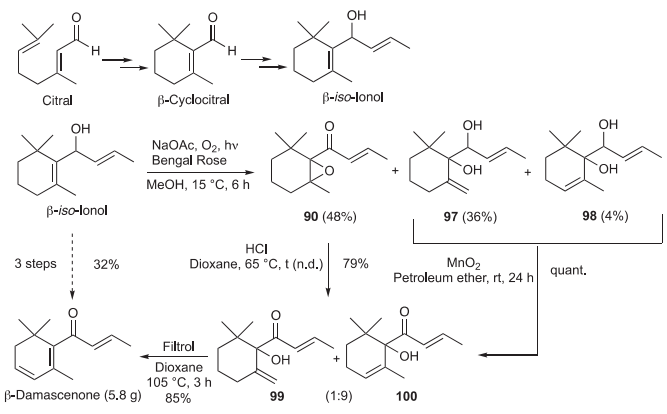
6.2.2. From pyronene (β-damascenone)

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].

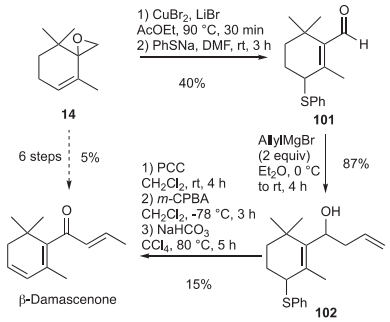
6.2.3. From cyclogeranate/safranate (α-, β- and γ-damascenones)

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).

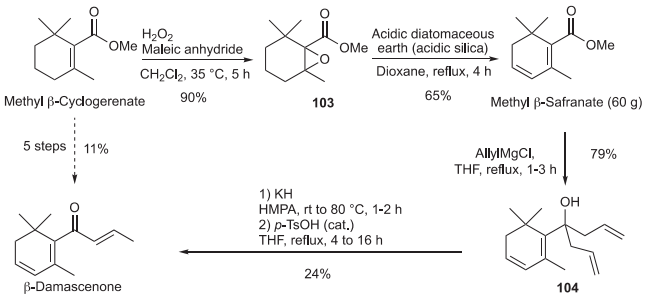
Ethyl β-safranate can be synthesized from keto-ester **105** *via* ethyl α-safranate by using a Wittig reaction followed by an acidic treatment (*p*-TsOH, refluxing benzene) (Scheme 63, eq 1) [103,104]. It is worth mentioning that a mixture of ethyl β- and γ-safranates was obtained in a 3:1 ratio with a yield of 80% in the presence of 20% of unreacted ethyl α-safranate. Ethyl α- and β-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



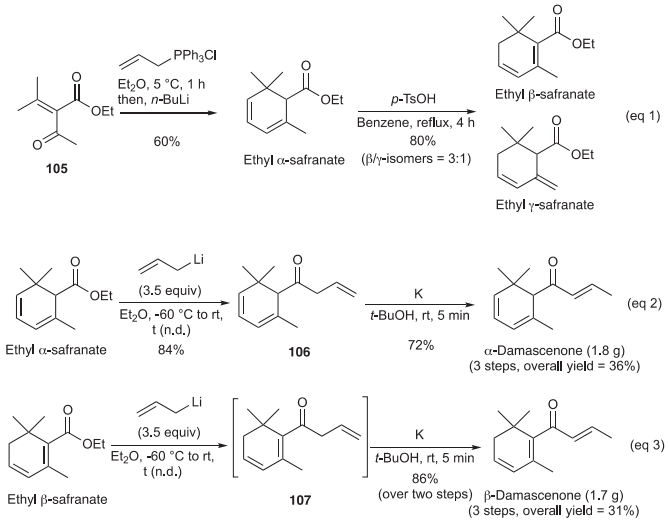
Scheme 60. Synthesis of β-damascenone by photo-oxidation of β-iso-ionol.



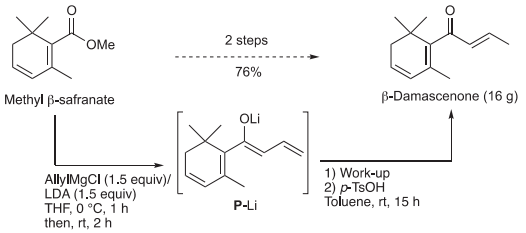
Scheme 61. Synthesis of β-damascenone from γ-epoxy-pyronene **14**.



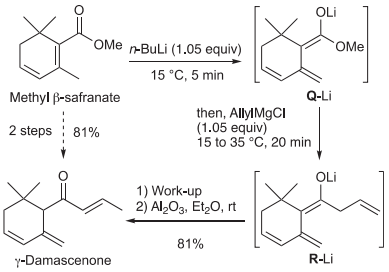
Scheme 62. Synthesis of β-damascenone from methyl β-cyclogeranate via methyl β-safranate.



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



Scheme 64. Synthesis of β-damascenone from methyl.



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

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**.

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].

6.2.3.1. 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].

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 allylithium (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).

6.2.4. Via cyclohexadienyl methylketone (β-damascenone)

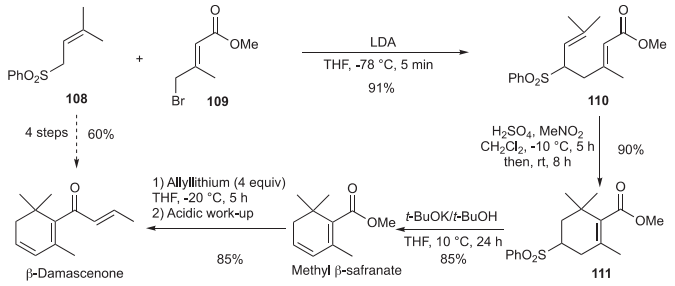
A normal Diels-Alder reaction between bromo-mesityl oxide and penta-1,3-diene was realized by Cookson et al. leading to bromo-cyclohexenyl methylketone **84** (as reported for δ-damascone, *cf* Scheme 55). After dehalogenation (LiF, Li_2CO_3, DMF, 120 °C), the resulting dienyl methylketone **112** was submitted to an aldolization/crotonization sequence producing β-damascenone with an overall yield of 22% (4 steps) (Scheme 67) [119,120].

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, CH_2Cl_2) β-damascenone was isolated (7 g were obtained by using this method) (Scheme 68) [127].

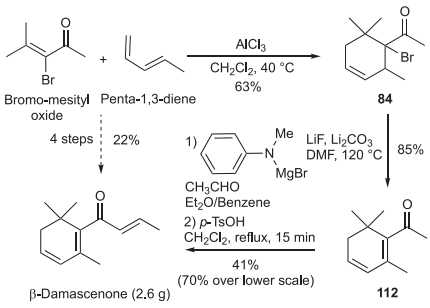
6.3. Miscellaneous

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

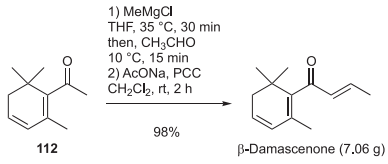
2,6,6-Trimethyl-cyclohexen-2-one **25** was used to efficiently produce β-damascenone using a Meyer-Shuster rearrangement [128,129]. 2,6,6-Trimethyl-cyclohexen-2-one **25** was deconjugated to enone **113** [(AlO^iPr)$_4$, 190 °C] and then treated with propargylic magnesium bromide **S**—MgBr (prepared in 2 steps from the corresponding propargylic alcohol **114**). The resulting tertiary propargylic alcohol **115** was rearranged to β-damascenone under acidic conditions (H_2SO_4, petroleum ether), according to the Meyer-Shuster rearrangement, with an excellent yield of 90%. By using



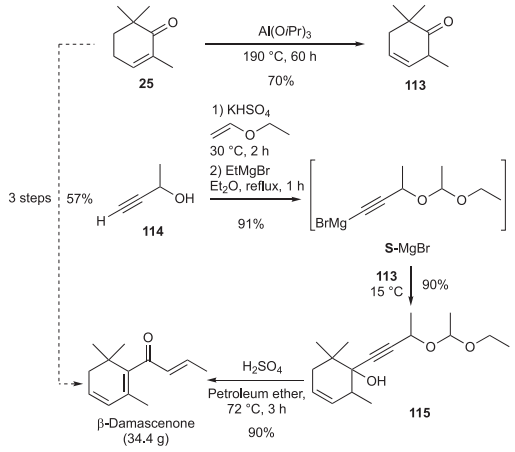
Scheme 66. Synthesis of β-damascenone from allylic sulfone derivative *via* methyl β-safranate.



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



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

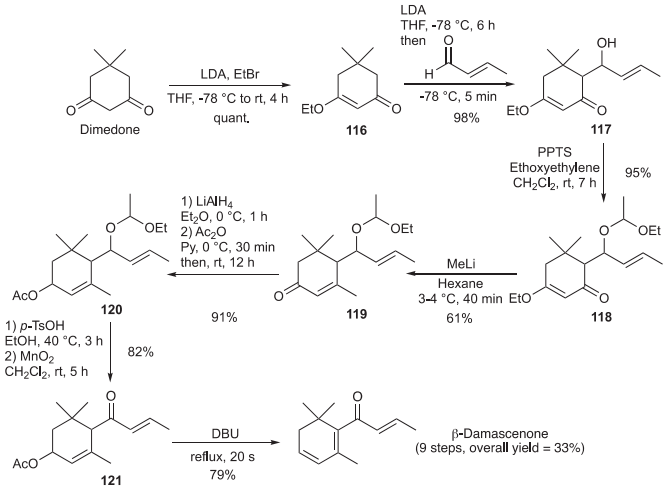


Scheme 69. Synthesis of β-damascenone from 2,6,6-trimethyl-cyclohexen-2-one.

this rearrangement, 34 g of β-damascenone were prepared (3 steps, overall yield = 57%) (Scheme 69).

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



Scheme 70. Synthesis of β-damascenone from dimedone.

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 four-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%–81%, Schemes 62–66), the synthesis of β-damascenone from 2,6,6-trimethylcyclohexen-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.

7. Conclusion

Due to the highly powerful organoleptic properties of damascones and damascenones and their importance for fragrance companies, many syntheses of the isomers and enantiomers of damascones, 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.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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