The Chemistry and Creative Legacy of Methyl Jasmonate and Hedione[a]

How the decoding of the essential oil constituents of *Jasminum grandiflorum* L. launched a dynamic story of chemistry and creativity

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Dedicated to Drs. Edouard Demole and Valentin Rautenstrauch, on the occasion of their 80th and 75th birthdays, respectively.

Edouard Demole discovered methyl jasmonate in 1957, accomplished a synthesis of Hedione (from *hedone*, meaning agreeable and pleasant) in 1958, synthesized methyl jasmonate in 1959, placed both materials under intellectual protection in 1960, and published these discoveries in 1962.[1–3] This simple timeline belies a more complex history of chemistry and creation; on the occasion of Hedione's 50th anniversary, we shall trace this landmark material's hectic history and legacy.

Discovery and Chemistry

In the late 1950s, Roger Firmenich instructed Demole to study in depth, as the subject of his doctoral thesis in E. Lederer's laboratories (Institut de Biologie Physico-Chimique, Paris, 1955–1959), the concrete of Mediterranean jasmine (*Jasminum grandiflorum* L.), in order to discover and determine the missing structures responsible for this typical olfactive signature. At the same time, he also sent a sample to Leopold Ruzicka,[b] as he was involved in a previous analysis in Geneva.[4] Indeed, although more than 87% of the jasmine essential oil constituents had already been determined, the full olfactive reconstitution was still impossible. The fundamental element responsible for this material's wonderful radiance and deep sweet floral character was hidden in the remaining unknown fraction. It should be noted that the price of one kilo of jasmine absolute, produced from *ca.* 1 ton of jasmine flowers and extracted with ethanol from 2.3 kg of jasmine concrete, could cost up to 20,000 CHF/Kg; at the time, world annual production was limited to *ca.* 6 tons of jasmine absolute.[5,6] The decision to decode jasmine essential oil constituents was motivated by premium cost of the ingredient and the old saying, "No perfume without jasmine." Up to the middle of the 20th century, *ca.* 80% of marketed fragrance compositions contained a basic note extracted from this precious handpicked flower; outstanding examples include *Jasmin* (Molinar, 1860), *Jasmin de Corse* (Coty, 1906), *Arpège* (Lanvin, 1927), *Joy* (Patou, 1935) and *Miss Dior* (Dior, 1947).[7]

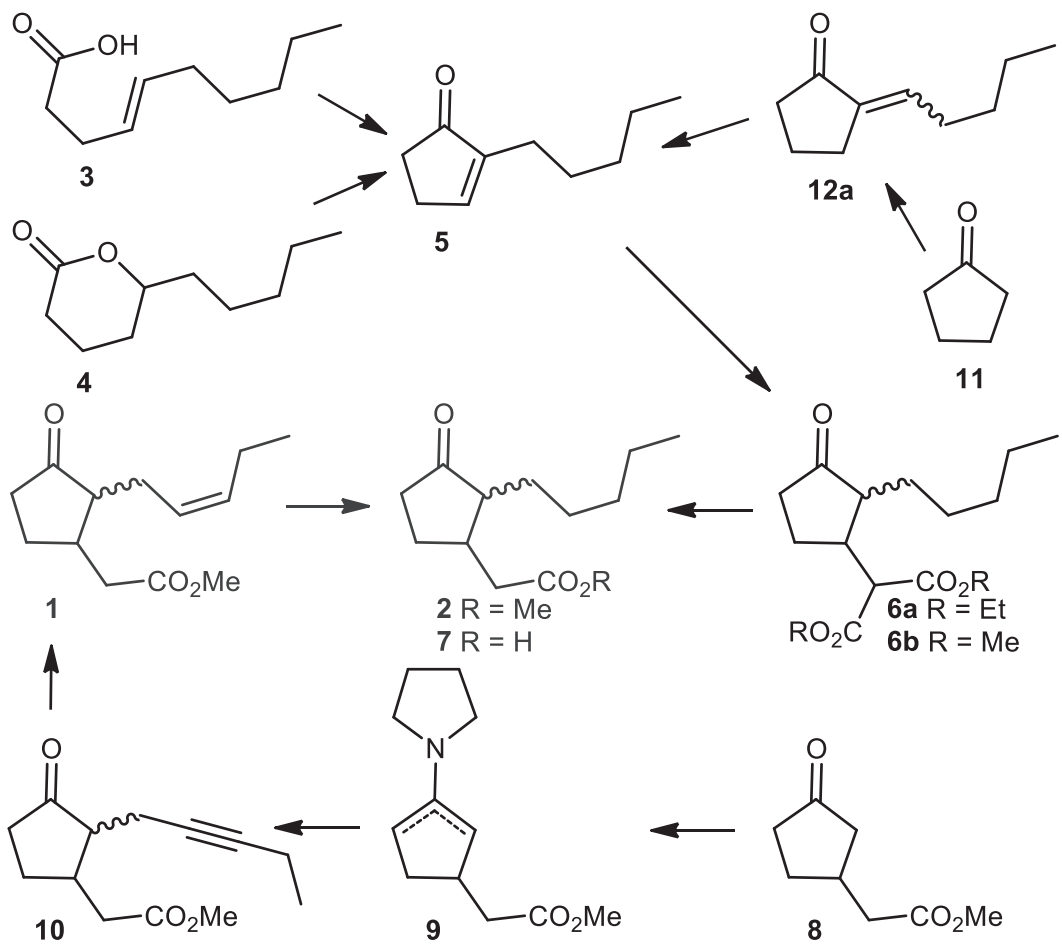
As mentioned, Demole first isolated methyl jasmonate **1**.[2] Its correct structure, based on biosynthetic considerations, consistent with IR, UV, MS and elemental, as well as degradative analyses, was suggested by George Büchi (Massachusetts Institute of Technology, Cambridge, consultant). This was soon confirmed by subsequent synthesis of its more simple dihydro analogue, Hedione **2**, which was initially obtained by simple hydrogenation during the analyses of natural **1** (**F-1**).[3,8]

Both new ingredients were levogyre and existed in a *ca.* 7:93 *cis/trans* thermodynamic mixture at ambient temperature.[9] The absolute configuration of natural (-)-(Z)-*trans* **1** was later determined by R. Hill and A. Edwards.[10] The first synthesis of **2** started from either the unsaturated acid **3**, or the corresponding δ-decalactone **4** via cyclization to form cyclopentenone **5**. The subsequent Michael addition of diethyl malonate, followed by saponification of **6a** and decarboxylation afforded the free acid **7**, which necessitated a reesterification. The first synthesis of methyl jasmonate **1** was longer and non-regioselective. It started from the ketoester **8**, accessible either in four steps from muconic acid, or by malonate Michael addition to 2-cyclopentenone. Alkylation of the intermediate enamine **9** afforded a 2:3 mixture, from which minor **10** could be isolated for monohydrogenation to (Z)-methyl-jasmonate **1**. Perfumers, such as U. Säuberli, were struck

[a]Hedione is a trademark of Firmenich.

[b]Then of Eidgenössische Technische Hochschule, Zürich; winner of the 1939 Nobel Prize for his work on macrocyclic musks, in collaboration with Firmenich.

Hedione 2, initially obtained by simple hydrogenation during the analyses of natural 1[3,8] **F-1**



by methyl jasmonate's exquisite jasmine, deep, fatty, floral and authentic aspect, and unanimously preferred it to its dihydroanalogue **2**, which was less radiant. Nevertheless, Roger Firmenich promoted the development of the economically more promising Hedione **2**.

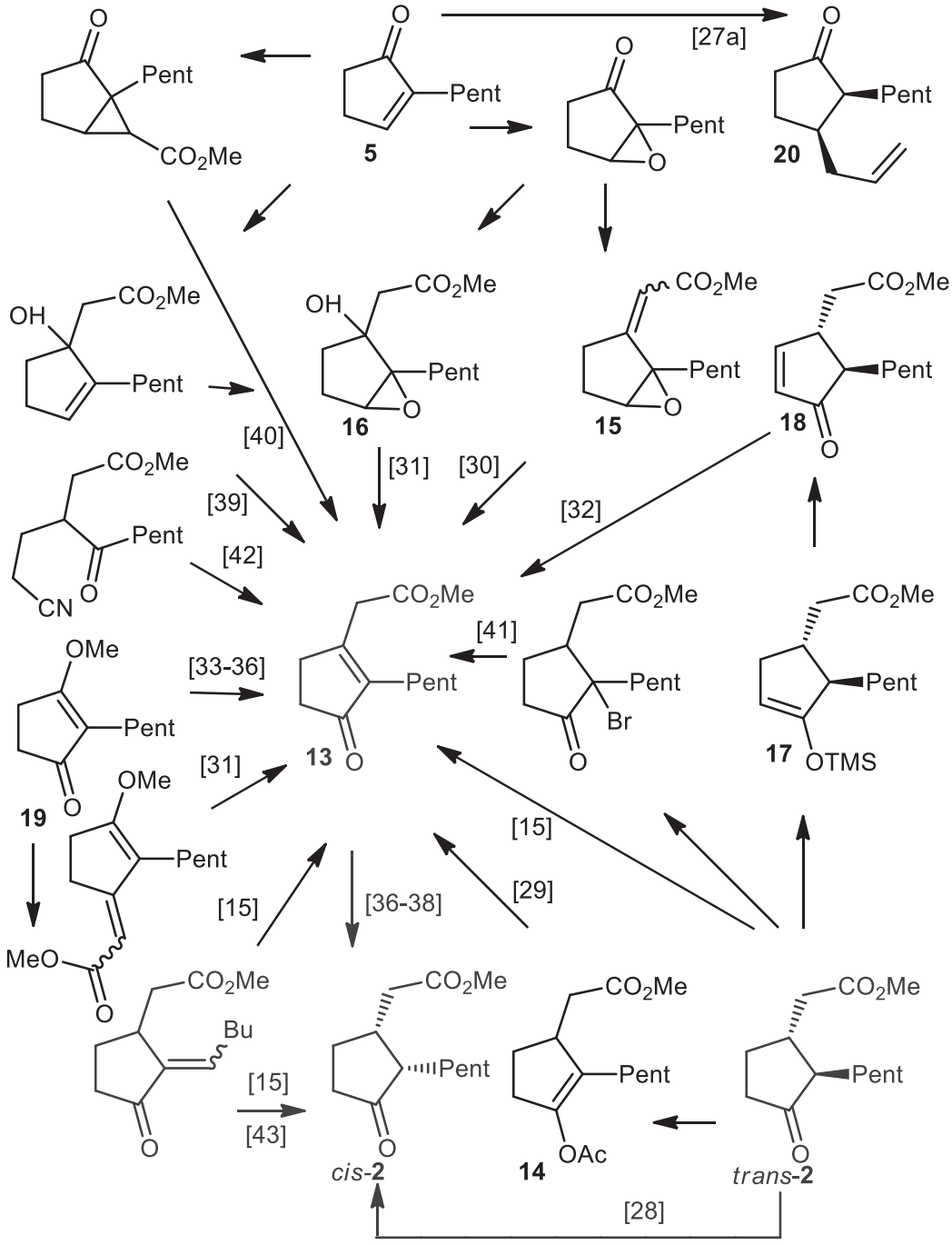
Commercialization of Hedione

A simplified version of Hedione synthesis based on the more affordable cyclopentanone **11**—a byproduct available from the synthesis of the adiponitrile intermediate in the nylon-6 process—was undertaken by Demole (**F-1**). This involved an aldol condensation with pentanal followed by treatment with either a Brönsted acid, or I_2, or Formier gas/Pd/C, or transition metal catalyzed isomerization of the *exo*-double bond of enone **12a**.[11–15] The Michael reaction was performed directly with dimethyl malonate, and decarbomethoxylation avoided final reesterification.

Hedione's adoption was particularly slow, so Roger Firmenich promoted the ingredient by sending samples to notable external perfumers, including Edmond Roudnitska, who used the ingredient to create the successful *Eau Sauvage* for Dior (1966; 2.5%).

Hedione's chemical process has been further ameliorated throughout its history by various researchers. A. Uijttewaal optimized the aldol conditions, and R.M. Weinstein, extending the initial studies of F. Mazenod and W. Keim (Max Planck Institute, Aachen, consultant), concentrated on the isomerization step. The Michael addition was revisited by J. Becker, and C. Golay, and the final decarbomethoxylation was optimized by A. Boschung and A. Zaslona.[16,17] At high volumes, each percentage point was extremely crucial. A robust continuous synthetic process resulted in the construction of fully automated manufacturing units, first in La Plaine (1983), then in Port Newark (1988). The initial price of Hedione was about 1,000 CHF/Kg and as a result, it was first confined to fine fragrances such as *Diorella* (Dior, 1972, 8%). The production cost—and, as a result, the market price—continuously decreased and allowed perfumers to use increasing quantities in their compositions, including *Chanel N°19* (Chanel, 1971, 12.6%); *First* (Van Cleef & Arpels, 1976, 18%); *Cristalle* (Chanel, 1993, 26%), and *Odeur 53* (Comme des Garçons, 1998, 65%), and to extend its use to other segments, such as body and home care products.[18]

DHH 13 was accessible by several published routes shown here **F-2**



It took perfumers a few years to learn how to integrate its particular properties in compositions. They realized that while Hedione itself had relatively low odor intensity, it provided a synergistic effect. Hedione rendered perfumes round, floral and diffusive; soap perfumes were found to possess significant in-use diffusion and an appealing lingering effect on skin after use. Certain agarbatti perfumes incorporating Hedione possess a greater faculty to fill a room with fragrance, as compared to the corresponding version lacking this ingredient. The strength of a composition does not necessarily increase, but more presence, noticeability, and diffusivity are bestowed by an addition of Hedione.[19] Several hypotheses were suggested for explaining these phenomena. The booster effect of Hedione could not be confirmed by W. Pickenhagen on specific symbiosis with Ambrox,[c] as the threshold detection value of the latter was not modified in the presence or absence of the former ingre-

[c]Ambrox is a trademark of Firmenich.

Cis/trans ratios and thresholds of past/current Firmenich qualities of 2 [23,25,26b] **T-1**

2 at Firmenich	*cis/trans ca.*	Odor threshold [ngL^{-1}]
Hedione	10:90	0.280
Cisdione[f]	30:70	0.093
Hedione HC	75:25	0.037
Hedione VHC	90:10	0.031
(+)-Paradisone[h]	94:6	0.015

dient. Alternatively, according to the measurements of I. Flament and M. Lindström, the addition of Hedione seems to modify the concentration of co-ingredients in the headspace, for example by decreasing the concentration of C_5-acids, or increasing that of Cedroxyde.[d] In addition, due to its unusual specific fixative properties, Hedione may modify the substantivity of co-ingredients.[20] The accurate sensorial measurements of C. Vuilleumier showed that the efficiency of Hedione, for partner discrimination enhancement by panelists, requires higher concentrations than its own detection threshold.[21] When patent protection for Hedione expired in the early 1980s, Nippon Zeon became a competitor by making a similar quality named Claigeon.[e] **T-1** contains the *cis/trans* ratios and thresholds of past and current Firmenich qualities of **2**.[23,25,26b]

The Advent of Hedione HC

Hedione, naturally occurring in trace amounts in tea flavor, Brazilian sweet Lima orange, and apparently in several other plants, was finally offered to external clients in 1970.[22,23] That same year, the minor *cis*-stereoisomer used in *Calandre* (Paco Rabanne, 1969, 5.8%) was suggested to be stronger.[24]

At the beginning of the 1990s Nippon Zeon commercialized a new quality, rich in *cis*-Hedione (30:70 *cis/trans*), called Cepionate.[g] It was obtained by continuous distillation in the presence of sodium carbonate, allowing for higher concentrations of the less volatile *cis*-isomer at elevated temperatures.[27] The immediate response was focused on two actions, namely the stereoselective synthesis of *cis*-Hedione and (+)-Paradisone.[26c] First, a stereoselective synthesis of the *cis* isomer, via hydrogenation of dehydrohedione **13** (DHH) and adapting the conditions developed by A.F. Thomas at the beginning of the 1970s, was performed on kilo scale by V. Rautenstrauch, thus confirming that this quality could be manipulated, distilled, stocked and used in perfumery. Indeed, DHH **13** was already accessible by several published routes, as summarized in **F-2**. Industrial methods were developed by K. Crawford, Rautenstrauch and Uijttewaal, involving a peracetic oxidation of enol acetates **14**, and by B. Winter, after either appropriate Wadworth-Emmons reaction, or nucleophilic addition via rearrangements of epoxides **15** or **16**.[28–30] These approaches were preferred over dehydrogenation of the TMS enolether **17**, followed by double bond isomerization of **18**, as explored by R.L. Snowden.[31] The Michael addition to 3-methoxy-2-pentyl-2-cyclopenten-1-one **19**, earlier reported, was recently patented by Givaudan and Asahi Kasei Chem. Corp.[32–35] The ultimate success resides in non-epimerizing hydrogenation conditions to produce Hedione HC (high *cis*) as a *ca.* 90:10 mixture directly after workup.[35–37] It may also be obtained, in a multistep academic sequence, from **5**, via an allyl cuprate 1,4-addition, followed by a stereoselective protonation using N-methylsalicylaldimine, completed by an ozonolysis with oxidative workup of **20**.[26a] The enriched HC quality is perceived as very powerful and tenacious, nicely floral and jasminelike, and is contained in the bestsellers *Pleasure* (Estée Lauder, 1995, 6.3%) and *Juicy Couture* (E. Arden, 2010, 6%).

(+)-Paradisone

The intrinsic olfactive values of each stereoisomer were determined by C. Vial via their HPLC-separated menthyl esters, or via direct sniffing by A. Morris at the outlet of chiral GC columns; these properties were later published (**F-3**).[23] Following the suggestion of G.M. Whitesides (Harvard University, Cambridge, consultant), Rautenstrauch prepared and evaluated grams quantities of each stereoisomer by resolution of the *cis*-dihydrocucurbic acid (**F-3**).[43]

Next, Rautenstrauch, assisted by J.-J. Riedhauser, D. Dobbs, and K.P. Vanhessche, a postdoctoral fellow, investigated the asymmetric hydrogenation of DHH **13**. Although nothing to date had been reported on tetrasubstituted double bonds, the initial success was obtained on the corresponding acid with either simple or sulfonated BINAP, or Et-Duphos ligands (90% ee), coordinated to unsaturated and more electrophilic Ru(II) as new precatalysts.[36] These conditions were then extended to DHH **13** using either Me-Duphos (64% ee), or the cheaper, tunable and versatile Josiphos derivatives (50–88% ee) in [Ru(Ligand)(H)-(η^6-1,3,5-cyclooctatriene)](BF_4).[45,46] Rautenstrauch closely collaborated with external specialists in the appropriate fields, including H.-U. Blaser (Novartis, Basel).[47,48] He collected the fruitful results of collaborations with J.-P. Genet (Université Pierre et Marie Curie, Paris), and S. Bergens (University of Alberta, Edmonton).[43] These chemical processes were further developed in La Plaine, by E. Brazi, P. Dupau and L. Bonomo, developing a procedure for industrial production with the support of Pierre-Yves Firmenich. This simple process, not always cited, was preferred over Cinchonia alkaloids catalyzed by asymmetric Michael addition of dimethyl malonate to **5**, in which a range of 80-90% ee was obtained, since they afford the undesired *trans*-stereoisomer.[49,50] Ignoring past methods, F. Liu also secured the *trans* disposition of the side chains via a 1,4-copper-hydride addition to (S)-(Z)-**18**, following a particularly efficient asymmetric Rh(I) catalyzed intra-

[d]Cedroxyde is a trademark of Firmenich.
[e]Claigeon is a trademark of Zeon.
[f]Cisdione is a trademark of Firmenich.
[g]Cepionate is a trademark of Zeon.
[h]Paradisone is a trademark of Firmenich.

molecular Alder-ene type cycloisomerization reaction of a (Z)-1,6-enyne in the presence of (*S*)-BINAP (99% ee) (**F-4**).[14,51] Using Paradisone, Olivier Cresp and Alberto Morillas recently created *Valentina* (Valentino, 2011, 7%), adding to the long list of perfumes incorporating this unique material, introduced by chemist-perfumer Pierre-Alain Blanc.

Impurities and Off-notes

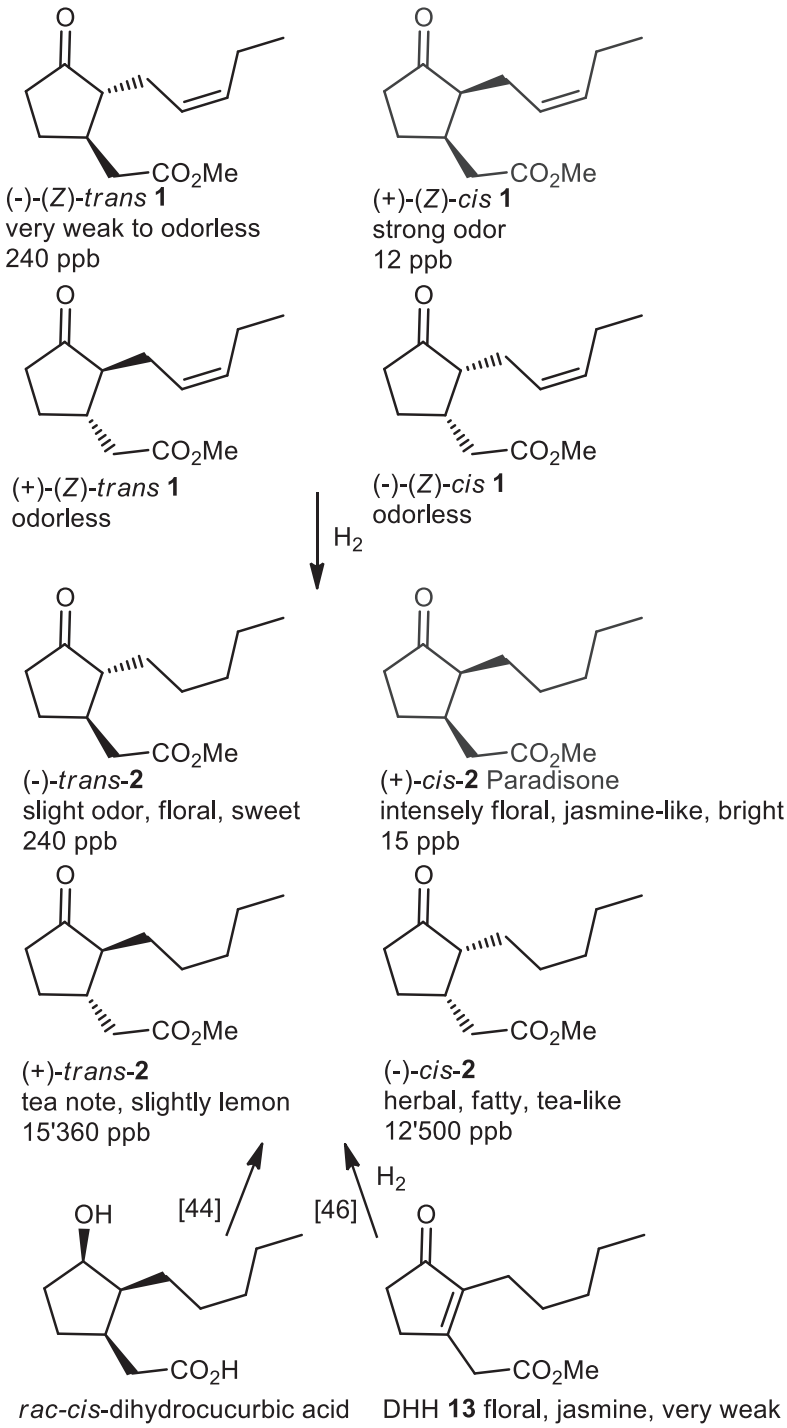
Hedione and its market equivalents vary in quality.[52] This results from variations in distillation techniques, which under ideal conditions suppress tiny impurities responsible for heavier and mushroomy off-notes. Several byproducts may destroy the olfactory impact of Hedione; these include the photochemical side-products of Hedione studied by W. Skorianetz, and traces of pentanoic acid or bicyclopentyliden-2-one found in the production finger-print analysis of S.D. Escher. While practically undetectable on the GC analytical traces, the most potent chemical responsible for the disagreeable mushroom odor—a mysterious diketone **21**—took time to be isolated and its structure determined (**F-5**). It was only a few years later, in 1980, that A. Eschenmoser (Eidgenössische Technische Hochschule, Zürich, consultant) could suggest a plausible explanation of the presence of a hexanoyl side chain.

Methyl Jasmonate

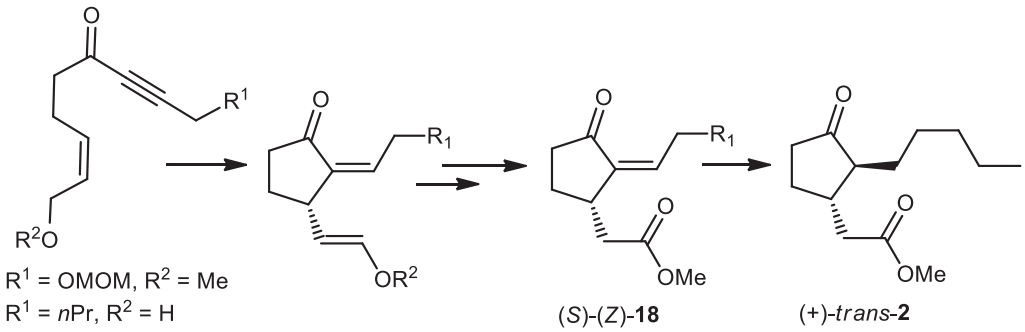
The relative and absolute configurations of the Hedione series, associated with their olfactory properties, parallel those of methyl jasmonate. The radiant methyl jasmonate **1** is considered nobler than Hedione, and when Fred-Henri Firmenich assumed the head of the company from Roger Firmenich, some tenacious perfumers requested this remarkable ingredient. This natural product occurs in Tunisian *Rosmarinus officinalis* L., in lemon peels as the *cis*-epimer, in sweet lemon (*Citrus limetta*), in Kimikan fruit (*Citrus flaviculpus*), and in tea flavor.[22a,53–59] Also, in the *cis*-form, this challenging molecule, pursued by the research division of G. Ohloff, has been found as a component of the sexual pheromone of the male oriental fruit moth (*Grapholitha molesta*).[60]

The ultimate epimerization step could be an artifact resulting from the extraction and isolation methods; the naturally active form was suggested to be the *cis*-stereoisomer.[60] (+)-*Cis*-**1** displays several biological activities, such as regulation of plant growth, defense and signal transmission in interplant communication.[61–64] Considering the many biosynthetic steps and the different subcellular locations of the biosynthetic enzymes, the entire pathway seems too complex to improve by direct evolution.[65] Therefore, the engineering

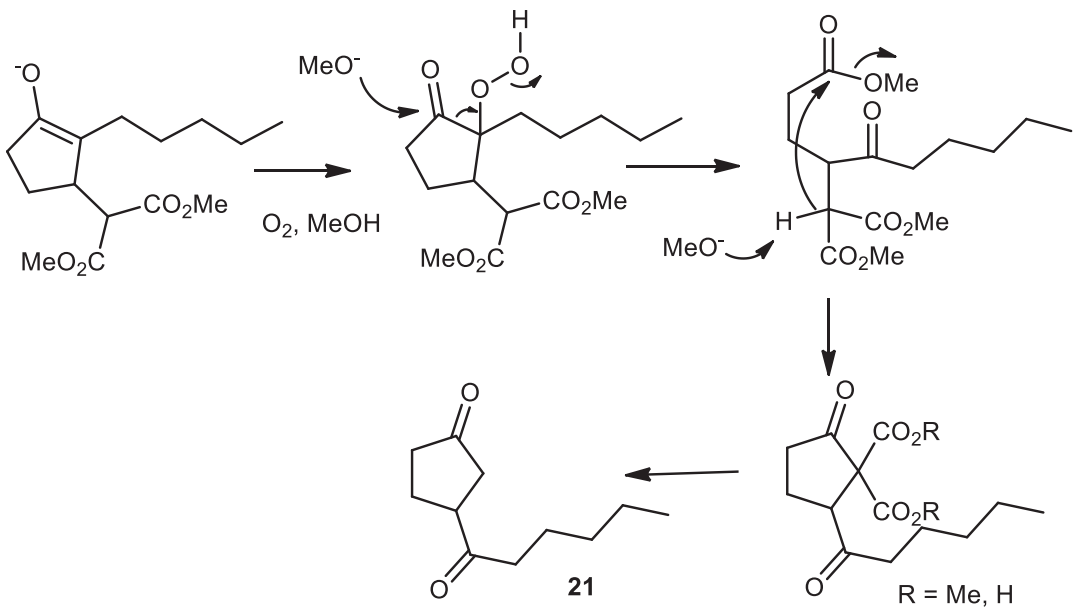
Stereoisomers of Hedione and methyl jasmonates, with their olfactive properties and respective thresholds[23,25a,44a] **F-3**



The *trans* disposition of the side chains via a 1,4-copper-hydride addition to (*S*)-(*Z*)-18, following a particularly efficient asymmetric Rh(I) catalyzed intramolecular Alder-ene type cycloisomerization reaction of a (*Z*)-1,6-enyne, in the presence of (*S*)-BINAP (99% ee)[51] **F-4**



A mysterious diketone 21 was in part responsible for a disagreeable mushroom odor **F-5**



of rate-limiting enzymes seems more promising, and with the work of I. Whitehead, Firmenich maintains a patent on a strategic step, useful for producing a quality of natural methyl jasmonate.[66]

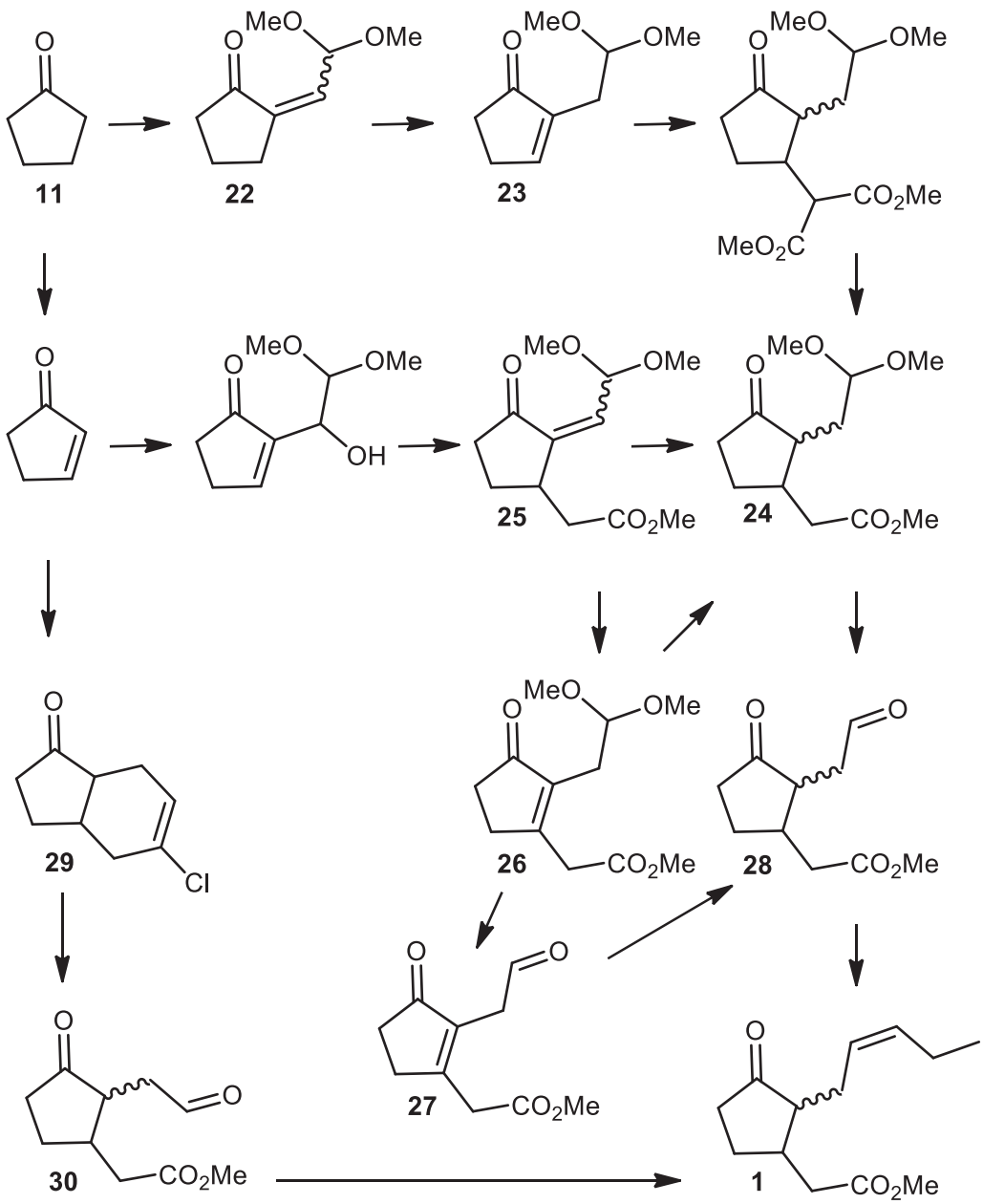
Since diverse approaches toward methyl jasmonate **1** are already discussed in two excellent reviews by Demole in 1982 and T. Sarkar in 1999, this subject will not be addressed exhaustively in this paper; rather, the author shall concentrate on the last decade, including the more promising industrial syntheses, as described for **2**.[23,32,67] In the wake of the seven-step practical approach of Büchi and B. Egger based on alkylation of dihydroresorcinol, it is one of the two shorter and particularly elegant industrial approaches designed by F. Näf which allowed D. Kastner to introduce methyl jasmonate **1** into the perfumer's palette.[68,69]

Next, Nippon Zeon developed the Tsuji synthesis, based on a Pd-catalyzed decarboxylation-dehydrogenation as the original key step of their *trans*-Jasmoneige[i] quality.[70]

More recently, J.M. Lem, Vanhessche and C. Mahaim presented a novel approach to build the unsaturated side chain, culminating with a Z-selective Wittig reaction (**F-6**).[71,72] Thus, condensation of dimethoxyacetaldehyde with cyclopentanone **11** afforded **22**, which was isomerized into the endocyclic cyclopentenone **23**. Intermediate **24** may also be obtained by a cascade Baylis-Hillman/Claisen reaction, via hydrogenation of the unsaturated dimethyl acetal **25**.[14] This latter was eventually isomerized to the tetrasubstituted analogue **26**. Either deprotection of **24**, or hydrogenation of **27** furnished aldehyde **28** for an ultimate Z-Wittig reaction. A particularly expeditious version also starts from

[i]Jasmoneige is a trademark of Zeon.

Novel approaches to build the unsaturated side chain, culminating with a *Z*-selective Wittig reaction[14,71–73] **F-6**



2-cyclopentenone and takes advantage of the previously described analogous Diels-Alder adducts.[72–74] It uses reactive chloroprene, used on a multi-ton scale by the plastic industry, to directly and regioselectively afford cycloadduct **29**, with the correct state of oxidation for further conversion to ester **30**. This three-step sequence culminates with the usual Z-selective Wittig reaction (**F-6**).[72,75]

Sensuous (Estée Lauder, 2008, 1.7%) enormously profits from methyl jasmonate **1** in its composition. To celebrate the 50-year anniversary, this ingredient will be commercialized under the name Splendione.[j]

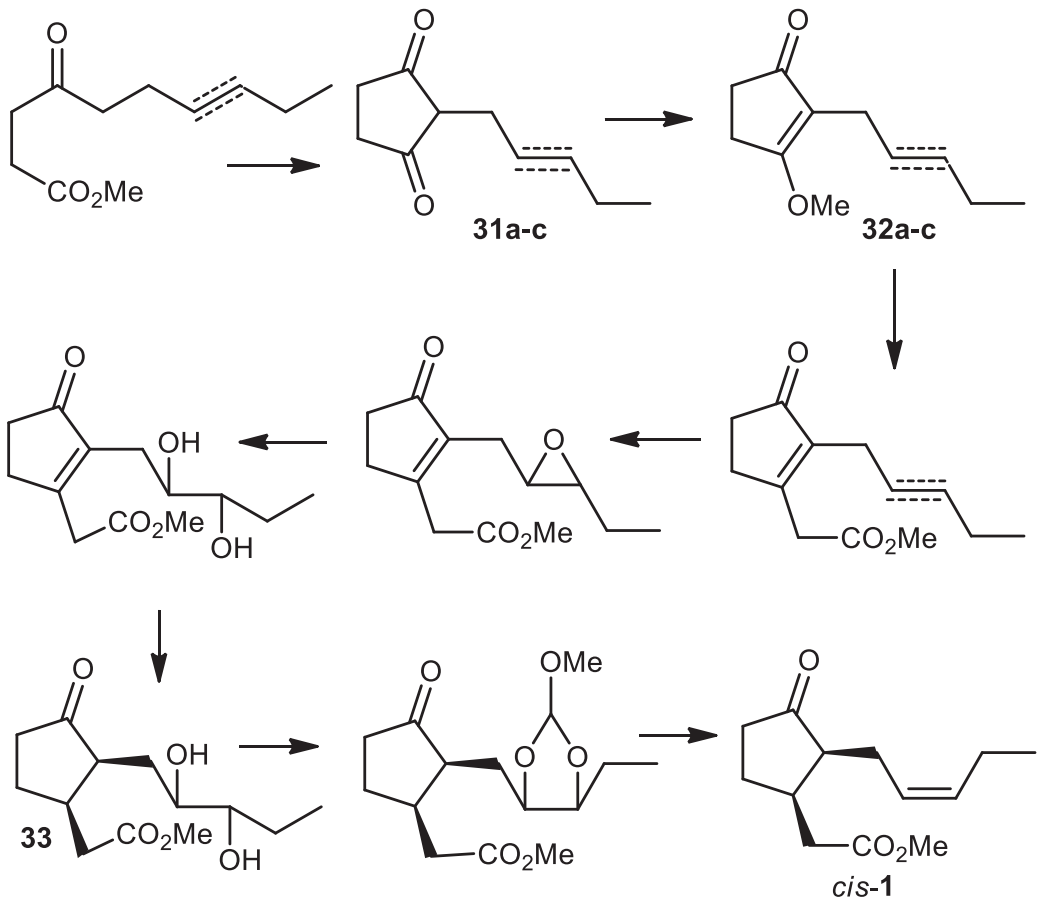
[j]Splendione is a trademark of Firmenich.

Methyl *cis*-Jasmonate

An industrially feasible approach was recently claimed by K. Shimizu and F. Matsushita (**F-7**).[35] Starting from suitable saturated or unsaturated 1,4-keto esters, they obtained by Claisen cyclization, 1,3-cyclopentadiones **31a-c**. Indeed, the corresponding methylenol ethers **32a-c** were subjected to Michael addition, thus affording, after decarbomethoxylation, the desired dehydrohedione **13**, and hence Hedione HC **2**. The only innovative aspect is the epoxidation of a *E*-double bond, since after transformation of this *trans*-epoxide into the corresponding diol, the thus protected side chain allowed for hydrogenation of the tetrasubstituted unsaturation into a *cis*-2,3 substituted

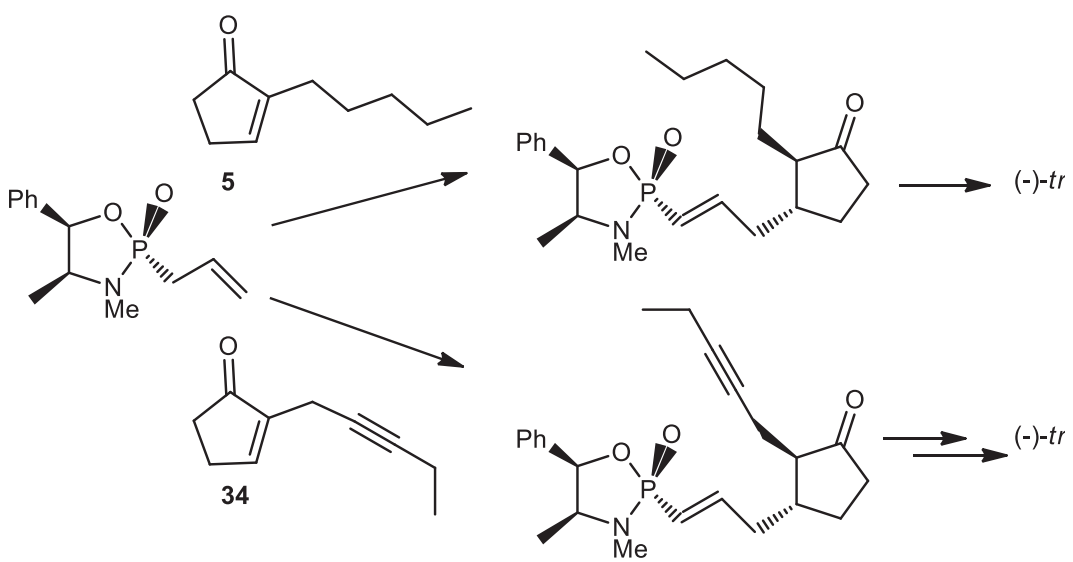
Methyl *cis*-jasmonate—an industrially feasible approach[35]

F-7

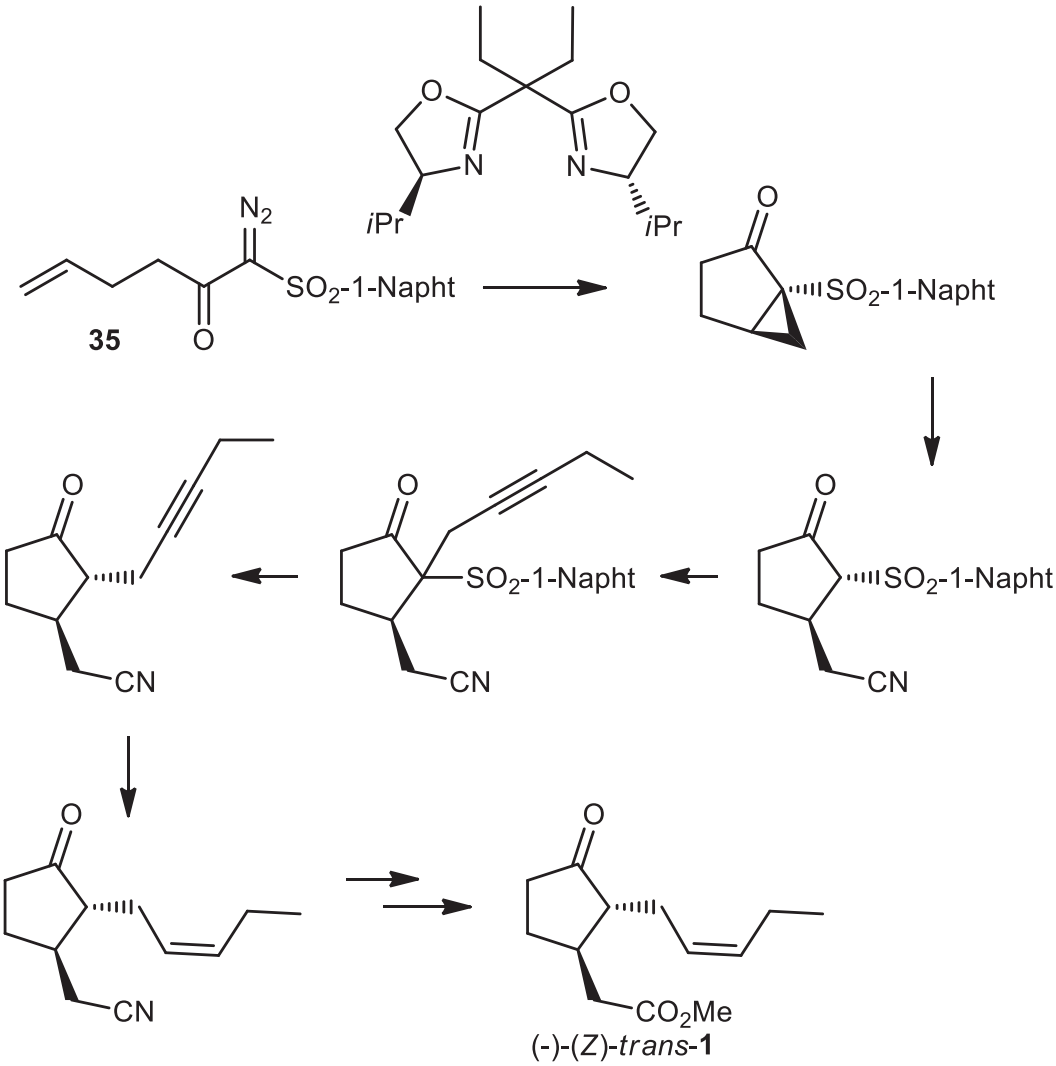


The asymmetric Michael addition of a chiral 2-propenylphosphonamide anion, derived from ephredrine, was reported by H. Hailes[77]

F-8



An alternative synthesis of (-)-methyl jasmonate consists of an asymmetric copper triflate catalyzed intramolecular cyclopropanation of diazosulfone 35[78] **F-9**



cyclopentanone **33** (**F-7**). Formation of a cyclic orthoester permitted the stereochemical control, so that regeneration of the Z-double bond finally afforded methyl epijasmonate **1**, as a 55:45 *cis/trans* mixture. By applying their allylcuprate addition to cyclopentenone **34** (**F-8**), followed by protonation with N-methylsalicylaldimine, N. Krause and S. Ebert also obtained *cis*-epijasmonate **1**.[26b]

(+)-Methyl *cis*-Jasmonate

In 1985 Japanese authors showed that solely the minor (+)-*cis*-enantiomer **1** gave rise to an intense odor, as later confirmed by synthesis of the practically odorless (-)-(Z)-*trans* methyl jasmonate by German authors.[44,76] The asymmetric Michael addition of a chiral 2-propenylphosphonamide anion, derived from ephredrine, was reported by H. Hailes (**F-8**).[77] This methodology, which necessitated chromatographic separation of the diastereoisomeric phosphonamides, was applied to both 2-substituted cyclopentenones **5** and **34**.

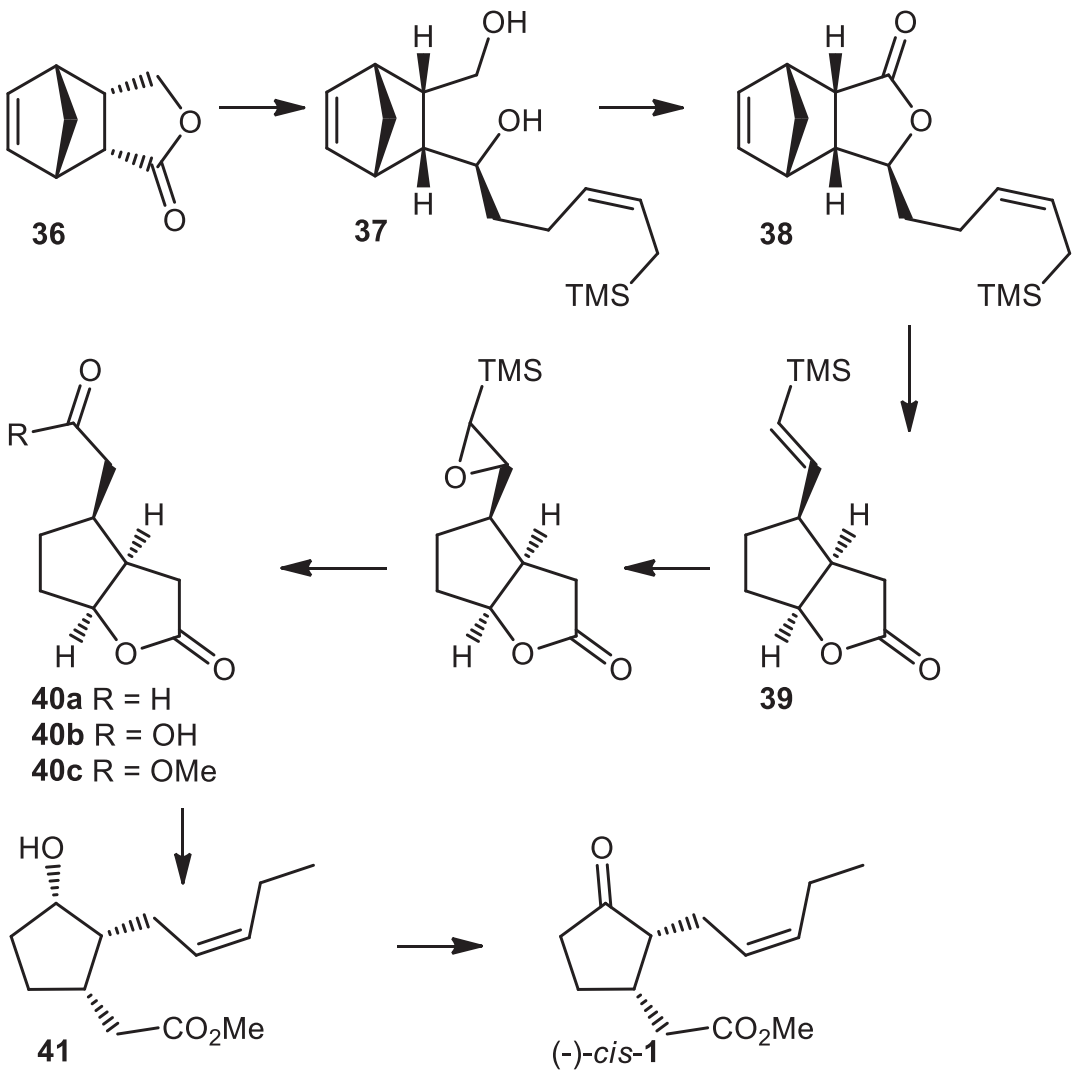
Cleavage of the prosthetic group was performed by ozonolysis in CH_2Cl_2/MeOH under basic nonreductive conditions. Unfortunately, despite a high 90% ee, either the thermodynamically more stable (-)-*trans*-**1** or (-)-*trans*-**2** was isolated.

An alternative synthesis of (-)-methyl jasmonate, reported by M. Nakada, consists of an asymmetric copper triflate catalyzed intramolecular cyclopropanation of diazosulfone **35** (**F-9**).[78]

Opening of the cyclopropane ring with NaCN allows, despite concurrent O-alkylation, for the side chain to be introduced regioselectively. Unfortunately, the last classical steps furnished (-)-(Z)-*trans*-**1** (**F-9**).

Another academic approach reported by K. Inomata is based on the availability of lactone (-)-**36**, which, after DIBAL reduction, was subjected to an excess of Grignard reagent, thus affording diol **37** (**F-10**).[79] Catalytic reoxidation furnished lactone **38** in moderate yield. This nevertheless afforded, via a tandem retro-Diels-Alder/ene

An ultimate mild Dess-Martin oxidation finally furnished the undesired antipodal (-)-(Z)-*cis*-methyl epijasmonate 1[80] **F-10**



reaction, the *cis*-fused bicyclic lactone **39**. Epoxidation of this produced, after concomitant acidic rearrangement and desilylation, aldehyde **40a**. An oxidation-esterification furnished **40c**, a key intermediate in the Montforts synthesis of the all *cis*-cucurbic acid methyl ester **41**, via a second DIBAL reduction and Wittig reaction. An ultimate mild Dess-Martin oxidation finally furnished the undesired antipodal (-)-(Z)-*cis* methyl epijasmonate **1**.[80]

Since all reported syntheses of (+)-*cis*-**1** are tedious, C. Fehr elaborated an alternative asymmetric approach, which proved to be similarly applicable to Paradisone (**F-11**).[67,81] The chiral starting materials **42a**,**b** were obtained either via asymmetric hydrogenation or Corey's oxazaborolidine reduction of the corresponding unsaturated ketones **5** and **43**, respectively, or by kinetic enzymatic resolution, with recycling of the undesired enantiomer by acidic epimerization.[68–70,82,83] Chirality transfer by Ireland-Claisen rearrangement led, after decarboxylation, to the unsaturated esters **44**. The key steps are a diastereoselective syn epoxidation, with subsequent stereocontrolled suprafacial 1,2-H-shift, to afford the (+)-*cis*-isomers **1** and **2** in high enantiomeric purity. This approach represents the only practical access to (+)-*cis*-methyl epijasmonate **1**, reported to date.

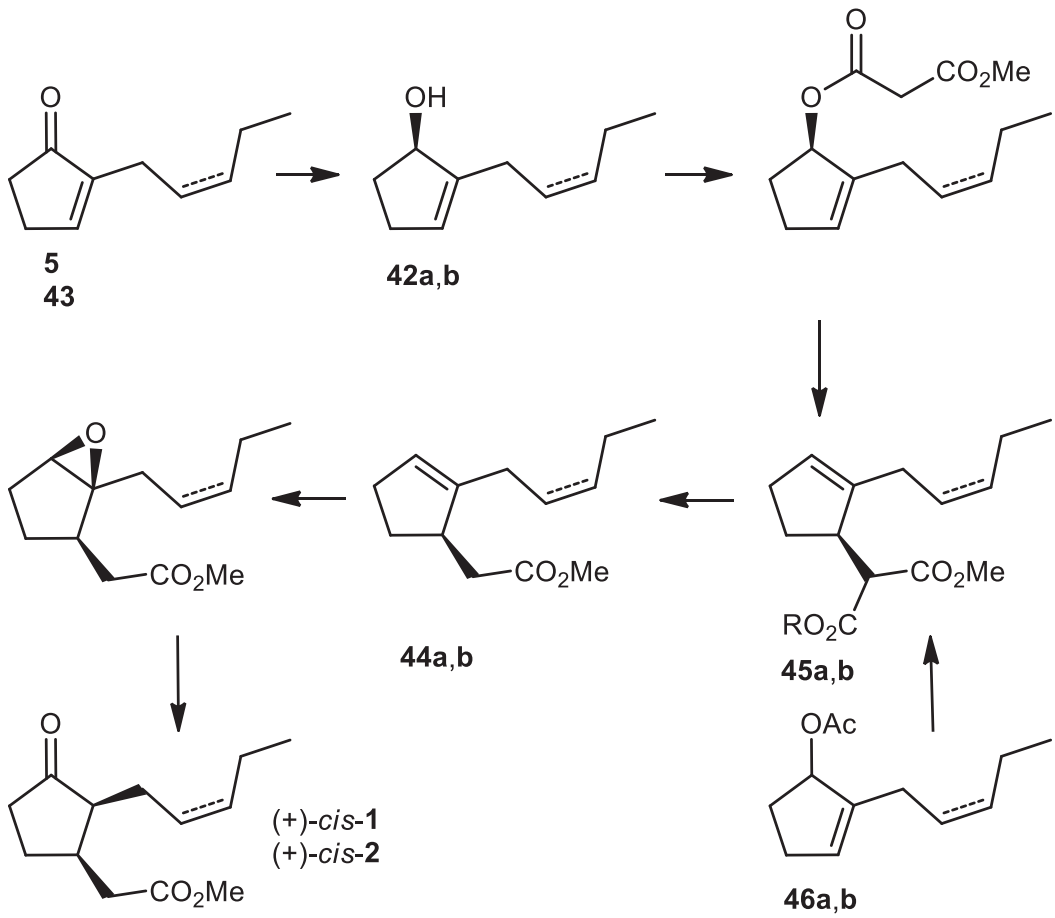
Based on the T. Kitahara Pd-catalyzed allylic substitution, an alternative entry to **45a,b** was also performed under G. Helmchen's asymmetric conditions, as reported from **46a** (99% ee), and analogously extended to the doubly unsaturated substrates **46b** → **45b** (98% ee), using 10 mol% of a diphenylphosphine derived from myrtenal.[84–87] These new syntheses and related products are currently being worked on by Firmenich's research and industrialization teams.

Isotopic Hedione and Splendione

Like much of the industry, Firmenich, under the direction of CEO Patrick Firmenich, is pursuing a sustainable and green orientation to its business by foregoing ecologically

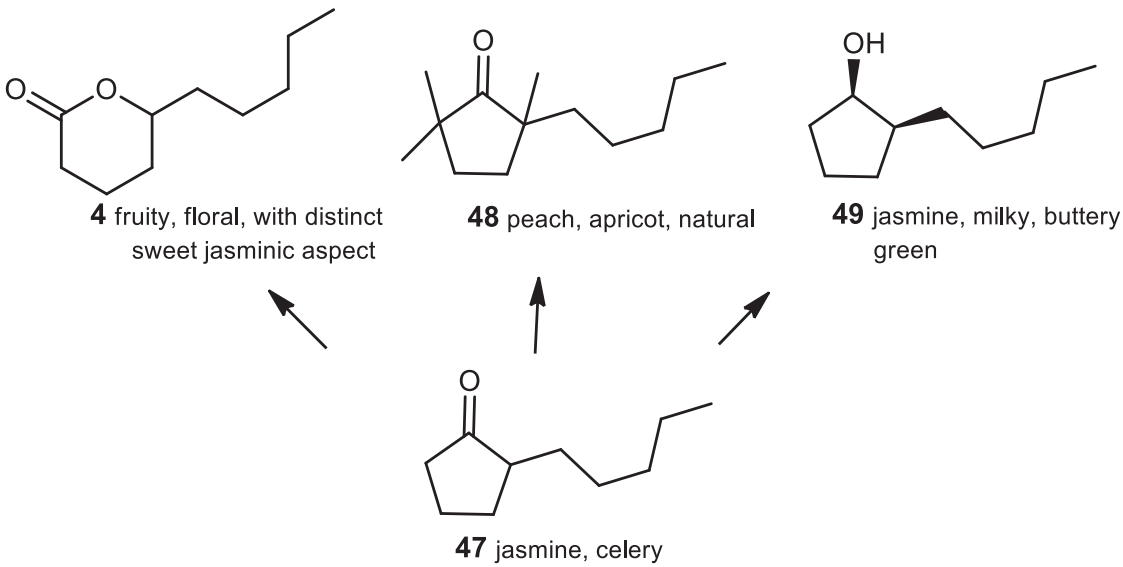
An alternative synthesis of (+)-*cis*-1, which proved to be similarly applicable to Paradisone[81]

F-11



The structures of Delphone 47, δ-decalactone 4, Veloutone 48 and Delphol HC 49 [97–100]

F-12



unfriendly ingredients. In accordance with the rapid evolution of legislation, such as the recent REACH directive of the European Union, it has become necessary to precisely know the biodegradation kinetics of large-volume ingredients and their persistence in waste or environmental waters.[88] This gave the impetus to A. Chaintreau to develop an accurate analytical GC/MS method for quantifying trace amounts, highly diluted in water, based on D_3 to D_5 labeled internal standards, while O. Haefliger has implemented a GC/MS method for bioaccumulation analysis in fish.[89–91] Furthermore, for substantivity, or diffusion studies on diverse materials or in complex matrices, Escher has synthesized OCT_3, $O^{14}CH_3$ and OCD_3 Hedione.[92] In this context, both analogous D-labeled and isotopic methyl jasmonate may similarly find their usefulness.[93,94] In the latter case, the synthetic approach of W. Kerr is reminiscent of the first catalytic Pauson-Khand reaction reported by Rautenstrauch for the synthesis of **5**.[95]

Compared to other large-volume compounds such as Furaneol, Habanolide, Cetalox, Dartanol and Damascones,[k] the Hedione process, with its diverse stereoisomeric and optical qualities, necessitated very important technological efforts and required the highest investment for a single ingredient.[96] This research also helped to produce several derived ingredients issued from common intermediates, such as Delphone[l] **47**, δ-decalactone **4**, as well as Veloutone[m] **48**, or Delphol HC[n] **49** (**F-12**).[97–100]

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[l]Delphone is a trademark of Firmenich.

[m]Veloutone is a trademark of Firmenich.

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