Optically Active Ionones and Derivatives: Preparation and Olfactory Properties

Elisabetta Brenna,*[a] Claudio Fuganti,[a] Stefano Serra,[a] and Philip Kraft[b]

Keywords: Enantioselective synthesis / Fragrances / Natural products / Olfaction / Synthetic methods / Resolution

The isomeric ionones **1**–**3** are of both academic and commercial interest. Since their first preparation at the end of the 19th century they have been widely used as fragrances and as starting materials or building blocks in the synthesis of many relevant products. The regioselective and/or enantioselective preparation of ionones has therefore been investigated with growing interest over the last decades. In this Microreview, we summarize the syntheses of optically active α- and γ-ionones (**1**, **3**) and the epoxy and dihydro ionones **4**–**7**. In addition, the olfactory properties of most of them are reported comprehensively.

Introduction

In the search for the odorous principle of violets, a mixture of isomeric ionones (**1**−**3**) was first synthesized in 1893 by Tiemann and Krüger;[1] indeed, even though Tiemann and Krüger did not anticipate it,[2] α- and β-ionone (**1**, **2**) make up almost 57% of the headspace of violets in bloom.[2b]

The initial synthetic route[1b] was based on the condensation of citral and acetone, which provided a mixture of regioisomeric aliphatic precursors known as pseudoionones (Scheme 1). Acid-catalyzed cyclization of these pseudoionones then afforded a mixture of the isomeric α-, β-, and γ-ionones (**1**−**3**).

After this fundamental discovery, many efforts to develop specific syntheses of the different double-bond isomers were undertaken. It was found that the acid catalyst clearly controls the stereochemical course of the cyclization.[3] α-Ionone (**1**), for instance, becomes the main product when phosphoric acid is used, but β-ionone (**2**) predominates

[a] Dipartimento di Chimica del Politecnico, Centro CNR per lo Studio delle Sostanze Organiche Naturali,
Via Mancinelli 7, 20131 Milano, Italy
Fax: (internat.) + 39-02/2399-3080
E-mail: elisabetta.brenna@polimi.it
[b] Givaudan Dübendorf AG, Fragrance Research,
Überlandstrasse 138, 8600 Dübendorf, Switzerland
Fax: (internat.) + 41-1/824-2926
E-mail: philip.kraft@givaudan.com

Elisabetta Brenna (top left), born in 1965, received her laurea (1989) and Ph.D (1993) in chemistry from the University of Milano, working on the synthesis and characterization of electroconducting polymers with Professor F. Sannicoló. After two years (1994−1996) spent as a fellow of the Advanced School of Polymer Science "G. Natta" of the Politecnico di Milano, she joined the Department of Chemistry of the same Politecnico as an Associate Researcher. She is currently working in the group of Professor C. Fuganti, devoting her main research interests to the enzyme-mediated synthesis of chiral fragrant substances and drugs.

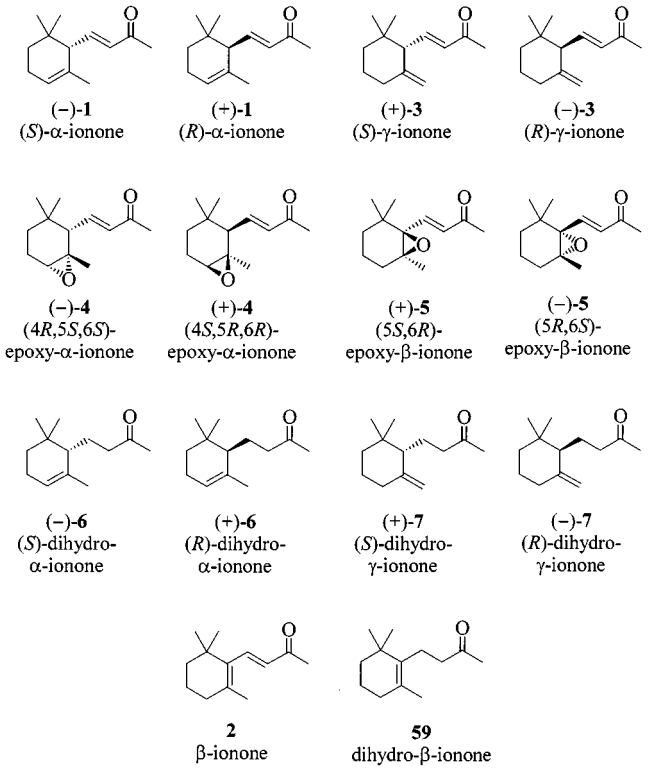
Claudio Fuganti (top right) was born in 1938. After two years of postdoctoral work on alkaloid biosynthesis with Prof. A. R. Battersby in the United Kingdom, he started his independent research activity at the Politecnico di Milano in 1969, working on different aspects of bioorganic chemistry. Current interests include the use of enzymes in organic synthesis, the biogeneration of flavor materials, and the determination of their origin by means of stable isotope analysis. From 1979 he has held the Chair of Organic Chemistry at the Politecnico di Milano.

Stefano Serra (bottom left), born in 1970, received his laurea (1995) at the University of Pavia, working on the synthesis of natural products with Professor G. Vidari. In 1996 he joined the group of Professor Fuganti and in 2000 he received his Ph.D. degree on the development of new synthetic methods for the preparation of flavor and fragrance ingredients. Currently he is working in the same group, devoting his research activity to the enantioselective synthesis of chiral compounds.

Philip Kraft (bottom right), born in 1969, received his diploma and doctorate degree (summa cum laude) from the University of Kiel (Germany), carrying out syntheses of medium- and large-ring compounds under the supervision of Professor W. Tochtermann. From 1990−1994 he received a scholarship from the Studienstiftung des Deutschen Volkes and from 1994−1996 a Chemiefond Stipendium des Verbandes der Chemischen Industrie. He joined Givaudan in Dübendorf in 1996, and is currently group leader in the Organic Synthesis of Fragrance Ingredients. His research activity centers on the synthesis and structure-odor correlation of floral odorants and musks.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

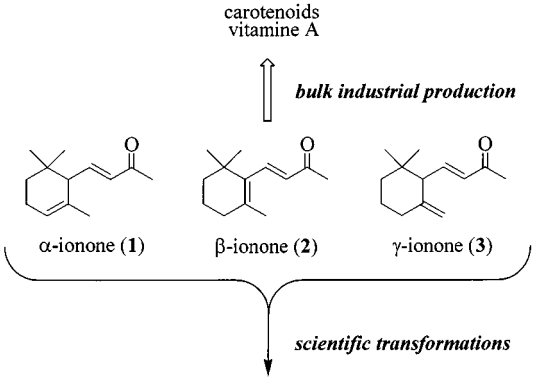
  1434−193X/02/0306−0967 $ 17.50+.50/0



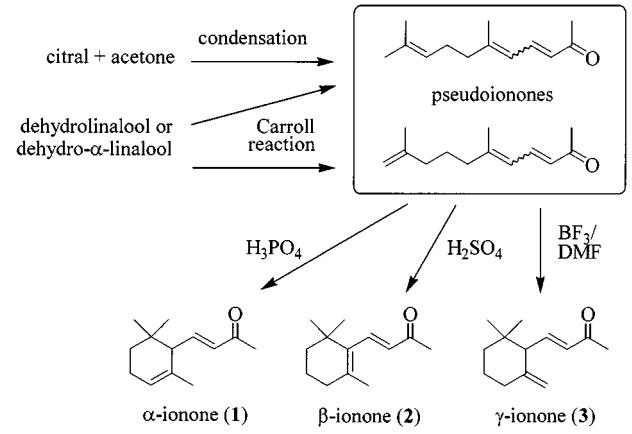
when sulfuric acid is employed. Use of a Lewis acid such as $BF_3{\cdot}Et_2O$ and a dipolar aprotic solvent, on the other hand, mainly affords γ-ionone (**3**).[4]

Starting in the second half of the 20th century, new processes for the preparation of pseudoionones were developed. In particular, the Carroll rearrangements[5] of the acetoacetyl esters of dehydrolinalool and dehydro-α-linalool became the most important synthetic routes to pseudoionones. The dehydrolinalool isomers are available on industrial scales through the addition of acetylene to 6-methylhept-5-en-2-one or 6-methylhept-6-en-2-one, which are in turn obtained from simple industrial building blocks such as isobutene, isoprene, and acetone.[6] These improvements allowed ionones to be synthesized from inexpensive petrochemical resources, at low cost, and in bulk quantities.

In spite of the availability of all double-bond isomers, only β-ionone (**2**) is widely used nowadays in industrial applications, as a starting material for the synthesis of vitamin A, for example (Scheme 2). This predominance of **2** in the chemical industry is compensated for by a great number of scientific chemical transformations that require ionone isomers **1** and **3** as starting materials. Several syntheses of natural products (such as carotenoids, edulan derivatives, and theaspiranes) as well as various odoriferous substances (such as Ambrox®, or a powerful minor constituent of Iso E Super®) made use of ionones **1** and **3** or their epoxy and dihydro derivatives **4**−**7** as starting materials. The synthesis of these compounds in enantiomerically pure forms requires optically active starting materials; and so the enantioselective preparation of these chiral building blocks (**1**, **3**−**7**) has become an important research topic, especially in the last decades. Moreover, compounds **1**−**7** are themselves precious fragrant substances, and their olfactory properties are also reviewed.



Scheme 2



Scheme 1

α-Ionone

(+)-α-Ionone (**1**) occurs quite abundantly, and was first found in the essence concrete of *Boronia megastima* Nees,[7] in costus root oil (*Aplotaxis lappa* Decaisne),[8] in the concrete of *Acacia farnesiana* Willd.,[9,10] and in raspberries (*Rubus idaeus* L.),[11] before finally being discovered in *Viola odorata* Linneus by Uhde and Ohloff.[12] Its absolute configuration was determined by correlation with manool.[13] Two different approaches for the preparation of (+)- and (−)-**1** have been reported in the literature, the resolution of the racemate[14−20] and enantioselective syntheses.[21,22]

a) Resolution of the Racemate

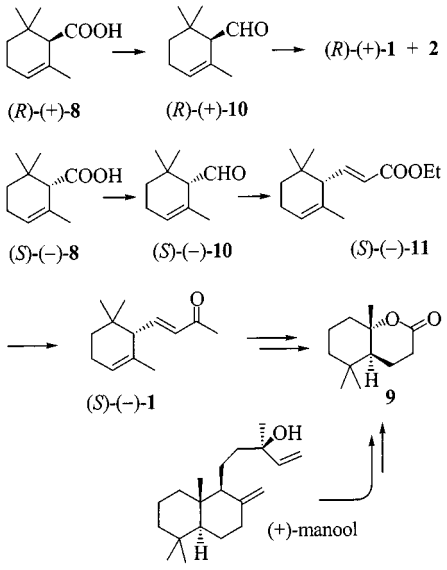
Classical Optical Resolution

(±)-α-Ionone was first resolved in 1943 by Sobotka et al.,[14] by fractional crystallization of suitable diastereoisomeric derivatives. Compound (±)-**1** was converted into a mixture of D- and L-α-ionone L-menthylhydrazones, which crystallized readily. Still, these were difficult to separate, because of only slight differences in their solubilities. However, the less soluble hydrazone was finally obtained in pure form after ten recrystallizations. The other diastereoisomer was obtained in modest yield and with lower optical purity after "*twice as many recrystallizations*". The procedure permitted the recovery of (−)-**1** from the less soluble hydrazone, and of (+)-**1** from the more soluble diastereoisomer, with $[\alpha]_D^{20}$ values of −406 and +347, respectively.

A few years later, in 1947, Naves[15] investigated the optical resolution of α-ionone by derivatization with menthyl aminocarbamate. This work was prompted by the fact that Naves had found (+)-α-ionone in the essence concrete of *Boronia megastigma* Nees.[7] He noticed that during the hydrolysis of the crystalline diastereoisomers in the presence of phthalic acid, oxalic acid, or sulfuric acid, isomerization to β-ionone took place rather than racemization. The phenomenon was verified by UV spectroscopy, and occurred to a greater extent in the recovery of D-α-ionone. He therefore considered purifying the obtained ionones by conversion into the corresponding semicarbazones, which should be hydrolyzable under milder conditions. The samples of (+)- and (−)-**1** he obtained in this way had $[\alpha]_D^{20}$ values of +401 and −408, respectively (c = 4, PhH). Naves also hydrogenated (−)-α-ionone [(−)-**1**] to dihydro- and tetrahydroionones, and characterized them by their semicarbazone and 2,4-dinitrophenylhydrazone derivatives.

The same procedure was employed by Eugster et al.[16] in the preparation of (+)- and (−)-α-ionones, required as precursors in the synthesis of the corresponding ε-carotene enantiomers. Recrystallizations of the L-menthyl hydrazones afforded (+)-**1** with $[\alpha]_D^{20}$ = +415 and (−)-**1** with $[\alpha]_D^{20}$ = −403 (EtOH). A higher optical rotation {$[\alpha]_D^{20}$ = +421, EtOH} was assigned to (+)-**1** by Eugster[17] in a later work. To avoid losses in optical activity, he performed the hydrolysis of the (+)-hydrazone in acetic acid in the presence of pyruvic acid. Unlike Naves, he attributed this decrease in the optical rotation to racemization under more strongly acidic conditions. Once optimized, this optical resolution process was exploited for the preparation of (+)- and (−)-α-ionone (**1**), starting materials in the synthesis of various carotenoid derivatives.[17,23]

In work[13,18] to assign the absolute configurations of the α-ionone enantiomers, (*S*)- and (*R*)-**1** were prepared from (*S*)- and (*R*)-α-cyclogeranic acid (**8**), and correlated to (+)- and (−)-manool, respectively (Scheme 3), through the key intermediate **9**, which was prepared both from α-ionone and from manool. The compounds (+)- and (−)-**8** were obtained by classical resolution of the racemate by fractional crystallization of their cinchonine salts.[24] All these reactions were performed with the express intention of correlating the absolute configurations, and thus had no preparative pretences. In the first publication,[18] (+)-**8** was reduced with $LiAlH_4$ to provide the corresponding alcohol, which was then submitted to a modified Oppenauer oxidation to give (+)-(*R*)-α-cyclocitral (**10**). This was then condensed with acetone to afford a mixture of β-ionone and (+)-α-ionone. The latter was recovered by preparative GC and had an $[\alpha]_D^{20}$ value of +33 (EtOH). In a later work by Eugster et al.,[13] an optimized procedure for the conversion of (−)-α-cyclocitral into (−)-α-ionone was described. This consisted of treatment of (−)-**10** with ethyl diethylphosphonoacetate, to afford the corresponding unsaturated ester **11**. This was then treated with methyllithium to furnish (−)-α-ionone, with an $[\alpha]_D^{20}$ value of −249.5 (EtOH). In both publications,[13,18] an isomerization of (−)-γ-ionone [(−)-**3**] into α-ionone was also described. Treatment of (−)-**3** with 85% phosphoric acid at room temperature yielded a mixture of 35% β-ionone and ca. 60% (−)-α-ionone. The latter was separated by preparative GC and had an $[\alpha]_D^{20}$ value of −17 (EtOH).

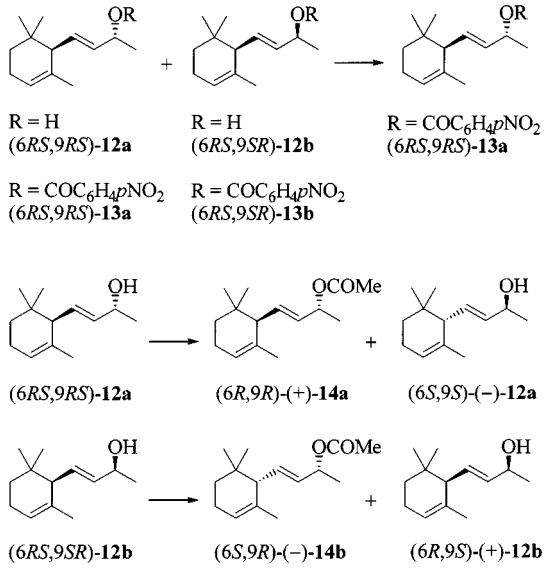


Scheme 3

Kinetic Resolution

A few years ago we started a research project directed towards the synthesis of enantiomerically pure fragrant substances from commercially available racemates by enzymatic methods. Our first objective was the preparation of (+)- and (−)-α-ionone[19] by kinetic enzymatic resolution of the easily accessible α-ionol (**12**), followed by MnO_2 oxidation. Commercial (±)-α-ionone was reduced with $NaBH_4$ to afford a 1:1 mixture of the two racemic diastereoisomeric α-ionols (*RS*,*RS*)-**12a** and (*RS*,*SR*)-**12b** (Scheme 4). In a first approach, (±)-**12a** and (±)-**12b** were converted into the crystalline 4-nitrobenzoates (±)-**13a** and (±)-**13b**, which were separated by fractional crystallization. Five crystallizations from hexane provided the racemic dia-

stereoisomer (*RS*,*RS*)-**13a** in 15−18% yield. The other racemic diastereoisomer (*RS*,*SR*)-**13b** could not be recovered from the mother liquors. It was thus synthesized from (*RS*,*RS*)-**13a** by saponification with methanolic potassium hydroxide and subsequent Mitsunobu esterification.

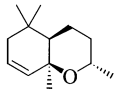


Scheme 4

The two diastereoisomeric α-ionols recovered from (*RS*,*RS*)-**13a** and (*RS*,*SR*)-**13b** were then separately submitted to enzyme-mediated acetylation (Scheme 4). Lipase PS mediated esterification of (*RS*,*RS*)-**12a** provided enantiomerically pure (*R*,*R*)-**14a**, and the remaining unmodified alcohol (*S*,*S*)-**12a** also showed high enantiomeric purity. Acetate (*S*,*R*)-**14b** and the corresponding alcohol (*R*,*S*)-**12b** were obtained upon lipase PS mediated esterification of the racemic diastereoisomer **12b**. Alkaline hydrolysis of the acetates (*R*,*R*)-**14a** and (*S*,*R*)-**14b** provided enantiomerically pure (*R*,*R*)-**12a** and (*S*,*R*)-**12b**, which were oxidized with MnO_2 to afford (*R*)-(+)- and (*S*)-(−)-α-ionone (**1**) with *ee* values of 98% and 97% (GC), respectively, in ca. 35% yield from the single racemic diastereoisomer. The enantiomeric α-ionones possessed $[\alpha]_D^{20}$ values of +420 and −418 (c = 1, $CHCl_3$), respectively. Oxidation of the recovered alcohols (*S*,*S*)-**12a** and (*R*,*S*)-**12b** provided (*S*)-(−)- and (*R*)-(+)-**1** in 87−93% *ee* values.

We also developed an alternative procedure consisting of the enzymatic hydrolysis of the two racemic acetate diastereoisomers (*RS*,*RS*)-**14a** and (*RS*,*SR*)-**14b** with *porcine pancreatic* lipase (PPL) in water at pH = 7.5. The stereoisomer (*S*,*R*)-**14b** was preferentially hydrolyzed to furnish (*S*,*R*)-**12b** with 98% *ee* and 55% *de*. The mixture of the unchanged acetates (*R*,*R*)-**14a**, (*S*,*S*)-**14a**, and (*R*,*S*)-**14b** was saponified with KOH in MeOH, and the recovered alcohols were submitted to lipase PS mediated acetylation. Acetate (*R*,*R*)-**14a** was thus obtained in 99% *ee* and 66% *de* [(*R*,*R*)-**14a**/(*R*,*S*)-**14b** = 88:22]. Two subsequent enzyme-catalyzed reactions afforded an enantiomerically pure acetate (*R*,*R*)-**14a**, which was obtained in diastereomerically pure form by two crystallizations of the corresponding 4-nitrobenzoates from hexane. Saponification and oxidation of the corresponding alcohol (6*R*,9*R*)-**12a** with MnO_2 provided enantiomerically pure (*R*)-(+)-α-ionone [(*R*)-(+)-**1**].[19]

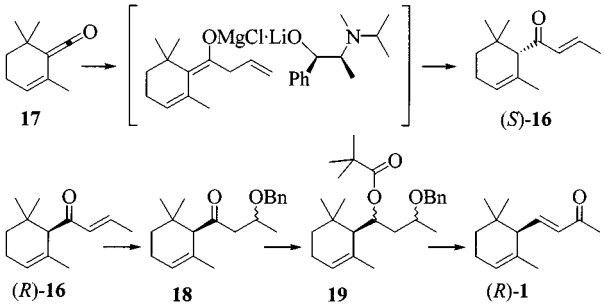
An alternative kinetic resolution of racemic α-ionone was attempted by Sugai et. al. in their synthetic studies on (−)-dihydroedulan II (**15**).[20] They accomplished the biochemical reduction of (±)-**1** with *Pichia miso* IAM 4682, which provided (*R*)-**1** and α-ionol [(*S*,*R*)-**12b**]. After MnO_2 oxidation, their sample of (*S*)-α-ionone had an $[\alpha]_D^{20}$ value of −220 (c = 1.06, EtOH), which corresponds to 55% *ee*. The unchanged (*R*)-(+)-α-ionone had an optical purity of just 5% {$[\alpha]_D^{20}$ = 20 (c = 1.06, EtOH)}, even when yeast reduction was carried out with a longer incubation period.



15

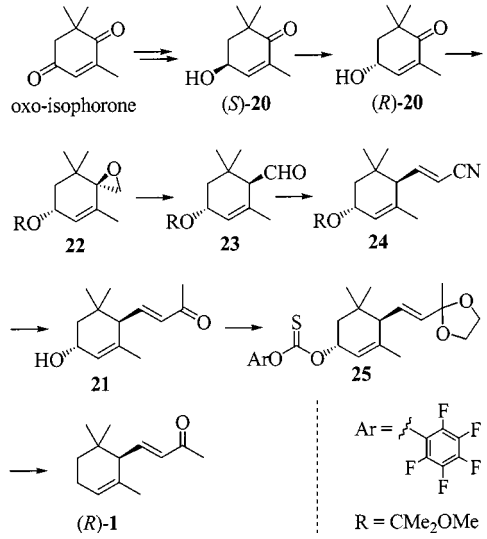
b) Enantioselective Syntheses

In order to prepare the pure α-ionone enantiomers for olfactory evaluation and for use as intermediates in the synthesis of other odorants, Fehr and Guntern[21] devised a method for the conversion of (*R*)- and (*S*)-α-damascone (**16**) into (*R*)- and (*S*)-α-ionone (**1**). Both enantiomers of **16** are accessible from ketene **17** by enantioselective protonation of an intermediate enolate (Scheme 5).[25] Addition of allylmagnesium chloride to ketene **17** was performed in the presence of the lithium salt of (+)- or (−)-*N*-isopropylephedrine. Once the enolate had been formed, additional chiral auxiliary was added prior to quenching of the reaction with HCl, affording (*R*)-(+)- and (*S*)-(−)-**16**, respectively. Michael addition of benzyl alcohol in the presence of 1,1,3,3-tetramethylguanidine then permitted (*R*)-(+)-damascone [(*R*)-(+)-**16**] to be transformed into a 7:3 mixture of **18** and the starting material. Compound **18** was then reduced and esterified by treatment with LDA and *t*BuCOCl to afford pivalate **19**. This was subjected to debenzylation, Jones oxidation, and base-catalyzed thermal elimination [$N(C_2H_4OH)_3$, 140 °C] to provide (*R*)-(+)-α-ionone in 99% *ee* {$[\alpha]_D^{20}$ = 407 (c = 0.04, $CHCl_3$)}. By the same procedure, (*S*)-(−)-damascone was transformed into (*S*)-(−)-α-ionone [(*S*)-(−)-**1**], also in 99% *ee* {$[\alpha]_D^{20}$ = −431 (c = 0.035, $CHCl_3$)}.



Scheme 5

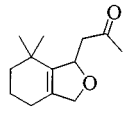
Pfander and Semadeni employed (*S*)-(−)-phorenol (**20**, 99% *ee*) as starting material in their synthesis of optically active (*R*)-(+)-α-ionone.[22] Compound (*S*)-**20** was prepared by a synthetic path involving Baker's yeast reduction of oxoisophorone[26,27] to produce an optically active starting material. This was then converted into (3*R*,6*R*)-3-hydroxy-α-ionone (**21**) according to a procedure by Mayer and Rüttimann (Scheme 6),[27] with the difference that the configuration at C-4 of **20** was inverted by Mitsunobu reaction rather than by acetate displacement. The hydroxy group was protected and the carbonyl function was converted into an oxirane ring with dimethylsulfonium methylide. The resulting epoxide **22** was then stereoselectively opened with catalytic amounts of $Me_2EtCOMgBr$, to afford the unstable aldehyde **23**. A Wittig−Horner−Emmons reaction between compound **23** and diethylphosphonoacetonitrile afforded **24.** Alkylation with MeLi and subsequent hydrolysis/deprotection furnished hydroxyionone **21**. Reductive deoxygenation of the *O*-pentafluorophenyl thiocarbonate derivative **25** with Bu_3SnH and AIBN according to a procedure reported by Barton[28] afforded (*R*)-(+)-α-ionone in 26% yield from **21**, after protection/deprotection of the carbonyl group. Despite the use of enantiomerically pure (*R*)-**20,** the prepared sample of (+)-**1** had an $[\alpha]_D^{20}$ value of only +345 (*c* = 0.52, EtOH), which corresponds to 85% *ee*. By the same route, (*S*)-(−)-α-ionone was prepared from (*S*)-**20**, but with a mere 45% *ee* {$[\alpha]_D^{20} = -124$ (*c* = 0.32, EtOH)}.



Scheme 6

γ-Ionone

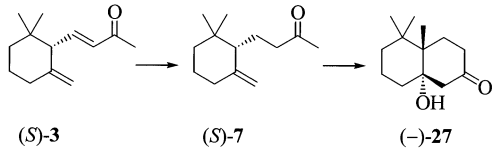
In terms of its natural occurrence, γ-ionone (**3**) is by far more exotic than α-ionone. It had been reported as a constituent of Qi Li Xiang rose oil (Rosa bankisa normalis),[29] but was only found quite recently as a constituent of the headspace of a living flower, by Kaiser.[30] The headspace of a previously undescribed Gongora orchid (Gongora 220/74, Dr. Gerlach) was comprised of 7(11)-epoxymegastigma-5(6)-en-9-one (**26**) (78%), which could be regarded as a biochemical precursor of γ-ionone.



26
(*78% in Gongora 220/74, Dr. Gerlach*)

Indeed, this headspace sample contained 0.02% of γ-ionone, but its optical activity was not investigated. Enantiopure samples of (+)- and (−)-γ-ionone have so far been prepared only by resolution techniques, classical resolution by fractional crystallization of menthyl derivatives[13,18,31] and kinetic resolution by enzymes.[32]

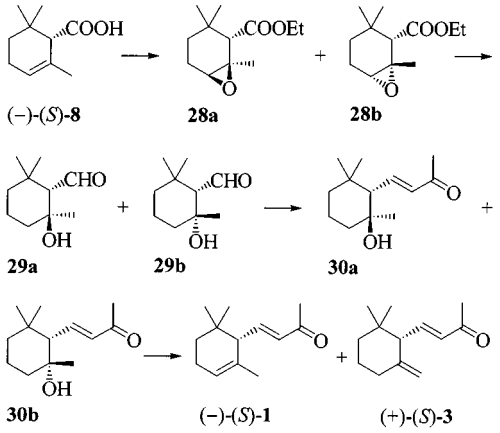
The first characterization of the γ-ionone enantiomers (**3**) dates back to 1969;[18] these initial data were completed by another publication by Ohloff et al.[13] A sample of (−)-γ-ionone [(−)-**3**] with an $[\alpha]_D^{20}$ value of −4 ($CHCl_3$) {$[\alpha]_D^{20}$ = −0.9 (neat)} was prepared by Sobotka's procedure for the resolution of α-ionone (vide supra). Compound (−)-**3** was isomerized in phosphoric acid to provide a mixture of β-ionone and (*S*)-(−)-α-ionone, and was also reduced to the (−)-dihydro-γ-ionone [(−)-**7**] {$[\alpha]_D^{20} = -1.5$, $CHCl_3$}, which was converted into (−)-hydroxydecalone **27**, the absolute configuration of which was known (Scheme 7).[33] The (*S*) configuration was accordingly attributed to (−)-**3** and (−)-**7**. Ohloff himself corrected the absolute configuration of dihydro-γ-ionone in 1977,[34] establishing that (+)-**7** had the (*S*) configuration (vide infra).



Scheme 7

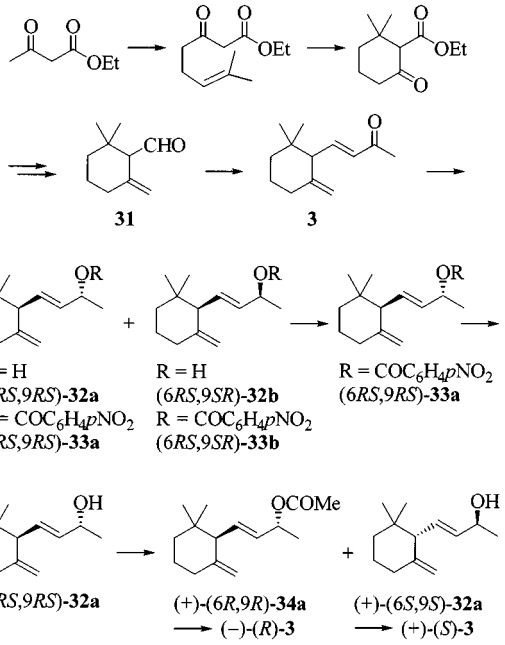
In 1983, Oritani and Yamashita[31] prepared γ-ionone from optically active cyclogeranic acid (Scheme 8), and found that (*S*)-γ-ionone had a positive $[\alpha]_D^{20}$ value. Optical resolution of racemic α-cyclogeranic acid with (−)- and (+)-α-methylbenzylamine provided (+)-(*R*)- and (−)-(*S*)-α-cyclogeranic acid **8**. The absolute configuration of **8** had been established by Ohloff[13,18] by transformation of (−)-α-cyclogeranic acid into (−)-α-ionone, the configuration of which was known to be (*S*) from chemical correlation with (+)-manool. Compound (*S*)-**8** was esterified with diazomethane, and epoxidized with 3-chloroperbenzoic acid to provide a mixture of *trans*- and *cis*-epoxy esters **28a** and **28b**, the latter being the prevailing diastereoisomer. The **28a/b** mixture was reduced with LAH and oxidized with PCC to give the hydroxy aldehydes **29a/b**. A Wittig reaction then afforded a mixture of the two diastereoisomeric hydroxy ketones **30a/b**, which was acetylated and subsequently pyrolyzed at 480 °C to furnish a mixture of (*S*)-γ-ionone (from **30a**) and (*S*)-α-ionone (from **30b**). These two ionones were separated by column chromatography on silica gel

(1.5% $AgNO_3$). The (*S*)-γ-ionone thus prepared possessed an $[\alpha]_D^{20}$ value of +19.5 (EtOH), and so the (*S*) configuration was established for (+)-γ-ionone.



Scheme 8

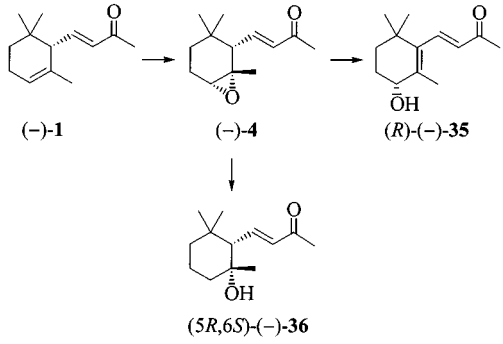
We recently reported on the enzyme-mediated kinetic resolution of racemic γ-ionone.[32] The key step was a Wittig reaction between γ-cyclocitral (**31**) and (acetylmethylene)triphenylphosphorane (Scheme 9), which provided racemic **3** and a small amount of isomerized β-cyclocitral. Notably, γ-ionone was the only adduct produced, even though β-cyclocitral was formed under the same reaction conditions. We then applied the strategy employed in the resolution of α-ionone.[19] $NaBH_4$ reduction of racemic **3** afforded a 1:1 mixture of the two racemic diastereoisomers (*RS*,*RS*)-**32a** and (*RS*,*SR*)-**32b**, which was converted into the corresponding 4-nitrobenzoates **33a** and **33b** to allow separation by fractional crystallization. Three crystallizations from hexane afforded (*RS*,*RS*)-**33a** (27% overall yield, 98% *de*), which was hydrolyzed with methanolic KOH to provide diastereomerically pure **32a**. The latter was treated with vinyl acetate in *t*BuOMe in the presence of lipase PS (*Amano*) to afford acetate (*R*,*R*)-**34a** and unchanged alcohol (*S*,*S*)-**32a**. The acetate (*R*,*R*)-**34a** was then hydrolyzed with methanolic KOH, and the resulting alcohol was oxidized with MnO_2 in refluxing $CHCl_3$ to furnish enantiomerically pure (−)-γ-ionone [(−)-**3**] {99% *ee*, $[\alpha]_D^{20} = -37.4$ (*c* = 1, $CHCl_3$), $[\alpha]_D^{20} = -30.9$ (*c* = 0.5, EtOH)}. Oxidation of (*S*,*S*)-**32** provided enantiomerically pure (+)-γ-ionone [(+)-**3**] {98% *ee*, $[\alpha]_D^{20} = +36.2$ (*c* = 1, $CHCl_3$), $[\alpha]_D^{20} = +30.2$ (*c* = 0.5, EtOH)}.



Scheme 9

4,5-Epoxy-4,5-dihydro-α-ionone

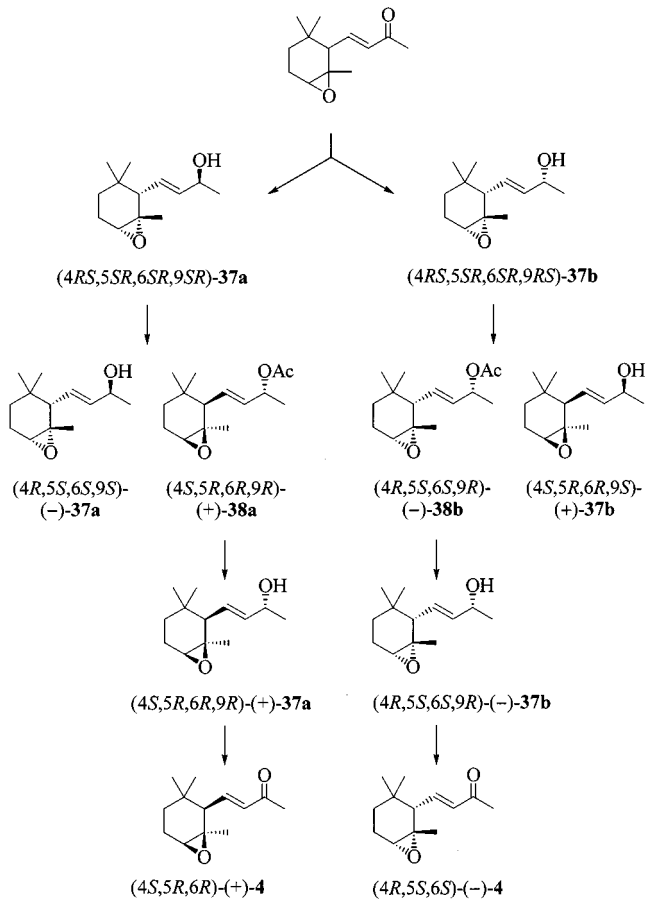
4,5-Epoxy-4,5-dihydro-α-ionone (**4**) is the main product of the treatment of α-ionone with 3-chloroperbenzoic acid,[35] and it was employed as a starting material in the synthesis of racemic γ-ionone by Ohloff and Mignat in 1962.[36] An optically active isomer, (−)-**4**, was first described by Eugster et al.[37] in 1980, in the context of the synthesis of (*R*)-(−)-4-hydroxy-β-ionone (**35**) and (5*R*,6*S*)-(−)-5-hydroxy-4,5-dihydro-α-ionone (**36**) from (*S*)-(−)-α-ionone [(*S*)-(−)-**1**] (Scheme 10). The latter compound was prepared by fractional crystallization of its menthylhydrazone from EtOH, and hydrolysis with pyruvic acid in AcOH. On treatment with monoperphthalic acid, (*S*)-(−)-α-ionone yielded (4*R*,5*S*,6*S*)-(−)-**4** with an $[\alpha]_D^{20}$ value of −208 (*c* = 0.60, EtOH) {$[\alpha]_D^{20} = -210$ (*c* = 0.59, $CHCl_3$)}. Treatment of (−)-**4** with sodium methoxide furnished (−)-**35**, while reduction with DIBAH afforded the tertiary alcohol (−)-**36**. Both (−)-**4** and (−)-**35** were used as key intermediates in the enantioselective synthesis and stereochemical assignment of carotenoid derivatives (see, for instance, refs.[38,39]).



Scheme 10

In 1999 we reported on the lipase-mediated kinetic resolution of epoxy-α-ionols **37a** and **37b** (Scheme 11) to give (+)- and (−)-**4**, from which (*R*)-(+)- and (*S*)-(−)-α-ionone can be prepared.[40] Treatment of α-ionone (**1**) with 3-chloroperbenzoic acid at 0 °C gave a 5:1 mixture of racemic *cis*-epoxy-α-ionone and racemic *trans*-epoxy-α-ionone, which was reduced with $NaBH_4$. The racemic diastereoisomers of

cis-epoxy-α-ionol **37a** and **37b** were separated by column chromatography.



Scheme 11

The more rapidly eluting *rac*-**37a** contained 6% of *trans*-epoxy-α-ionol (84% *de*[41]), and was submitted to lipase PS mediated acetylation to provide the enantiopure acetate (+)-**38a** (84% *de*) and unchanged alcohol (−)-**37a** in 47% *ee* and 84% *de*. Saponification of (+)-**38a** with methanolic KOH afforded enantiopure (+)-**37a** (84% *de*), which was oxidized with MnO_2 to provide (+)-4,5-epoxy-α-ionone [(+)-**4**] {> 99% *ee*, 64% *de*, $[\alpha]_D^{20}$ = 141 (*c* = 1.3, EtOH)}. (+)-4,5-Epoxy-α-ionone [(+)-**4**] was then obtained in diastereoisomerically pure form by silica gel column chromatography {$[\alpha]_D^{20}$ = +207 (*c* = 1.2, EtOH)}. A further extension of this work was the conversion of the dextrorotatory *cis*-epoxy-α-ionone {$[\alpha]_D^{20}$ = +141} into (*R*)-(+)-α-ionone by treatment with Me_3SiCl and NaI in MeCN.[42] The resulting (*R*)-(+)-**1** was found to be enantiomerically pure by chiral GC analysis, which established that the *trans*-epoxide by-product that had lowered the *diastereomeric excess* of (+)-**4** had the same configuration at C-6.

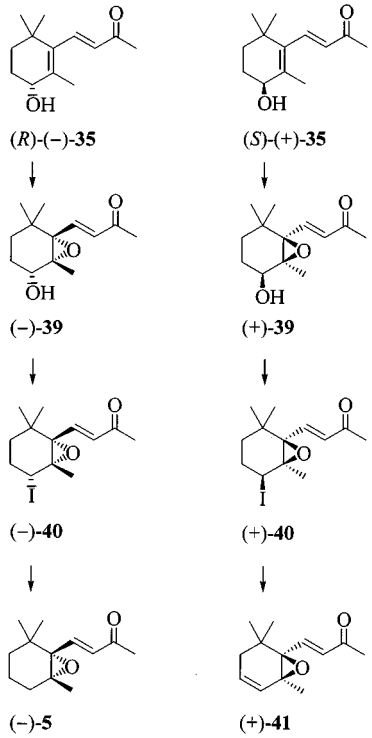
The subsequently eluting diastereoisomer **37b** was contaminated with the corresponding *trans*-epoxide stereoisomer (66% *de*). Lipase PS mediated acetylation of **37b** allowed us to obtain the enantiopure acetate (−)-**38b** in 67% *de*, together with enantiomerically enriched alcohol (+)-**37b** (91% *ee*, 65% *de*). Saponification of (−)-**38b** then afforded *cis*-epoxy-α-ionol (−)-**37b** (> 99% *ee*, 88% *de*), which was converted into enantiopure (−)-**4** (89% *de*) {$[\alpha]_D^{20}$ = −199 (*c* = 0.61, $CHCl_3$)} analogously to the synthesis of its enantiomer. An enantiopure sample of (*S*)-(−)-ionone (**1**) was also prepared from levorotatory **4** {$[\alpha]_D^{20}$ = −199}, which also makes this route attractive for the synthesis of the α-ionone (**1**) enantiomers.

5,6-Epoxy-5,6-dihydro-β-ionone

Epoxy-β-ionone **5** has been found in nature in tomatoes,[43] carrots,[44] raspberries,[45] black tea,[46] and tobacco,[47] and has been prepared in enantiomerically enriched forms both by resolution[40,48,49] and by enantioselective synthesis.[50]

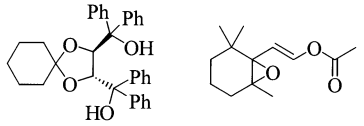
a) Resolution of the Racemate

Optically active 5,6-epoxy-5,6-dihydro-β-ionones were prepared for the first time in 1981, by Eugster et al.,[48] and their absolute configurations were determined from the starting materials, the optically active α-ionones (**1**). The (−)- and (+)-4-hydroxy-β-ionones **35** were prepared[37] from the corresponding *cis*-epoxy-α-ionones, and submitted to Sharpless oxidation to provide *cis*-hydroxyoxirane **39** (Scheme 12). Compounds (−)- and (+)-**39** were then converted into the iodides (−)- and (+)-**40** by treatment with TsCl in pyridine, and nucleophilic substitution with NaI in DME. Enantiomer (−)-**40** was reduced to (−)-**5** {$[\alpha]_D^{20}$ = −85 (*c* = 0.638, EtOH)} by treatment with $NaBH_3CN$ in HMPT at 60 °C, while (+)-**40** was converted into (+)-**41** by dehydrohalogenation with DBN in DME. (−)-Epoxy-β-ionone [(−)-**5**] was employed by Eugster et al. in the synthesis of epoxy carotenoids.[51]



Scheme 12

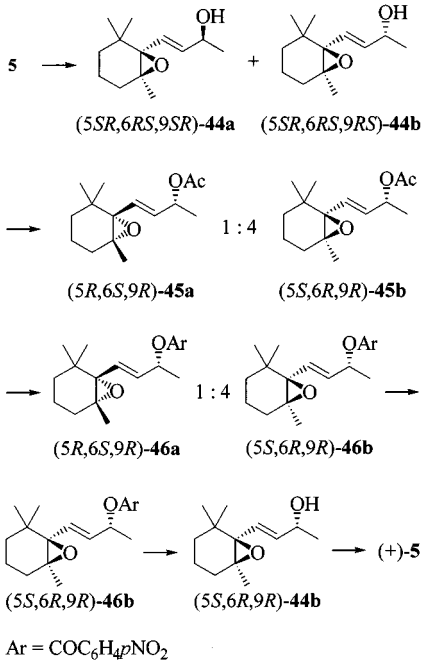
In 1990, a solid-state kinetic resolution of epoxy-β-ionone was reported by Toda et al.[49] A 1:1 inclusion complex between racemic β-ionone and the optically active host (−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[5.4]decane (**42**) was treated with 3-chloroperbenzoic acid. When equimolar amounts of peracid were employed, only racemic **5** was obtained, but in the presence of 2−3 equiv. of peracid, (+)-**5** was recovered together with (−)-**43**. However, only racemic **43** was obtained with 4 equiv. of 3-chloroperbenzoic acid.



(−)-**42** **43**

These results were interpreted in terms of an enantioselective inclusion complex of (+)-**5** and the host (−)-**42**, with the remaining uncomplexed (−)-**5** being further oxidized to (−)-**43**. As the oxidation of (−)-**5** proceeded, the optical purity of (+)-**5** increased; however, only *rac*-(±)-**43** was recovered when the oxidation was complete.

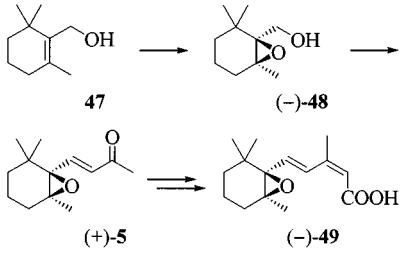
In 1999, we reported[40] the enzyme-mediated kinetic resolution of racemic epoxy-β-ionone. A 1:1 mixture of the two racemic 5,6-epoxy-5,6-dihydro-β-ionol diastereoisomers **44a** and **44b** was prepared by treatment of racemic epoxy-β-ionone (**5**) with $NaBH_4$ (Scheme 13). However, these two diastereoisomers could not be separated by column chromatography, as had been possible for the epoxy-α-ionols **37a** and **37b**. PPL-mediated acetylation of **44a/b** was therefore carried out, and this furnished a 4:1 mixture of the enantiopure acetates **45b** and **45a**. These were hydrolyzed in methanolic KOH and transformed into the corresponding 4-nitrobenzoates (**46b/46a** = 4:1). Crystallization from MeOH afforded diastereoisomerically pure **46b**, which was converted into the corresponding alcohol **44b** by saponification. Oxidation with MnO_2 then afforded the enantiopure dextrorotatory epoxy-β-ionone **5** {$[\alpha]_D^{20}$ = +99 (c = 0.66, $CHCl_3$)}.



Scheme 13

b) Enantioselective Synthesis

A completely different approach for the preparation of these ionone derivatives was reported by Oritani and Yamashita in 1983 (Scheme 14).[50] Katsuki−Sharpless epoxidation of β-cyclogeraniol **47** with *tert*-butyl hydroperoxide, titanium tetraisopropoxide, and (+)-diethyl tartrate provided (−)-(1*S*,2*S*)-(1,2-epoxy-2,6,6-trimethyl-1-cyclohexyl)-methanol [(−)-**48**] in 95% *ee*. Similarly, the asymmetric epoxidation of **47** in the presence of (−)-diethyl tartrate afforded (+)-**48** with the same enantiomeric excess. Swern oxidation of (+)- and (−)-**48**, followed by a Wittig reaction with $MeCOCH{=}PPh_3$, afforded both epoxy-β-ionone enantiomers, (+)-**5** with an $[\alpha]_D^{20}$ value of 104.7 (c = 0.7, $CHCl_3$) and (−)-**5** with an $[\alpha]_D^{20}$ value of −103 (c = 0.7, $CHCl_3$). These were employed in the synthesis of the two enantiomers of (2*Z*,4*E*)-5-(1′,2′-epoxy-2′,6′,6′-trimethylcyclohexyl)-3-methyl-2,4-pentadienoic acid (**49**), the plant growth inhibitory activities of which were to be evaluated.

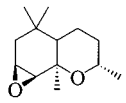


Scheme 14

Dihydro-α-ionone

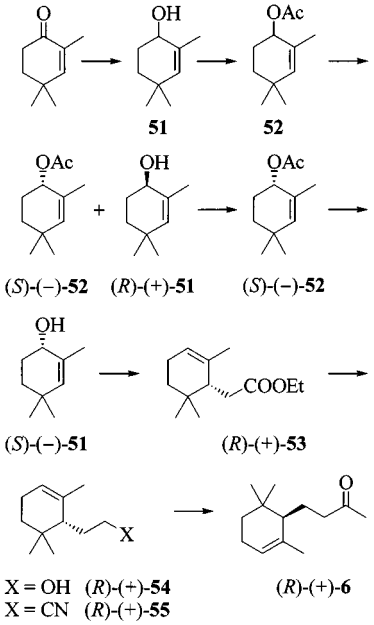
The dextrorotatory enantiomer of dihydro-α-ionone [(*R*)-(+)-**6**] was isolated from costus root oil (*Aplotaxis lappa* Decaisne, *Sassaurea lappa* Clarke);[8,52] it had an $[\alpha]_D^{20}$ value of +167. It was also found in violet flower oil, with a reported $[\alpha]_D^{20}$ value of +160.[12]

An (*S*)-configured enantiomer of **6** was an intermediate in the assignment[13,18] of the absolute configuration of (*S*)-(−)-α-ionone by correlation with manool (vide supra). This sample of **6** had a negative $[\alpha]_D^{20}$ value of −125 (EtOH),[13,18] and so the (*S*) configuration was deduced for (−)-**6**. A sample of (*R*)-(+)-**6** with only 17% *ee* {$[\alpha]_D^{20}$ = +24.9 (c = 0.555, EtOH)} was obtained by Francke et al.[53] by selective hydrogenation of a (*R*)-α-ionone sample of 18.7% *ee* with Pd/C in alkaline solution. It was used as an intermediate in the synthesis of epoxytetrahydroedulan (**50**), a terpenoid from the hairpencils of *Euploea* (Lep: Danainae) butterflies.



50

In 1991, Mori et al.[54] described the conversion of the chiral building block (*S*)-**51** into enantiomerically pure (*R*)-(+)-dihydro-α-ionone [(*R*)-(+)-**6**] (Scheme 15). 2,4,4-Trimethyl-2-cyclohexenone was reduced with either LAH or $NaBH_4/CeCl_3$ to provide (±)-**51**, which was acetylated to give (±)-**52** and submitted to enzymatic hydrolysis. PLE treatment in 0.1 M phosphate buffer with 20% MeOH at pH = 7.5 afforded (+)-(*R*)-**51** (100% *ee*) and (−)-(*S*)-**52** (41% *ee*) after 65.5 h at −10 °C. The enantiomeric excess of acetate (−)-**52** was increased to 100% by means of a further PLE hydrolysis, followed by crystallization of the corresponding 3,5-dinitrobenzoate derivative. An *ortho*-ester Claisen rearrangement of (−)-**51** provided (+)-**53**, which was reduced with LAH to (+)-**54**. This last compound was elongated by one carbon atom by cyanide substitution of the tosylate. A Grignard reaction between the resulting nitrile (*R*)-(+)-**55** and MeMgI provided, after acidic workup, (*R*)-(+)-**6** with an $[\alpha]_D^{20}$ value of +138.4 (*c* = 0.615, EtOH).

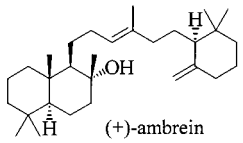


Scheme 15

Dihydro-γ-ionone

(+)-Dihydro-γ-ionone (**7**) {$[\alpha]_D^{20}$ = +12.8 (neat)} was first isolated by Ruzicka[55] from ambergris, one of the most precious raw materials of perfumery. The olfactory active components of ambergris make up less than 0.3% of the material, and are formed by the autoxidative degradation of the tricyclic triterpene ambrein. Although (+)-dihydro-γ-ionone [(+)-**7**] does not contribute very much to the characteristic odor of ambergris, it has been the object of several studies.[56] In addition, it has also been found in the hexane extracts of *Bellardia trixago* L.[57]

Ohloff first assigned the (*S*) configuration to levorotatory dihydro-γ-ionone [(−)-(**7**)], prepared by Raney-Ni reduction of γ-ionone (**3**) in MeOH at room temperature,[13,18] but corrected his assignment a few years later.[34] On treatment of natural (+)-ambrein with potassium permanganate, he obtained (*S*)-dihydro-γ-ionone [(+)-**7**], which possessed an $[\alpha]_D^{20}$ value of +17.75 (*c* = 0.69, $CHCl_3$) {$[\alpha]_D^{20}$ = +15.0 (neat)}. Oritani and Yamashita[31] were able to confirm this later assignment by reduction of (*S*)-(+)-γ-ionone [(+)-**3**] to (*S*)-(+)-dihydro-γ-ionone [(+)-**7**] {$[\alpha]_D^{20}$ = +14.6 (*c* = 2, $CHCl_3$)} with Pd/C in EtOAc.

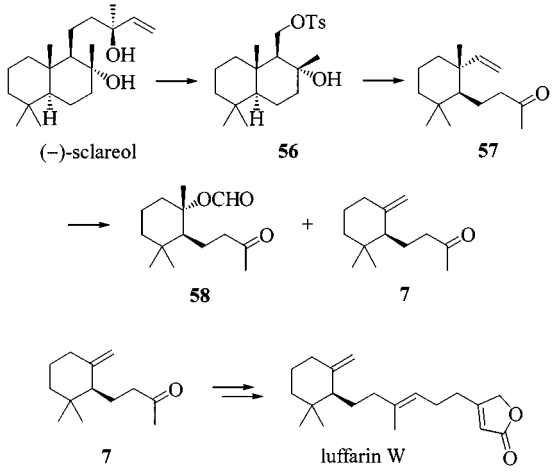


In our own work[32] on the enzymatic syntheses of (+)- and (−)-γ-ionone (**3**), we reported the reduction of chemically and enantiomerically pure (+)- and (−)-**3** to the corresponding dihydroionones (**7**). A preliminary hydrogenation experiment with Raney-Ni was unsatisfactory, because partial isomerization of the double bond occurred, and a small amount (< 10%) of the dihydro-α-ionone was formed. However, a reduction procedure[58] employing Bu_3SnH and catalytic amounts of $(PPh_3)_2PdCl_2$ smoothly converted (*R*)-(−)-γ-ionone [(−)-**3**] into enantiopure (−)-**7** {99% *ee*, $[\alpha]_D^{20}$ = −19.8 (*c* = 1.3, $CHCl_3$)} and (*S*)-(+)-**3** into (+)-**7** {98% *ee*, $[\alpha]_D^{20}$ = +19.4 (*c* = 1.2, $CHCl_3$)} without isomerization of the double bond. We were thus able to confirm the assignments of the absolute configurations.

In 2000, Barrero et al.[59] reported a synthesis of dihydro-γ-ionone [(+)-**7**] from (−)-sclareol. The latter compound was converted into **56**,[60] which was then subjected to a Grob fragmentation to provide the *seco*-sesquiterpene **57**.[61] Thermal rearrangement of the ozonide of **57** furnished a mixture of formate **58** and dihydro-γ-ionone (+)-**7**, but no data on the optical purity were provided. This dihydro-γ-ionone (+)-**7** was then employed in the synthesis of the marine metabolite luffarin W (Scheme 16).

Olfactory Evaluation

When Sobotka[14] first prepared (+)- and (−)-α-ionone (**1**) he noticed "*a distinct difference in odor between the* D- *and* L-*form*". In 1947, Naves[15] submitted his samples of (+)- and (−)-**1** to olfactory evaluation by skilled perfumers. Both antipodes of α-ionone were found to possess the same odor tonalities as the racemic ionone [(±)-**1**]. However, their odors were reported to be less intense than that of the racemic material. Both enantiomers possessed the same odor quality and threshold (2−8 ng/l of air), but a lower



Scheme 16

threshold value was found for (±)-**1** (0.25−0.5 ng/l of air). Although we also found the odor characteristics of the racemate and the two optical isomers to be quite similar, we could not confirm these threshold differences. While (*S*)-(−)-α-ionone was slightly more powerful (2.7 ng/l of air), the racemate had (within experimental error) the average threshold of the two isomers (3.0 ng/l of air).

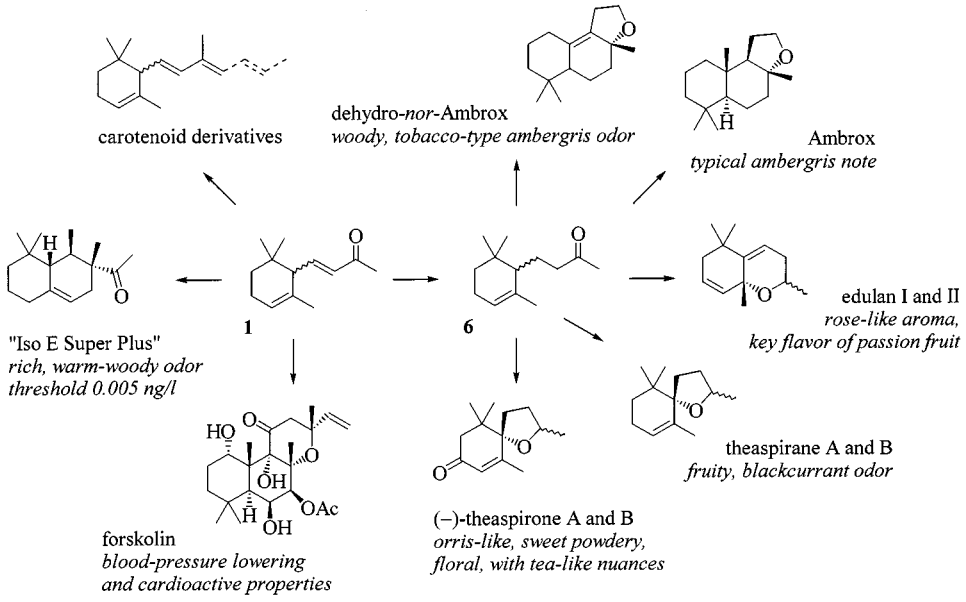
In 1989, Polak[62] measured the human odor response to the α-ionone enantiomers. Surprisingly, he found that relative sensitivities to (+)-and (−)-**1** diverged widely, with some subjects being more sensitive to one or the other of the optical antipodes. He suggested that odor discrimination of α-ionone enantiomers therefore involves more than one receptor, with different chiral selectivities, and that their distribution could vary independently in the human population.

β-Ionone is among the substances with the highest rates of anosmia, and about 34% of the European population cannot smell it. This β-ionone anosmia does influence the threshold determination of ionones severely, and so we excluded anosmic persons from the test panels in our studies. Having done this, we did not find strong deviations in the thresholds of the α-ionone enantiomers. Another source of error is, of course, the purity of the samples, and because of this our odor thresholds were measured by GC/olfactometry and confirmed by using chiral phases.

Haarmann & Reimer researchers[63] reported in 1991 a violet-like, fruity, raspberry-type, floral odor with a threshold of 0.5−5 ppb for (*R*)-(+)-α-ionone, and a woody, cedarwood-type odor with a threshold of 20−40 ppb for its enantiomer. These olfactory differences were validated by Firmenich perfumers in 1992,[21] but we were not able to

Table 1. Odor descriptions and GC detection thresholds of the ionone isomers investigated

Substrate	Olfactory description	Odor threshold [ng/l of air]
(*R*)-(+)-α-Ionone [(*R*)-(+)-**1**]	Floral-woody note, with an additional honey aspect. Slightly weaker than the (*S*)-(−) isomer.	3.2
(*S*)-(−)-α-Ionone [(*S*)-(−)-**1**]	Floral-woody note, with an additional honey aspect. Slightly more powerful than the (*R*)-(+) isomer.	2.7
rac-(±)-α-Ionone [(±)-**1**]	Floral-woody note, with an additional honey aspect.	3.0
β-Ionone (**2**)	Typical floral-woody note.	0.12
(*R*)-(−)-γ-Ionone [(*R*)-(−)-**3**]	Weak green, fruity, pineapple-like odor with metallic aspects, quite different from the typical ionone odor; however, slightly woody, ionone-type nuances are also present.	11
(*S*)-(+)-γ-Ionone [(*S*)-(+)-**3**]	Linear, very pleasant, floral, green, woody odor with a very natural violet tonality; the most powerful and pleasant isomer.	0.07
(*R*)-(+)-Dihydro-α-ionone [(*R*)-(+)-**6**]	Floral, violet-type odor with slightly fruity aspects. Also possesses a woody side, but less pronounced than in dihydro-β-ionone.	31
(*S*)-(−)-Dihydro-α-ionone [(*S*)-(−)-**6**]	Exhibits a floral orris-type odor, with woody aspects and a distinct honey note.	100
(*R*)-(−)-Dihydro-γ-ionone [(*R*)-(−)-**7**]	Emanates a fatty, earthy odor with floral, orris-type nuances.	6.2
(*S*)-(+)-Dihydro-γ-ionone [(*R*)-(−)-**7**]	Fatty-floral odor, less orris-type than the other compounds of the dihydro series. An animalic undertone is also present.	39
Dihydro-β-ionone (**59**)	Possesses a β-ionone-type odor of floral-woody, orris-type tonality, with green, earthy undertones.	1.7



Scheme 17

confirm such strong deviations in the odor profiles or thresholds of the α-ionone enantiomers.

Our research in the field of ionones allowed us to have in hand the enantiomers of α-ionone (**1**), γ-ionone (**3**), dihydro-α-ionone (**6**),[64] and dihydro-γ-ionone (**7**), with high optical and chemical purities. Careful olfactory evaluation of all these derivatives was performed by an expert perfumer on blotter over a period of 24 h, and detection odor thresholds were measured by GC/olfactometry. The results are collected in Table 1, together with the data for *rac*-α-ionone (**1**), β-ionone (**2**), and dihydro-β-ionone[65] (**59**). Except for α-ionone, there is a difference of at least one order of magnitude between the threshold values of the enantiomeric pairs, and even of three orders of magnitude in the case of γ-ionone. (+)-(*S*)-γ-Ionone is the most powerful and most pleasant odorant of the investigated ionones.

Conclusions

This microreview summarizes the different synthetic approaches to the optically active ionones and derivatives **1** and **3**−**7**, which are of interest for their olfactory properties and their use as chiral building blocks in the synthesis of natural − but not only natural − products. Some interesting examples (Scheme 17) of the synthetic value of ionones and derivatives from the literature include carotenoids,[16,17,23,38,48,51] drimane terpenoids (e.g., forskolin),[66] and degradation products of carotenoids,[67] such as theaspiranes[68] and edulan derivatives,[20,53] as well as odorants such as Ambrox® [69][70] and analogues,[71] or a powerful minor constituent of the commercial fragrance material Iso E Super®.[72]

The easy availability of enantiopure ionones and derivatives facilitates synthetic access to these substances and new related compounds. We have been working on this topic for the last four years,[19,32,40] and have shown that, by a combination of selective enzymic reactions (lipase-mediated acetylation and hydrolysis) and classical methods of diastereoisomer separation (chromatography or fractional crystallization), enantiopure compounds can be derived from the corresponding racemic materials with ease.

Acknowledgments

We are grateful to C. Denis of Givaudan Dübendorf for the olfactory characterization, and to H. Koch, also of Givaudan Dübendorf, for the GC/olfactometry threshold measurements. COFIN-Murst (Italy) is acknowledged for financial support.

[1] [1a] F. Tiemann, P. Krüger, *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 2675−2708. [1b] F. Tiemann, *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 808−866.
[2] [2a] P. Kraft, *Synthesis* **1999**, 695−703. [2b] M. Gautschi, J. A. Bajgrowicz, P. Kraft, *Chimia* **2001**, *55*, 379−387.
[3] H. Hibbert, L. T. Cannon, *J. Am. Chem. Soc.* **1924**, *46*, 119−130.
[4] G. Ohloff, G. Schade, *Angew. Chem.* **1962**, *74*, 944.
[5] G. Ohloff, *Scent and Fragrances: The Fascination of Fragrances and their Chemical Perspectives*, Springer-Verlag, Berlin, **1994**, pp. 117−118.
[6] G. Ohloff, *Scent and Fragrances: The Fascination of Fragrances and their Chemical Perspectives*, Springer-Verlag, Berlin, **1994**, pp. 107−113.
[7] Y. R. Naves, G. R. Parry, *Helv. Chim. Acta* **1947**, *30*, 419−422.
[8] Y. R. Naves, *Helv. Chim. Acta* **1949**, *32*, 1064−1069.
[9] D. La Face, *Helv. Chim. Acta* **1950**, *33*, 249−256.
[10] Y. R. Naves, *Perfum. Essent. Oil Rec.* **1964**, *55*, 658−659.
[11] M. Winter, E. Sundt, *Helv. Chim. Acta* **1962**, *45*, 2195−2211.

[12] G. Uhde, G. Ohloff, *Helv. Chim. Acta* **1972**, *55*, 2621−2625.
[13] R. Buchecker, R. Egli, H. Regel-Wild, C. Tscharner, C. H. Eugster, G. Uhde, G. Ohloff, *Helv. Chim. Acta* **1973**, *56*, 2548−2563.
[14] H. Sobotka, E. Bloch, H. Cahnmann, E. Feldbau, E. Rosen, *J. Am. Chem. Soc.* **1943**, *65*, 2061−2062.
[15] Y. R. Naves, *Helv. Chim. Acta* **1947**, *30*, 769−774.
[16] C. Tscharner, C. H. Eugster, P. Karrer, *Helv. Chim. Acta* **1958**, *41*, 32−34.
[17] W. Eschenmoser, P. Uebelhart, C. H. Eugster, *Helv. Chim. Acta* **1979**, *62*, 2534−2538.
[18] C. H. Eugster, R. Buchecker, C. Tscharner, G. Uhde, G. Ohloff, *Helv. Chim. Acta* **1969**, *52*, 1729−1731.
[19] E. Brenna, C. Fuganti, P. Grasselli, M. Redaelli, S. Serra, *J. Chem. Soc., Perkin Trans. 1* **1998**, 4129−4134.
[20] T. Sugai, T. Yokochi, N. Watanabe, H. Ohta, *Tetrahedron* **1991**, *47*, 7227−7236.
[21] C. Fehr, O. Guntern, *Helv. Chim. Acta* **1992**, *75*, 1023−1028.
[22] H. Pfander, P. A. Semadeni, *Aust. J. Chem.* **1995**, *48*, 145−151.
[23] P.-A. Bütikofer, C. H. Eugster, *Helv. Chim. Acta* **1983**, *66*, 1148−1174.
[24] D. J. Bennet, G. R. Ramage, J. L. Simonsen, *J. Chem. Soc.* **1940**, 418−419.
[25] C. Fehr, J. Galindo, *J. Am. Chem. Soc.* **1988**, *110*, 6909−6911.
[26] H. G. W. Leuenberger, W. Bogurth, E. Widmer, R. Zell, *Helv. Chim. Acta* **1976**, *59*, 1832−1849.
[27] H. Mayer, A. Rüttimann, *Helv. Chim. Acta* **1980**, *63*, 1451−1455.
[28] D. H. R. Barton, S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.
[29] Z. Liu, C. T. Liu, G. Fu, Y. Xu, S. Sun, Z. Chen, A. Li, *Youji Huaxue* **1982**, 443−446; *Chem. Abstr.* **1983**, *98*, 149449j; AN 1983:149449.
[30] R. Kaiser, unpublished results, headspace analysis of Gongora 220/74 (Dr. G. Gerlach, Botanischer Garten München), Givaudan Dübendorf, 21 October, **1997**·
[31] T. Oritani, K. Yamashita, *Agric. Biol. Chem.* **1987**, *51*, 1271−1275.
[32] C. Fuganti, S. Serra, A. Zenoni, *Helv. Chim. Acta* **2000**, *83*, 2761−2768.
[33] L. Caglioti, H. Naef, D. Arigoni, O. Jeger, *Helv. Chim. Acta* **1959**, *42*, 2557−2570.
[34] G. Ohloff, C. Vial, *Helv. Chim. Acta* **1977**, *60*, 2767−2769.
[35] C. Fehr, *Angew. Chem.* **1998**, *110*, 2509−2512; *Angew. Chem. Int. Ed.* **1998**, *37*, 2407−2409.
[36] G. Ohloff, S. Mignat, *Justus Liebigs Ann. Chem.* **1962**, *652*, 115−126.
[37] A. Haag, W. Eschenmoser, C. H. Eugster, *Helv. Chim. Acta* **1980**, *63*, 10−15.
[38] A. Haag, C. H. Eugster, *Helv. Chim. Acta* **1982**, *65*, 1795−1803.
[39] P. Uebelhart, A. Baumeler, A. Haag, R. Prewo, J. H. Bieri, C. H. Eugster, *Helv. Chim. Acta* **1986**, *69*, 816−834.
[40] J. Aleu, E. Brenna, C. Fuganti, S. Serra, *J. Chem. Soc., Perkin Trans. 1* **1999**, 271−278.
[41] As in the case of epoxy-α-irol derivatives, diastereoisomeric excesses are used to express the ratio between the diastereoisomeric *cis*- and *trans*-epoxides.
[42] R. Caputo, L. Mangoni, O. Neri, G. Palumbo, *Tetrahedron Lett.* **1981**, *22*, 3551−3552.
[43] Y. R. Naves, *J. Soc. Cosm. Chem.* **1971**, *22*, 439−456.
[44] J. E. Ayers, M. J. Fishwick, D. G. Land, T. Swain, *Nature* **1964**, *203*, 81−82.
[45] M. Winter, P. Enggist, *Helv. Chim. Acta* **1971**, *54*, 1891−1898.
[46] F. Müggler-Chavan, R. Viani, J. Bricout, J. P. Marion, H. Machtler, D. Reymond, R. H. Egli, *Helv. Chim. Acta* **1969**, *52*, 549−550.
[47] E. Demol, D. Berthet, *Helv. Chim. Acta* **1971**, *54*, 681−682.
[48] M. Acemoglu, W. Eschenmoser, C. H. Eugster, *Helv. Chim. Acta* **1981**, *64*, 2691−2695.
[49] F. Toda, K. Mori, Y. Matsuura, H. Akai, *J. Chem. Soc., Chem. Commun.* **1990**, 1591−1593.
[50] T. Oritani, K. Yamashita, *Phytochemistry* **1983**, *22*, 1909−1912.
[51] M. Acemoglu, C. H. Eugster, *Helv. Chim. Acta* **1984**, *67*, 184−190.
[52] P. Dubs, H.-P. Schenk, *Helv. Chim. Acta* **1978**, *61*, 984−989.
[53] W. Francke, S. Schulz, V. Sinnwell, W. A. König, Y. Roisin, *Liebigs Ann. Chem.* **1989**, 1196−1201.
[54] K. Mori, P. Puapoomchareon, *Liebigs Ann. Chem.* **1991**, 1053−1056.
[55] L. Ruzicka, C. F. Seidel, M. Pfeiffer, *Helv. Chim. Acta.* **1948**, *31*, 827−831.
[56] E. Jegou, J. Polonsky, E. Lederer, K.-H. Schulte-Elte, B. Egger, G. Ohloff, *Nouv. J. Chim.* **1977**, *1*, 529−531.
[57] A. F. Barrero, J. F. Sanchez, F. G. Cuenca, *Phytochemistry* **1988**, *27*, 3676−3678.
[58] Y. I. M. Nilsson, A. Aranyos, P. G. Andersson, J. E. Bäckvall, J. L. Parrain, C. Ploteau, J. P. Quintard, *J. Org. Chem.* **1996**, *61*, 1825−1829.
[59] A. F. Barrero, E. J. Alvarez-Manzaneda, R. Chahboun, J. M. Cuerva, A. Segovia, *Synlett* **2000**, 1269−1272.
[60] A. F. Barrero, E. J. Alvarez-Manzaneda, J. Altarejos, S. Salido, J. M. Ramos, M. S. J. Simmonds, W. M. Blaney, *Tetrahedron* **1995**, *51*, 7435−7450.
[61] A. F. Barrero, E. J. Alvarez-Manzaneda, R. Chahboun, M. C. Paiz, *Tetrahedron Lett.* **1998**, *39*, 9543−9544.
[62] E. H. Polak, A. M. Forobon, C. Tilquin, P. H. Punter, *Behav. Brain Res.* **1989**, *31*, 199−206.
[63] P. Werkhoff, W. Bretschneider, M. Guentert, R. Hopp, H. Surburg in *Flavor Science and Technology* (Eds.: Y. Bessiere, A. F. Thomas), J. Wiley & Sons, New York, **1990**, pp. 33−36.
[64] Compounds (+)- and (−)-**6** were prepared by catalytic hydrogenation of (+)- and (−)-**4** and deoxygenation.
[65] Derivative **56** was prepared by reduction of β-ionone with Bu_3SnH and $(PPh_3)_2PdCl_2$ as described in ref.[32]
[66] M. I. Colombo, J. Zinczuk, E. A. Ruveda, *Tetrahedron* **1992**, *48*, 963−1037.
[67] P. Weyerstahl, T. Meisel, *Liebigs Ann. Chem.* **1994**, 415−427.
[68] Y. Nakatani, T. Yamanishi, *Tetrahedron Lett.* **1969**, *24*, 1995−1998.
[69] K. Mori, S. Aki, M. Kido, *Liebigs Ann. Chem.* **1994**, 319−324.
[70] K. Mori, H. Tamura, *Liebigs Ann. Chem.* **1990**, 361−368.
[71] G. Frater, J. A. Bajgrowicz, P. Kraft, *Tetrahedron* **1998**, *54*, 7633−7703.
[72] P. Kraft, J. A. Bajgrowicz, C. Denis, G. Frater, *Angew. Chem.* **2000**, *112*, 3106−3138; *Angew. Chem. Int. Ed.* **2000**, *39*, 2980−3010.

Received July 24, 2001
[O01361]