**REVIEW**

# The Jubilee of Methyl Jasmonate and *Hedione*®

by **Christian Chapuis**

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Dedicated to Dr. *A. Estreicher* on the occasion of her birthday

An internal historical point of view is presented on the discovery and development of both methyl jasmonate and its saturated analogue *Hedione*®. A discussion of the synthetic approaches performed during the last decade, and structure–activity relationships of analogous structures are also presented.

**Introduction.** – The title in itself may seem ambiguous since a jubilee refers to either a twenty five or fifty years period in Rome or Jerusalem, respectively. Moreover, which event should motivate these festivities: the discovery of methyl jasmonate (N378) in October 1957 by *Edouard Demole*, his synthesis of *Hedione*®[1]) (N378B), accomplished in 1958 and completed in May 1959 with that of methyl jasmonate, or their intellectual protection in February 1960 [1], the first 50 kg production of *Hedione*® in 1961, or their publications in 1962 [2][3]? It was recently decided that 2012 would be the official anniversary. We thus shall try to follow together the hectic history of this fascinating adventure.

**Discovery.** – In the late 1950s, *Roger Firmenich*, the then director[2]), much respected 'Monsieur *Roger*', instructed *E. Demole* to study in depth, as subject of his doctoral thesis in Prof. *E. Lederer*'s laboratories[3]), the concrete of Mediterranean jasmine (*Jasminum grandiflorum* L.), a variety of *Jasminum officinale* L., ubiquitous in the lower valleys of the Himalayas, in order to find and determine the missing structures responsible for this typical olfactive signature. At the same time, he also sent a generous sample to Prof. *L. Ruzicka*[4]), as he was initially involved in a previous analysis in Geneva [5]. Indeed, although more than 87% of the jasmine essential oil constituents had already been determined, the full olfactive reconstitution was still impossible. Thus

[1]) For the Epicureans, '*Hedone*', meaning agreeable and pleasant, was the quest for pleasure that would have only good consequences.

[2]) Son and successor of *Fred Firmenich*.

[3]) Institut de Biologie Physico-Chimique, Paris (1955–1959).

[4]) First director of Research at *Firmenich* (1925, then called *Naef & Cie*) [4], he then accepted a professorship at the University of Utrecht (1927), and finally at the Eidgenössische Technische Hochschule, Zürich (1929); laureate of the 1939 Nobel Prize for his work on polymethylenes and higher terpenes.

the fundamental element responsible for this wonderful radiance and deep sweet floral character was obviously hidden in the remaining unknown fraction. It is noteworthy that the price of one kilo of jasmine absolute[5]) could cost up to 20000 CHF [6], and the world production at that time was limited to *ca.* six tons/year [7]. This decision was motivated by the old saying 'no perfume without jasmine'. Indeed, up to the middle of the 20th century, *ca.* 80% of the marketed compositions contained a basic note extracted from this precious handpicked flower [8], such as for example *Mitsouko* (*Guerlain*, 1919), *Chanel N°5* (*Chanel*, 1921), or *L'air du Temps* (*Nina Ricci*, 1948).

From five kilos of Egyptian jasmine concrete, *E. Demole* first isolated methyl jasmonate (**1b**; $< 0.8\%$ in the absolute, $C_{13}H_{20}O_3$) [2], and its correct structure, based on biosynthetic considerations, consistent with IR, UV, MS, and elemental, as well as degradation analyses, was suggested by Prof. *G. H. Büchi*[6]) (for **1a** and **1c**–**1g**, see last *Section* and *Table 2* below). It was very soon confirmed by subsequent synthesis of its more simple dihydro analogue *Hedione*® (**2e**) [3a], initially obtained by simple hydrogenation during the analyses and synthesis of natural **1b** [3b][9] (*Scheme 1*) (for **2a**–**2d** and **2f**–**2k**, see last *Section* and *Table 2* below). Both new ingredients were laevorotatory and existed in a *ca.* 5:95 to 10:90 *cis*/*trans* thermodynamic mixture at room temperature [10]. The absolute configuration of natural (−)-*trans*-**1b** ((*Z*) double bond), hence (−)-*trans*-**2e**, was later determined by *R. K. Hill* and *A. G. Edwards* [11]. The first synthesis of **2e** started from either the unsaturated acid **3** [12] or the corresponding δ-decalactone **4** [13] *via* cyclization to form cyclopentenone **5** [14], under either $ZnCl_2$- or $H_3PO_4$-catalyzed *Friedel–Craft* conditions, respectively. The subsequent *Michael* addition of diethyl malonate, followed by saponification of **6a** and decarboxylation afforded the free acid **7**, which necessitated a re-esterification.

The first synthesis of methyl jasmonate (**1b**) was longer and nonregioselective. It started from the keto ester **8**, accessible either in four steps from muconic acid, or by malonate *Michael* addition to the more expensive cyclopent-2-en-1-one. Alkylation of the intermediate enamine **9** with 1-bromopent-2-yne afforded a 2:3 regioisomer mixture, from which minor **10** could be isolated for mono-hydrogenation to the (*Z*)-configurated methyl jasmonate (**1b**). Perfumers were fascinated by the exquisite jasmine, deep, fatty, heavy buttery, floral, and authentic aspect of methyl jasmonate, and unanimously preferred it to its dihydro analogue **2e**, which is less radiant. Nevertheless, *Roger Firmenich* wisely promoted the development of the economically more promising *Hedione*® (**2e**).

***Hedione*® (2e).** – The synthesis of *Hedione*® was undertaken by *E. Demole*, who designed a simplified version based on cyclopentanone (**11**), a cheap byproduct in the industrial production of adiponitrile (key intermediate in the *Nylon-6* process). This involved an aldol condensation with pentanal followed by treatment with either a

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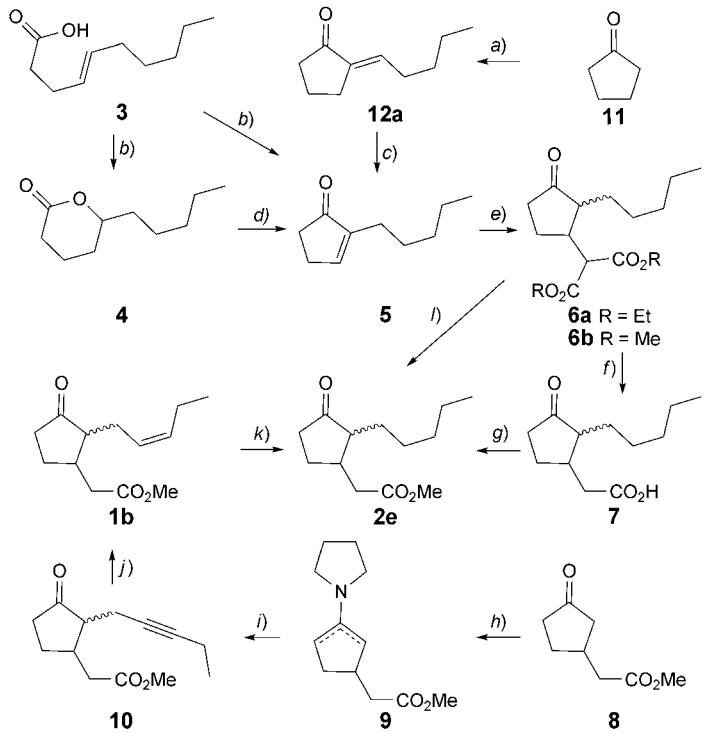
5) Extracted with EtOH from 2.3 kg of jasmine concrete, itself obtained from *ca.* one ton of jasmine flowers (1500–2500 $m^2$ of cultivated area).

6) Massachusetts Institute of Technology, Cambridge, U.S., consultant.

*Scheme 1*




*a*) Pentanal, $H_2O$, NaOH; 84%. *b*) TfOH, $MeNO_2$ or $ZnCl_2$; 18%. *c*) HCl, BuOH, 90°; 87%. *d*) $H_2SO_4$ or $H_3PO_4$; 92%. *e*) Diethyl or dimethyl malonate, EtOH or MeOH, EtONa or MeONa; >95%. *f*) NaOH, $H_2O$, EtOH, or MeOH, 64–78°; >90%. *g*) MeOH, $H_2SO_4$; 97%. *h*) Pyrrolidine, TsOH, cyclohexane, 82°, $-H_2O$; 96%. *i*) $BrCH_2CCEt$, dioxane, 90°, then $H_3O^+$; 66% based on bromide. *j*) $H_2$, *Lindlar* catalyst, cyclohexane; 92%. *k*) $H_2$, MeOH, $PtO_2$; 98%. *l*) $H_2O$, DMSO, 190°; 63%.

*Brønsted* acid [15], or $I_2$ [16], or *Formier* gas/Pd/C [17][7]), or, as advised by Prof. *W. Keim*[8]), a transition-metal-catalyzed isomerization of the exocyclic double bond of enone **12a** [19]. The *Michael* reaction was performed directly with dimethyl malonate[9]), and de(methoxycarbonyl)ation avoided final re-esterification[10]) (*Scheme 1*). Its perfumistic take off was particularly slow so that *Roger Firmenich* promoted the ingredient by sending samples to external known perfumers, amongst whom *E. Roudnitska* who created the successful *Eau Sauvage* for *Dior* (1966; 2.5% of the content). The chemical process was further ameliorated during all the lifetime of *Hedione*® since, at high volumes, each percentage point was both crucial and beneficial.

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[7]) These isomerization conditions were already earlier reported in [18].

[8]) RWTH, Aachen, Germany, consultant.

[9]) For the rediscovery of the wheel, see [20].

[10]) See [21a]. For the rediscovery of the spare wheel, see [21b].

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 more than 1000 CHF/kg and, as a result, it was first confined to fine fragrances such as *Diorella* (*Dior*, 1972; 8%). The production cost, however, continuously decreased and allowed perfumers to use increasing quantities of *Hedione*® in their compositions such as in *Charlie* (*Revlon*, 1973; 7%), *Métal* (*Paco Rabanne*, 1977; 8%), *Beautiful* (*Estée Lauder*, 1986; 17.2%), *Samsara* (*Jean-Paul Guerlain*, 1990; 16.3%), *Charlie Red* (*Revlon*, 1993; 17%), *Cristalle* (*Chanel*, 1993; 26%), or *Odeur 53* (*Comme des Garçons*, 1998; 65%!) [22]. Its use was also extended to other segments such as body- and home-care products, including cosmetics, toiletries, shampoos, soaps, and detergents[11]).

It took perfumers a few years to learn how to properly use the particular and extraordinary properties of *Hedione*® in compositions. They realized that while *Hedione*® itself had relatively low odor intensity, it provided an incredible synergistic effect. *Hedione*® rendered perfumes round, floral, and diffusive; soap perfumes were found to possess wonderful in-use diffusion and an appealing lingering effect on skin after use. Certain agarbatti (incense-stick) 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 diffusability are bestowed [23]. Several hypotheses were suggested for explaining these attractive phenomena. The booster effect of *Hedione*® could not be confirmed by specific symbiosis with *Ambrox*®, as the threshold detection value of the latter was not modified in the presence or absence of the former ingredient [24]. 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*®. Similarly, *D. Berthier* studied in detail the deviation of *Raoult*'s law in the presence of *Hedione*®, and showed that it resulted in an increased volatility for dihydromyrcenol, (3*Z*)-hex-3-en-1-ol, or *Zestover*®[12]). In addition, due to its unusual specific fixative properties, *Hedione*® may modify the substantivity of partners [25]. The headspace partition coefficient of *Hedione*® itself may, however, strongly depend on the paper quality of the smelling strips [26]. As such, these observations are not remarkable, since any solvent may influence the physical properties of a mixture. 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 [27]. Furthermore, the so-called inactive diastereoisomers are also thought to be involved in these biological/physical processes.

*Hedione*®, naturally occurring in trace amounts in tea flavor [28], Lima orange, a nonacidic, intensely sweet orange popular in Brazil [29], and apparently in several other fruits and flowers [29], was finally offered to external clients in 1970. When *Hedione*® lost its patent protection in the early 1980s, *Nippon Zeon* became a competitor by making a similar quality named *Claigeon*®.

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[11]) As compared to its initial price and produced volume, these currently internally decreased by two orders and increased by five orders of magnitude, respectively.

[12]) 2,4-Dimethylcyclohex-3-ene-1-carboxaldehyde.

***Hedione*® HC (High *cis*).** – In the early 1970s, the minor *cis*-stereoisomer, used in *Calandre* (*Paco Rabanne*, 1969; 5.8%), was claimed to be stronger [30][13]). At the beginning of the 1990s, *Nippon Zeon* commercialized a new-quality version, rich in *cis-Hedione*® (*cis*/*trans* 30:70), called *Cepionate*®. It was obtained by continuous distillation in the presence of a base, such as sodium carbonate, allowing for higher concentrations of the less volatile *cis*-isomer at elevated temperatures [31] (*Table 1*).

Table 1. cis/trans *Ratios and Thresholds of Diverse Qualities of* **2e** [32][33b]

| | *cis*/*trans ca.* | Odor threshold [ng $l^{-1}$] |
|---|---|---|
| *Hedione*® (*Firmenich*) | 10:90 | 0.280 |
| *Cisdione*™ (*Firmenich*)[a]) | 30:70 | 0.093 |
| *Kharismal*® (*IFF*) | 60:40 | 0.046 |
| *Jasmodione*® (*Takasago*) | 70:30 | 0.040 |
| *Hedione*® HC (*Firmenich*) | 75:25 | 0.037 |
| *Hedione*® VHC (*Firmenich*) | 90:10 | 0.031 |
| *Paradisone*® (*Firmenich*) | 94:6 | 0.015 |

[a]) Obtained by mixing in appropriate amounts *Hedione*® and *Hedione*® HC, for matching the quality of *Cepionate*®.

The immediate response from *Firmenich* was focused on two actions, namely the stereoselective synthesis of *cis-Hedione*®, and its optically active version named *Paradisone*®. First of all, in collaboration with Prof. *E. Wenkert*[14]), *C. Vial* and *F. Näf* performed a synthesis of pure *cis-Hedione*® (*cis*-**2e**), astonishingly stable towards chromatographic purification, *via* a *Diels–Alder* reaction onto a fulvene derivative [34]. Alternatively, adapting the conditions developed by *A. F. Thomas* at the beginning of the 1970s for GC/NMR response/stability studies, a more simple stereoselective synthesis, *via* hydrogenation of didehydrohedione (= DHH) **13** was then performed on a kg-scale by *V. Rautenstrauch*, thus demonstrating that this quality could be manipulated, distilled, stocked, and used in perfumery, under controlled $5 < pH > 7$ or stabilized conditions. Indeed, DHH **13** (*Scheme 2*), whose synthesis was optimized in-house by *Y. Mentha*, was already accessible, as intermediate target, by either direct chromium trioxide oxidation of **14** [35], or by bromination/HBr elimination of *trans-Hedione*® (*trans*-**2e**) [36][15]). It could also be obtained *via* the electro-reductive intramolecular coupling of a keto nitrile **15** [37], or, as explored by

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13) Considering an infringement to the initial patent, *E. Demole* personally brought, by train, commercial samples, bought, certified, and sealed by a notary, to deliver them directly in proper hands of Prof. *M. Fétizon*, appointed as an expert, who confirmed the analyses done in Geneva. The court of justice of Paris finally invalidated the French patent and its extensions.

14) University of California San Diego, San Diego, U.S., on sabbatical at *Firmenich* at that time.

15) The chloro analogue shows the following analytical data: $^1$H-NMR: 0.88 (*t*, *J* = 7, 3 H); 1.08–1.18 (*m*, 1 H); 1.26–1.35 (*m*, 4 H); 1.36–1.47 (*m*, 1 H); 1.70–1.80 (*m*, 1 H); 1.80–1.92 (*m*, 1 H); 2.03–2.13 (*m*, 1 H); 2.13–2.23 (*m*, 2 H); 2.50 (*dd*, *J* = 9, 16, 1 H); 2.58–2.68 (*m*, 2 H); 2.73 (*dd*, *J* = 4, 16, 1 H); 3.74 (*s*, 3 H). $^{13}$C-NMR: 209.4 (*s*); 172.4 (*s*); 75.5 (*s*); 51.9 (*q*); 41.1 (*d*); 35.1 (*t*); 35.0 (*t*); 34.7 (*t*); 32.0 (*t*); 24.7 (2*t*); 22.3 (*t*); 13.9 (*q*). MS: 260 (1, $M^+$), 224 (18), 190 (8), 169 (10), 154 (100), 151 (51), 133 (11), 117 (22), 109 (24), 95 (25), 81 (14), 79 (18), 74 (19), 67 (16), 55 (15), 41 (13). The nonepimerizing 2-fluoro analogue was never reported.

*R. L. Snowden*, *via* a *Tsuji*-like dehydrogenation of its trimethylsilyl enol ether **16** [38], followed by double-bond isomerization of **17** [39][16])[17]), or unselectively from **5**, *via* addition of methyl diazoacetate [41]. Nevertheless, these approaches were either academic or too expensive, like *F. Näf*'s malonate addition [42] to the thermally rearranged aldol adduct [43] of pent-2-enal to cyclopentanone **11** [44], or the cascade *Baylis–Hillman*/*Claisen* ortho-ester rearrangement towards the common intermediate **18**[18]), accompanied by either direct hydrogenation [18], 1,4-hydride addition [45], or optional double-bond isomerization [18], or the more recent direct $HIO_3$ oxidation of *Hedione*® (**2e**) [18]. More industrial methods were developed, either by *K. Crawford*, *V. Rautenstrauch*, and *A. P. Uijttewaal*, involving a peracetic oxidation of the regioisomeric enol acetate **19** [46], or by *B. Winter*, after either appropriate *Wadsworth–Emmons* reaction or nucleophilic addition, *via* the $BF_3 \cdot OEt_2$ rearrangements of either epoxides **20** [47] or **21** [48]. The *Michael* addition to 3-methoxy-2-pentylcyclopent-2-en-1-one (**22a**), as mentioned by *E. Demole* in his review [49], was detailed three years later by a Chinese group [50], and recently patented by both *Givaudan* [51] and *Asahi Kasei Chem. Corp.* [52a]. The ultimate success resides in nonepimerizing hydrogenation conditions to produce *Hedione*® Very High *cis* (VHC) from **13** as a *ca.* 92 : 8 to 98 : 2 mixture directly after workup [52a][53][54]. It may also be obtained in a multistep academic sequence from **5**, *via* an allyl cuprate 1,4-addition, followed by a stereoselective protonation with *N*-methylsalicylaldimine, completed by an ozonolysis with oxidative workup of **23**, followed by mild esterification with unstable diazomethane [33a]. The enriched HC quality is perceived as very powerful and tenacious, nicely floral and jasmine-like, and is contained, for example, in the bestsellers *Armani Code Homme Sport* (*Armani*, 2004), *Rock me* (*Anna Sui*, 2009), and *Axe Music Star* (*Unilever*, 2010). Last but not least, in a flavor application, $CO_2$-containing beverages spiked with *Hedione*® HC were studied, resulting in a 50 : 50 *cis*/*trans* mixture after storage during three months at 4° [55].

***Paradisone*® ((+)-*cis*-2e).** – The intrinsic olfactive values of all stereoisomers of *Hedione*® (**2e**) were determined either by *C. Vial via* HPLC separation of their menthyl esters, or directly sniffed by *A. Morris* at the outlet of chiral GC columns[19]), and these properties were later published by *P. Werkhoff et al.* [29]. Following the suggestion of Prof. *G. M. Whitesides*[20]), *V. Rautenstrauch* prepared and submitted for evaluation

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[16]) Data of **16**: $^{13}$C-NMR: 210.8 (*s*); 171.9 (*s*); 165.1 (*d*); 133.8 (*d*); 51.8 (*q*); 51.3 (*d*); 44.1 (*d*); 38.5 (*t*); 31.9 (*t*); 30.7 (*t*); 26.5 (*t*); 22.5 (*t*); 14.0 (*q*). Data of **17**: B.p.: 95–100°/0.05 Torr. $R_f$ (toluene) 0.32. IR: 2930, 1731, 1645, 1438, 1254, 1199. $^1$H-NMR: 0.20 (*s*, 9 H); 0.88 (*t*, *J* = 7, 3 H); 1.20–1.40 (*m*, 6 H); 1.53 (*m*, 1 H); 1.84 (br. *d*, *J* = 16, 1 H); 2.06 (*m*, 1 H); 2.25–2.60 (*m*, 5 H); 3.66 (*s*, 3 H); 4.47 (br. *s*, 1 H). $^{13}$C-NMR: 173.5 (*s*); 156.2 (*s*); 99.3 (*d*); 51.3 (*d*); 51.0 (*q*); 41.0 (*t*); 37.4 (*d*); 33.8 (*t*); 32.3 (*t*); 26.5 (*t*); 22.7 (*t*); 14.1 (*q*); 0.0 (3*q*). MS: 298 ($M^+$, 3), 241 (6), 225 (100), 167 (30), 155 (9), 73 (78).

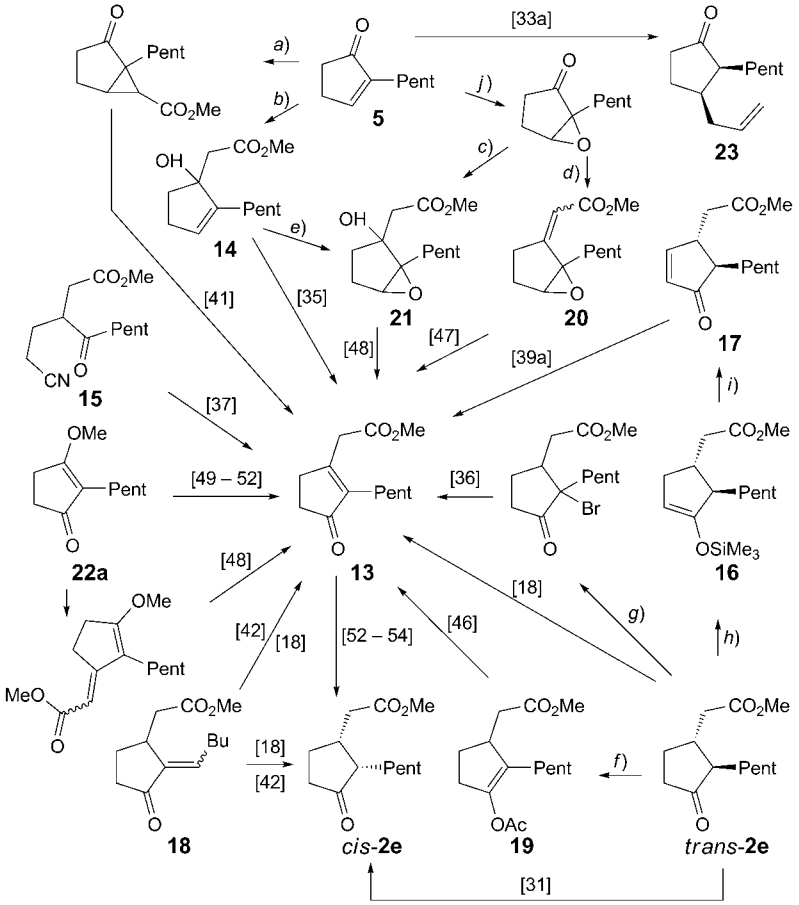
[17]) The corresponding methyl didehydrojasmonate analogue [10a][39][40] exhibits a floral, green scent. Furthermore, the approach *via Michael* addition of either diallyl or methyl allyl malonate to **5** failed at the *Tsuji* dehydrogenation step, as attempted by *F. Näf* and *R. Decorzant*.

[18]) Ester **18** [18][42] exhibits jasmine-like scents associated with fruity citrus aspects.

[19]) This perfumer suggested the harmonizing effect of *Hedione*® in composition.

[20]) Harvard University, Cambridge, U.S., consultant.

*Scheme 2*

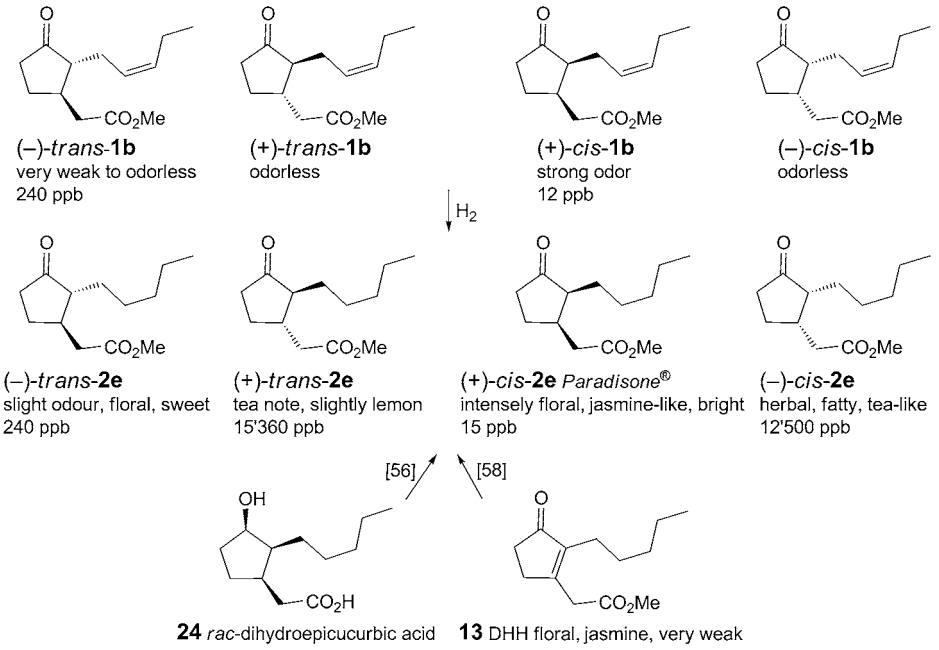



*a*) $N_2CH_2CO_2Me$, 70–230°; 26%. *b*) $BrCH_2CO_2Me$, Zn; 75%. *c*) $MeCO_2Me$, lithium hexamethyldisilazanide (LiHMDS), THF, −78°; 87%. *d*) $(MeO)_2P(O)CH_2CO_2Me$, MeONa, pentane; 91%. *e*) 3-Chloroperbenzoic acid (*m*CPBA), $CH_2Cl_2$; 84%. *f*) $Ac_2O$, TsOH; 92%. *g*) $Br_2$, AcOH. *h*) Lithium diisopropylamide (LDA), $Me_3SiCl$, THF, −60°; 83%. *i*) $AllylOCO_2Me$, $[Pd(OAc)_2]$, MeCN, 82°; 88%. *j*) $H_2O_2$, KOH, $K_2CO_3$, MeOH, 20°; 61%.

gram quantities of each stereoisomer by resolution of dihydroepicucurbic acid **24** [56] (*Scheme 3*).

Then, under the leadership of *V. Rautenstrauch*, assisted by *J.-J. Riedhauser*, *D. Dobbs*, and a post-doctoral fellow, *K. P. Vanhessche*, the asymmetric hydrogenation of DHH **13** was investigated, although at that time, nothing had been reported for tetrasubstituted double bonds. The first successes were obtained with the corresponding acid and either simple or sulfonated binap, or Et-duphos ligands (90% ee), coordinated to unsaturated more electrophilic $Ru^{II}$, used as new precatalysts [53] (binap = [1,1′-binaphthalene]-2,2′-diylbis[1,1-diphenylphosphine]; duphos = 1,1′-(1,2-phenylene)-bis[phospholane]). These conditions were then extended to the methyl ester **13** with

Scheme 3. *Stereoisomers of Methyl Jasmonate* **1b** [32a][57a] *and* Hedione® **2e** [29], *with Their Olfactive Properties and Respective Thresholds*




either Me-duphos (64% ee) [58], or the cheaper, tunable and more versatile josiphos derivatives (50–88% ee) which, for the production of (+)-*cis*-**2e**, turned out to be the most effective of all the screened diphosphine ligands in [Ru(ligand)(H)($\eta^6$-cycloocta-1,3,5-triene)]($BF_4$) [59] (josiphos = 1-phosphino-2-(1-phosphinoethyl)-substituted ferrocene). *V. Rautenstrauch* also closely collaborated with external specialists in the appropriate fields, such as *H.-U. Blaser*'s team[21]) [60]. After putting them on the right track, he could collect the fruitful results of collaborations with Profs. *J.-P. Genet*[22]) who replaced isopropyl alcohol as H-atom donor by $CH_2Cl_2$ as appropriate solvent [56] and *S. H. Bergens*[23]) [61]. It may take some time to make the decision between keeping secret or protecting an industrial process[24]). In fact, even with the greatest discretion, it

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[21]) *Solvias*, Basel.

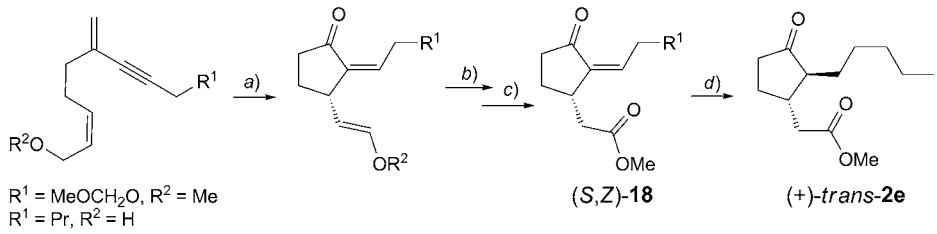
[22]) Ecole Nationale Supérieure de Chimie, Paris.

[23]) University of Alberta, Edmonton.

[24]) A typical case in point is the three-year delay in filing a patent on the optically active diastereoisomers of *Norlimbanol*®/*Limbanol*® (1-(2,2,6-trimethylcyclohexyl)hexan-3-ol/1-(2,2,3,6-tetramethylcyclohexyl)hexan-3-ol), which was finally filed nationally with a one day priority over that of a Japanese competitor [62a][62b]. The WIPO (World Intellectual Property Organization) in Geneva even refused to consider the line of date change, as simultaneity geographical argument. As stated by *A. J. Hutt* 'A potential commercial problem could arise if a single isomer of a previously marketed racemate could be patented but by a company other than the compounds' originator. In this situation, obviously the competitive position of the originator in the market place would be difficult, to put it mildly.' [62c].

often appears that identical ideas spontaneously emerge practically simultaneously in diverse groups, and therefore, it is always advisable to protect the invention as soon as possible. Thus, for example, development of the synphos diphosphine ligand (synphos = 1,1′-(2,2′,3,3′-tetrahydro[5,5′-bi-1,4-benzodioxin]-6,6′-diyl)bis[1,1-diphenylphosphine]), carried out in Geneva in 1998 (see Scheme 26 in [63]), was independently discovered later in Paris (see priority date in [64]). Sometimes also, discretion may originate from competing teams, who are reluctant to cite the original work [65]. Finally, with the constant support of *Pierre-Yves Firmenich*, as well as the efforts of the development team, a robust procedure could be transferred to industrial production of *Paradisone*® ((+)-*cis*-**2e**). This simple process was preferred to *Cinchonia* alkaloid catalyzed asymmetric *Michael* addition of dimethyl malonate to **5**, where a range of ee, culminating in 80–90%, was obtained depending on the phase-transfer catalyst and reaction conditions used, since this procedure afforded essentially the undesired *trans*-stereoisomer of *Paradisone*® [66], which may have other fixative or antagonistic influential properties. Ignoring the prior art [18], *F. Liu et al.* also secured the *trans* disposition of the side chains *via* a copper hydride 1,4-addition to (*S*,*Z*)-**18**, following a particularly efficient asymmetric $Rh^I$-catalyzed intramolecular *Alder*-ene-type cycloisomerization reaction of a (*Z*)-1-en-6-yne, tethered by an appropriate chain, in the presence of (*S*)-binap (99% ee), with subsequent oxidation ($NaClO_2$, $H_2O_2$) and esterification ($Me_3SiCHN_2$) [45] (see *Scheme 4*).

*Scheme 4*



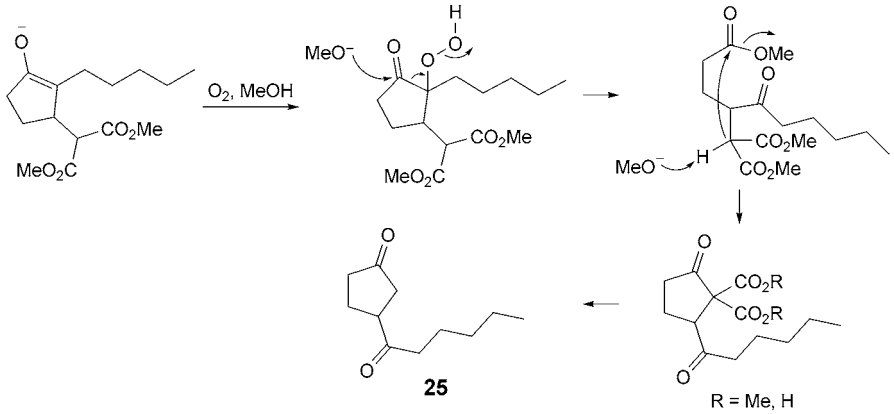

*a*) $[Rh(cod)Cl]_2$ (cod = cycloocta-1,5-diene), (*S*)-binap, $AgSbF_6$; 89–93%. *b*) $NaClO_2$, $H_2O_2$, MeCN, $H_2O$, $KH_2PO_4$. *c*) $Me_3SiCHN_2$, THF, MeOH; 40% over two steps. *d*) $[Cu(PPh_3)H]_6$, benzene; 62%.

Recently, *Paradisone*® ((+)-*cis*-**2e**) was incorporated in *Mystery* (*Naomi Campbell*, 2003; 21%) and *Ange ou Démon* (*Givenchy*, 2006; 25%), amongst other outstanding examples. Its commercial utilization also necessitated a few years of experience from the perfumers' side. I can remember a disappointing situation in '*a parte*' of the Bürgenstock Conference, when I was approached by a colleague from the competition, who told me that they specifically analyzed a few of our compositions, and according to them, the optical purity of *Paradisone*® was far from that claimed in the original publication! After a rapid internal survey, it appeared that some perfumers used to mix *Hedione*® with either *Hedione*® HC or *Paradisone*®, claiming a positive influence of the odorless stereoisomers on the compositions [67a].

**Impurities and Off-Notes.** – *Hedione*®, now produced by many companies, is not of even quality [67b]. This results from mastery of distillation techniques, as performed at

both *Firmenich's* pilot or production plants by, amongst many others, *F. Delay*. This eliminates tiny impurities, responsible for the heavier and mushroomy off-notes. In fact, several by-products may destroy the charm, and, besides the photochemical by-products of *Hedione*®, studied by *W. Skorianetz*, it is the production fingerprint analysis of *S. D. Escher* and *A. Morris*, which helped to bring some of them to the open, like traces of either pentanoic acid, or 2-cyclopentylidenecyclopentan-1-one[25]). While practically undetectable on the GC analytical traces, the most potent chemical responsible for the disagreeable mushroom-like odor took time to be isolated, and its structure was determined to be the mysterious diketone derivative **25** [69] (*Scheme 5*). It was only a few years later, in 1980, during an internal brainstorming that Prof. *A. Eschenmoser*[26]) proposed a plausible explanation for the presence of a hexanoyl side chain, as represented in *Scheme 5*.

*Scheme 5*




**Methyl Jasmonate (1b).** – The radiant methyl jasmonate (**1b**) is considered nobler than *Hedione*®, and when *Fred-Henri Firmenich* took over from *Roger Firmenich*, some tenacious perfumers requested this elating ingredient. This ubiquitous natural product occurs in Tunisian *Rosmarinus officinalis* L. [70], in lemon peels as the *cis*-epimer [71], in fresh bergamot fruits from Vilfrido Raymo (*Simone Gatto*, Messina, Italy) and sweet lemon (*Citrus limetta*) [72], as well as in ki-mikan fruit (*Citrus flaviculpus*) [73], in tea flavor [28][74][75], in longoza concrete [76], extracted from *Hedychium flavum* (Zingiberaceae), a flower growing in Madagascar, as well as in white champaca (*Cestrum nocturnum* L.), a plant growing in the Philippines [77]. Also identified, in the *cis*-form, as a component of the sexual pheromone of the male oriental fruit moth

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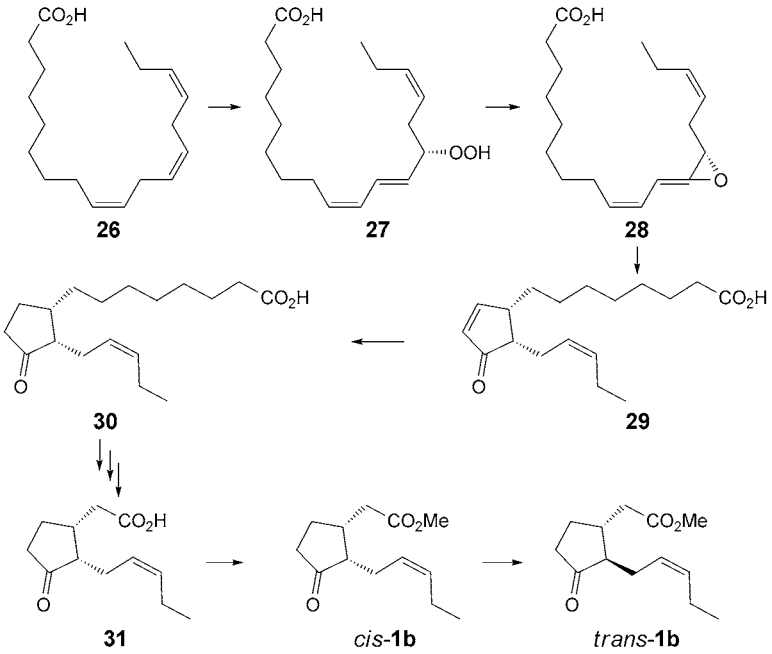
[25]) Another derived impurity, methyl 2-cyclopentyl-3-oxocyclopentane-1-acetate, exhibits nice jasmine, *Hedione*®, lemon, and hydroxycitronellal notes [68]. $^1$H-NMR: 1.20–1.80 (*m*, 9 H); 1.89 (*m*, 1 H); 2.00 (*m*, 1 H); 2.3–2.4 (*m*, 4 H); 2.45 (*m*, 1 H); 2.62 (*m*, 1 H); 3.70 (*s*, 3 H). $^{13}$C-NMR: 219.7 (*s*); 172.7 (*s*); 56.8 (*d*); 51.6 (*q*); 40.3 (*d*); 39.6 (*t*); 38.0 (*t*); 37.5 (*d*); 30.0 (*t*); 29.7 (*t*); 27.0 (*t*); 25.0 (*t*); 24.9 (*t*). MS: *trans* 224 (1, $M^+$), 156 (23), 151 (13), 83 (100), 82 (21), 67 (11); *cis* 224 (1, $M^+$), 156 (23), 83 (100), 82 (23), 67 (13).

[26]) Eidgenössische Technische Hochschule, Zürich, consultant.

(*Grapholitha molesta*) [73], this challenging molecule was avidly tackled by *Firmenich's* research division under *G. Ohloff*.

The ultimate epimerization step could be an *artifact* resulting from the extraction and isolation methods, and the naturally active form of methyl jasmonate was suggested to be the *cis*-stereoisomer [78]. The stereoisomer (+)-*cis*-**1b** shows biological activity [79], such as regulation of plant growth [80], or defense [81], as well as signal transmission in interplant communication [82]. Its biosynthesis, described in *Scheme 6*, is adapted from the pioneering work of *B. A. Vick* and *D. C. Zimmerman* [83]. $\alpha$-Linolenic acid (**26**) affords, after treatment with a lipoxygenase [84], the intermediate hydroperoxy derivative **27** which is transformed by an allene oxide synthase [85] into epoxy derivative **28**. An allene oxide cyclase [86] promotes the ring formation (→**29**), and the endocyclic unsaturation is subjected to a 12-oxo-phytodienoic acid reductase [87] (→ **30**). Successive $\beta$-oxidations degradate the side chain (→ **31**), which is finally esterified by a jasmonic acid carboxyl methyl transferase [88]. 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. Nevertheless, the engineering of rate-limiting enzymes seems, therefore, more promising, and *Firmenich* holds a patent on a strategic step, useful for producing a quality of methyl jasmonate NAT [89].

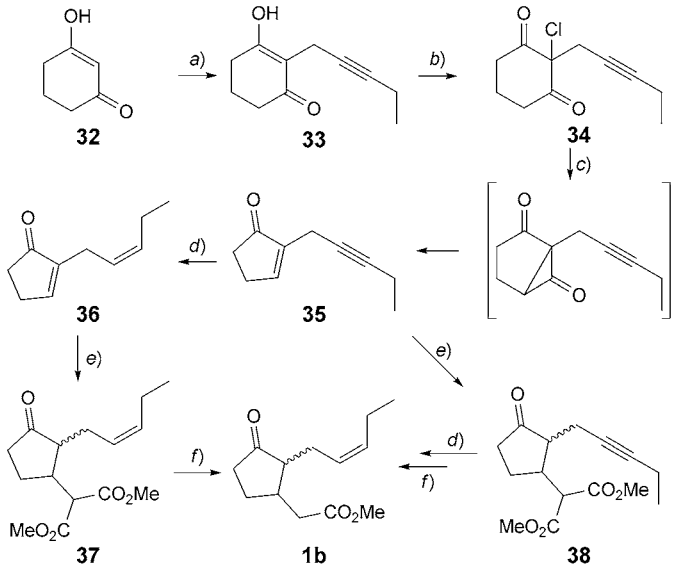
*Scheme 6*




Since diverse approaches towards methyl jasmonate (**1b**) are already discussed in two excellent reviews by *E. Demole* in 1982 [49], as well as *T. K. Sarkar* and *B. K. Ghorai* in 1999 [90], this subject shall not be covered exhaustively, but we shall

concentrate our attention on the last decade, including the industrially more promising syntheses, as we discussed it for **2e** [29]. Besides the first nonregioselective synthesis already cited in the introduction, it is worthwhile mentioning the seven-step practical approach of *G. H. Büchi* and *B. Egger* [91] (*Scheme 7*). The first step involves alkylation of dihydroresorcinol (=cyclohexane-1,3-dione; **32**) with 1-bromopent-2-yne to yield the masked diketone **33**. Further treatment with hypochlorite produced the chlorodione **34**, which, *via* ring contraction and CO extrusion, readily gave cyclopentenone **35**, after treatment with sodium carbonate in refluxing xylene. The synthesis was completed by the standard reaction steps; in this case, the *Michael* addition and the mono-hydrogenation over *Lindlar* catalyst may eventually be inverted (**35** → **36** → **37** → **1b** or **35** → **38** → **1b**).

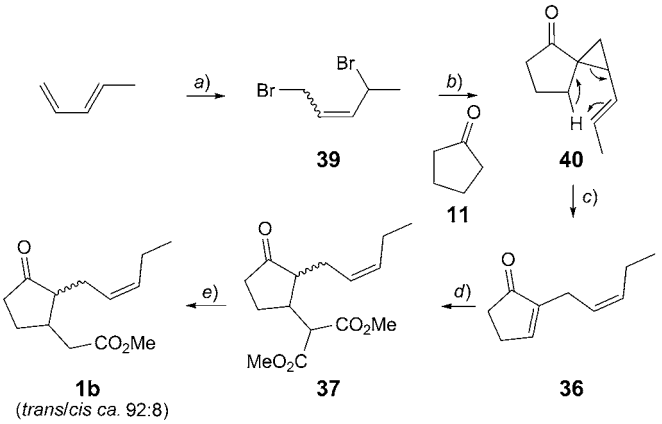
*Scheme 7*




*a*) Aq. KOH, $BrCH_2CCEt$; 82%. *b*) $^t$BuOCl, $CHCl_3$, $-15°$; 76%. *c*) Xylene, $Na_2CO_3$, 140°; 74%. *d*) $H_2$, *Lindlar* catalyst, BuOH; 95%. *e*) Dimethyl malonate, MeONa, MeOH; 95%. *f*) NaOH, $H_2O$, MeOH, then $H_2SO_4$, 60°, then MeOH, $H_2SO_4$, >90%, or hexandioic acid, 190°; 90%.

Introduction of methyl jasmonate (**1b**) into the perfumer's palette was rendered possible after development of one of the two shorter industrial approaches designed by *F. Näf* [92] (*Scheme 8*). The (*Z*)-configuration in the side chain of **1b** was very elegantly introduced *via* a homodienyl 1,5-H shift. Indeed, after bromination of piperylene (=(3*E*)-penta-1,3-diene) to form dibromide **39**, and its subsequent alkylation of cyclopentanone (**11**), a pyrolysis promoted the equilibration of the diastereoisomer mixture **40** to the more favorable *trans* cyclopropyl stereoisomer, followed by stereoselective rearrangement to introduce the desired (*Z*)-configuration

*Scheme 8*




*a*) $Br_2$, *N*-butylthiazolium bromide, 20°; 95%. *b*) $NaHCO_3$, THF, $H_2O$; 67%. *c*) 240–350°; 89%. *d*) Dimethyl malonate, MeONa, MeOH; 92%. *e*) MeOH, $H_2O$, 250°; 96%.

in enone **36**. The following synthetic steps were identical to those for *Hedione*® and afforded *via* **37** methyl *trans*-jasmonate **1b** in racemic form[27]).

Again extremely competitive, *Nippon Zeon* developed the *Tsuji* synthesis of **1b**, based on a Pd-catalyzed decarboxylation–dehydrogenation of either allyl keto esters **43** or **44** (obtained from **41** or **42**), as the original key step [44b] (*Scheme 9*). They more conveniently proceeded *via* the acetylenic intermediates **35** to afford the major *trans*-isomer **1b** (*Jasmoneige*®).

More recently, *J. M. Lem*, *K. P. Vanhessche*, and *C. Mahaim* presented a novel approach to build the unsaturated side chain of **1b** [93], culminating in a known (*Z*)-selective *Wittig* reaction [94] (*Scheme 10*). Thus, following *E. J. Corey*'s protocol [95], condensation of dimethoxyacetaldehyde with cyclopentanone afforded **45**, which was isomerized into the endocyclic cyplopentenone **46**. The usual dimethyl malonate *Michael* addition–de(methoxycarbonyl)ation sequence afforded, after acidic deprotection (*via* **47** and **48**), the known *trans*-aldehyde derivative **49**, which was submitted to *Torii*'s conditions to deliver methyl jasmonate (**1b**) [94]. Intermediate **48** may also be

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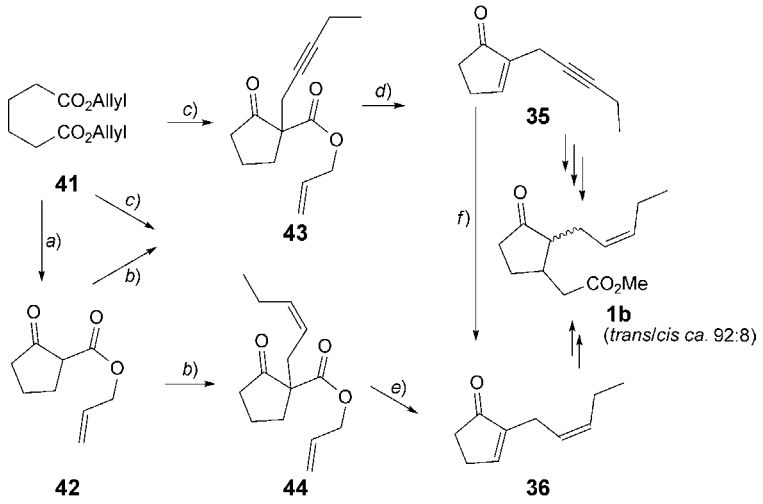
[27]) *Firmenich SA*, La Jonction, is situated practically in the heart of Geneva, close to the exit of the lake, where the tumultuous river Arve runs its sandy waters into the calm and limpid Rhône river. In 1984 during the development of this synthesis, a *Teflon*® gasket broke in a reactor, and several kilos of bromine escaped into the atmosphere. Carried away by the wind, the yellow smog slowly hydrolyzed into a cloud of diluted teargas over the city. When the siren started to howl, the present writer was on the opposite bank, in the office of late Prof. *W. Oppolzer* (University of Geneva), correcting the last details of his Ph. D. Thesis, when very soon Prof. *U. Burger* entered in hurry and said '*Wolfgang*, this is not an exercise!'. Police, equipped with gas masks and megaphones, asked the population to stay indoors and to close their windows. This was not perceived as the best means of communication, so that a few years later when the police headquarters moved to the borders of *Firmenich*'s site alongside the river Arve, the population sarcastically called their new address 'Quai des Bromes', thus referring to 'Quai des Brumes' as immortalized by the now classic French movie of *Marcel Carné* (1938), in which *Jean Gabin* whispers to *Michèle Morgan* his famous rejoinder 'You have beautiful eyes, you know!'. Knowing the epilogue, the public certainly also wept bitter tears at that time.

*Scheme 9*




*a*) Na, toluene; 48%. *b*) $K_2CO_3$, acetone, $ClCH_2CCEt$ or (2*Z*)-1-chloropent-2-ene, 66°; 87–88%. *c*) NaH, toluene, 90–100°, $ClCH_2CCEt$ or (2*Z*)-1-chloropent-2-ene; 86–88%. *d*) [$Pd(OAc)_2$], $Ph_3P$, MeCN, 82°; 81%. *e*) [$Pd(OAc)_2$], 1,1′-(ethane-1,2-diyl)bis[1,1-diphenylphosphine], MeCN, 82°; 55%. *f*) $H_2$, *Lindlar* catalyst, BuOH; 95%.

obtained from cyclopent-2-en-1-one (**50**) by the cascade *Baylis–Hillman*/*Claisen* reaction, earlier presented for the synthesis of DHH **13**, *via* **51** and hydrogenation of the unsaturated dimethyl acetal derivative **52** [18]. This latter was eventually isomerized to the tetrasubstituted double-bond analogue **53**, before deprotection and submission of **54** to a *Wittig* reaction, affording, after saponification, the natural acid **55b**, isolated from *Vicia faba* L. [96]. This approach also potentially opens an entry to the optically active version of **1b** by applying the *Paradisone*® conditions to the tetrasubstituted double-bond intermediate **53**, for example.

A particularly expeditious synthesis of **1b** [97] also started from cyclopent-2-en-1-one (**50**) [98] and took advantage of the previously described analogous *Diels–Alder* adducts [94][99]. Thus, the cheap and reactive chloroprene (=2-chlorobuta-1,3-diene), used in large quantities by the plastic industry, reacted with **50** to regioselectively afford, in the presence of a catalytic amount of $SnCl_4$, the cycloadduct **56**, with the correct oxidation state for conversion to an ester functionality. Indeed, ozonolysis of the C=C bond and reductive workup in the presence of sodium hydrogen carbonate and methanol directly furnished the methyl ester **49**. This three-step sequence culminated in the usual (*Z*)-selective *Wittig* reaction [94][100] (*Scheme 10*). *Tentatrice* (*Shiseido*, 1990; 25%), created by *K. Tokuda* and reminiscent of the Chinese *Cymbidium* orchids, incorporates a large proportion of methyl jasmonate (**1b**) in its composition[28]).

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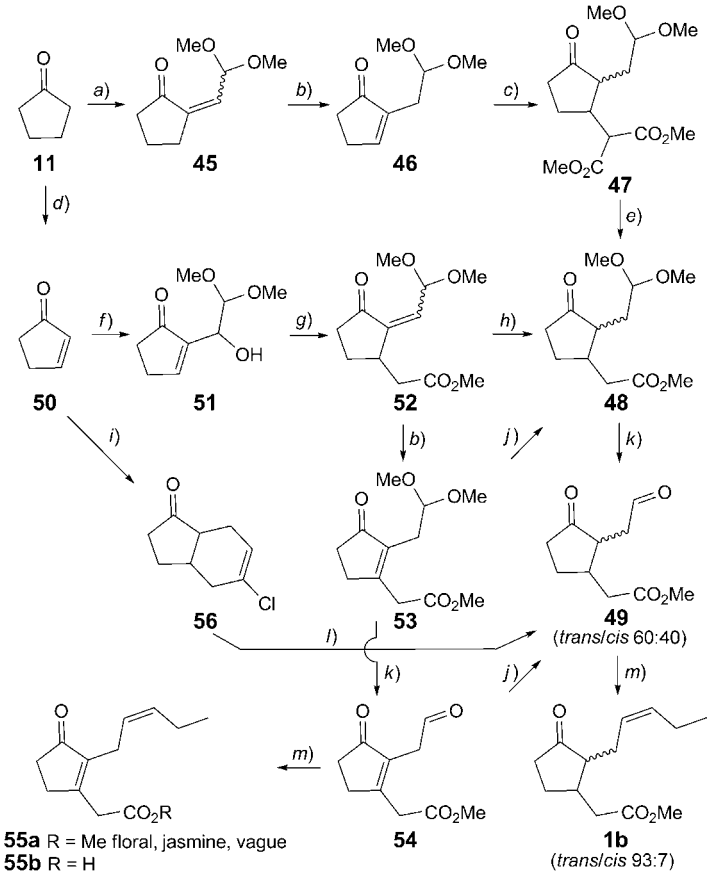
[28]) To celebrate this 50 year anniversary, this ingredient is now commercialized by *Firmenich* under the name *Splendione*™.

*Scheme 10*

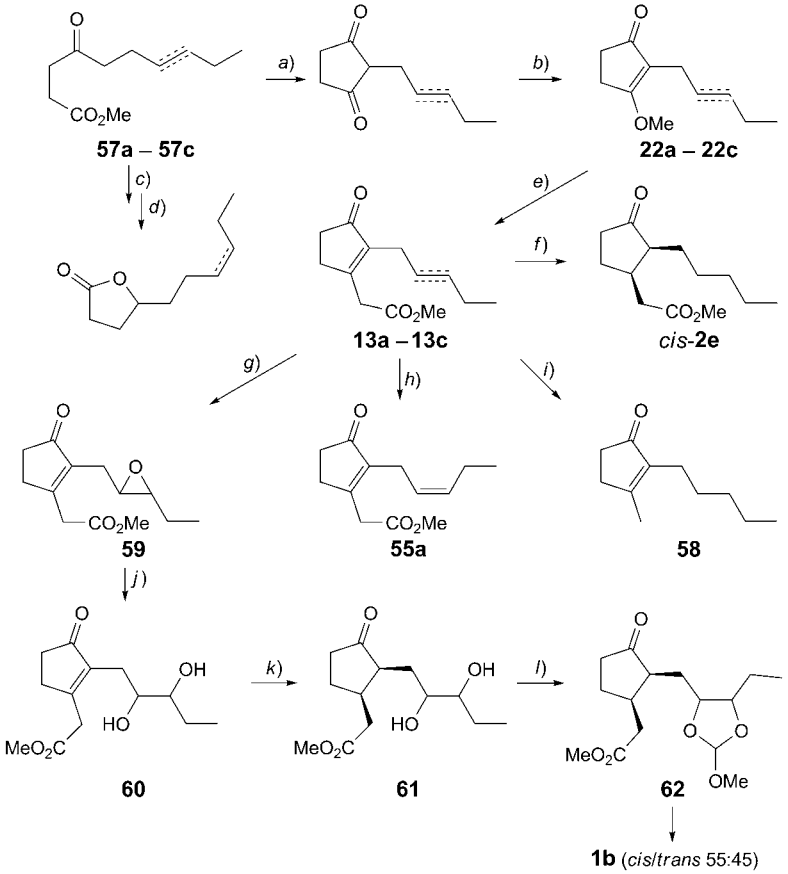



*a*) Morpholine, TsOH, then glyoxal dimethyl acetal (=2,2-dimethoxyacetaldehyde), cyclohexane, 25°; 70%. *b*) HCl, MeOH; 87–90%. *c*) Dimethyl malonate, MeONa, MeOH, then $H_3PO_4$; 92%. *d*) $HIO_3$, 74%, or $Et_3N$, $Na_2HPO_4$, $^t$BuOOH, $O_2$, $Pd(OH)_2$/C, $CH_2Cl_2$, 25°; 88%. *e*) NMP (1-methylpyrrolidin-2-one), $H_2O$, 160°; 81%. *f*) Glyoxal dimethyl acetal, $Bu_3P$, binol ([1,1′-binaphthalene]-2,2′-diol), THF, 20°; 96%. *g*) $MeC(OMe)_3$, pivalic acid (=2,2-dimethylpropanoic acid), 110°; 96%. *h*) $H_2$, Pd/C, cyclohexane; 95%. *i*) Chloroprene, $SnCl_4$, $CH_2Cl_2$; 75%. *j*) $H_2$, Pd/C, MeOH; 78–80%. *k*) AcOH, $H_2O$, 40°; 80–83%. *l*) $O_3$, AcOEt, −78°, then $Me_2S$, then MeOH, $NaHCO_3$; *m*) $(Ph_3PPr)Br$, $NaN(SiMe_3)_2$, THF, −60° to 20°; 44–88%.

**Methyl *cis*-Jasmonate (*cis*-1b).** – By applying their allylcuprate addition to cyclopentenone **35** (*Scheme 9*), followed by protonation with *N*-methylsalicylaldimine, *N. Krause* and *S. Ebert* obtained *cis*-jasmonate *cis*-**1b**, after neutral oxidation ($O_3$, $CH_2Cl_2$, −78°, then $Me_2S$, then $NaH_2PO_4 \cdot H_2O$, $NaClO_2/H_2O_2$, MeCN, $H_2O$), diazomethane esterification and final *Lindlar* hydrogenation in hexane (89% global yield) [33b].

An industrially feasible approach to *cis*-**1b** was recently claimed by *K. Shimizu* and *F. Matsushita* [52a] (*Scheme 11*). Starting from suitable saturated or unsaturated $\gamma$-keto

*Scheme 11*




*a*) MeONa, DMSO; 86–93%. *b*) HCl, MeOH, then $NaHCO_3$; 80–86%. *c*) $NaBH_4$, $H_2O$; 92–96%. *d*) $H_2SO_4$, $Na_2HPO_4$, 20°; 60–70%; *e*) Dimethyl malonate, MeONa, MeOH, then 62°; 89–91%; *f*) $H_2$, Pd/C, cyclohexane, 0°; 97%. *g*) *m*CPBA (3-chloroperbenzoic acid), $CH_2Cl_2$; 88%. *h*) $H_2$, *Lindlar* catalyst, MeOH; 88%. *i*) NaCl, $H_2O$, DMSO, 160°; 82%. *j*) $HClO_4$, $H_2O$, then $NaHCO_3$; 82%. *k*) $H_2$, Pd/C, AcOEt; 90%. *l*) $CH(OMe)_3$, TsOH, then $NaHCO_3$; 95%.

esters **57a**–**57c**, by simple reduction with $NaBH_4$, they could access either $\gamma$-decalactones or $\gamma$-jasmolactones. Moreover, by *Claisen* cyclization [101], they also obtained cyclopenta-1,3-diones [102], suitably substituted at C(2)[29]). Indeed, the corresponding methyl enol ethers **22** were subjected to *Michael* addition with dimethyl malonate [51][30]), thus affording, after de(methoxycarbonyl)ation, the desired didehydrohedione **13** or methyl didehydrojasmonate **55a**, allowing access to both *Hedione*®

[29]) This kind of approach was internally also studied in detail by Drs. *A. S. Williams* and *M. Marty* in 1998–1999.

[30]) As alternative mechanism, the 1,2-addition affords the same intermediate after hydrolysis.

HC (*cis*-**2e**) and dihydrojasmone (**58**), by hydrogenation or de(methoxycarbonyl)-ation, respectively. Epoxidation of the (*E*)-double bond in the side chain with *m*CPBA allowed, after transforming the resulting *trans*-epoxide derivative **59** into the corresponding diol derivative **60** ($H_2O/HClO_4$), to protect the side chain during hydrogenation of the tetrasubstituted C=C bond into a 1,2-*cis*-substituted cyclopentaneacetate **61**. Following a known procedure [52b], formation of a cyclic ortho ester permitted stereochemical control ($CH(MeO)_3$, TsOH), so that treatment of **62** with acetic anhydride regenerated the (*Z*)-double bond of methyl jasmonate (**1b**), finally obtained as a 55:45 *cis*/*trans* mixture. Neither hydrogenation of the didehydro ortho ester, nor the asymmetric version was presented or discussed in [52a].

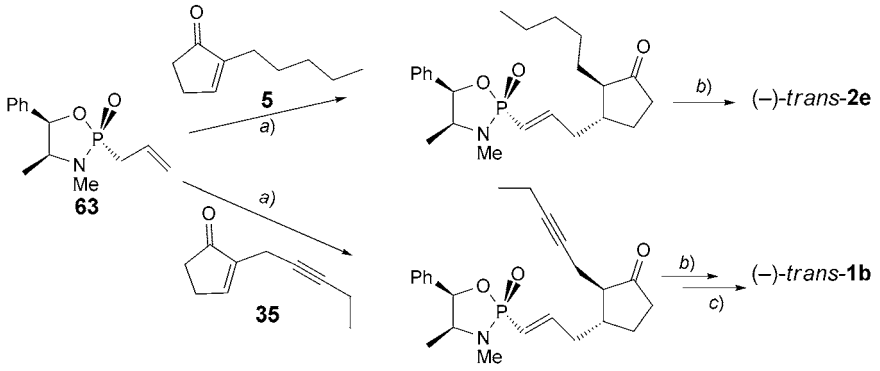
**(+)-Methyl *cis*-Jasmonate ((+)-*cis*-1b).** – (−)-Methyl *trans*-jasmonate ((−)-*trans*-**1b**) may be obtained by either resolution of the racemic acid with (+)-1-(*p*-tolyl)ethylamine, followed by esterification [103], or by convergent lipase-catalyzed resolution of racemic methyl 7-epicurcubate, obtained *via* $NaBH_4$ reduction of methyl jasmonate [104]. In 1985, Japanese authors showed that solely the minor (+)-*cis*-(1*R*,2*S*)-enantiomer **1b** gave rise to an intense odor [57], as later confirmed by synthesis of the practically odorless (−)-methyl *trans*-jasmonate by German authors [105]. Thus, although all four stereoisomers may exert synergic effects or improve a perfume composition as fixatives or enhancers, under equilibrating conditions, racemic **1b** only contains *ca*. 3% of the olfactively active (+)-methyl *cis*-jasmonate ((+)-*cis*-**1b**).

The asymmetric *Michael* addition of a chiral prop-2-enylphosphonamidate **63**, as an anion derived from ephedrine, and generated with BuLi at −78°, was reported by *H. C. Hailes* and co-workers [106]. This methodology, which necessitated chromatographic separation of the diastereoisomeric phosphonamidates, was applied to both 2-substituted cyclopentenones **5** and **35**. Cleavage of the prosthetic group was performed by ozonolysis in $CH_2Cl_2$/MeOH under basic (NaOH) nonreductive conditions, thus affording directly the corresponding methyl esters. As usual, the (*Z*)-configuration in the side chain resulted from hydrogenation over *Lindlar* catalyst. This strategy is based upon the fact that a triple bond is more resistant to ozonolysis than a C=C bond. Unfortunately, despite a high 90% ee, either the thermodynamically more stable (−)-*trans*-**1b**, or (−)-*trans*-**2e** was isolated. Furthermore the authors did not comment on recovery of the chiral auxiliary (*Scheme 12*).

An alternative synthesis of (−)-methyl jasmonate, reported by *M. Nakada* and co-workers [107], consists of an asymmetric copper triflate ($CuOSO_2CF_3$)-catalyzed intramolecular cyclopropanation of the advanced diazo(sulfonyl)alkenone **64**. Opening of the cyclopropane ring with NaCN allowed, despite concurrent O-alkylation, for the side chain to be introduced regioselectively. Desulfonylation was performed with 2.5 mol-equiv. excess of $SmI_2$ at −78°, while the hydrogenation over *Lindlar* catalyst, followed by hydrolysis of the cyano moiety under basic conditions, and final esterification secured the configuration of (−)-*trans*-**1b** (*Scheme 13*).

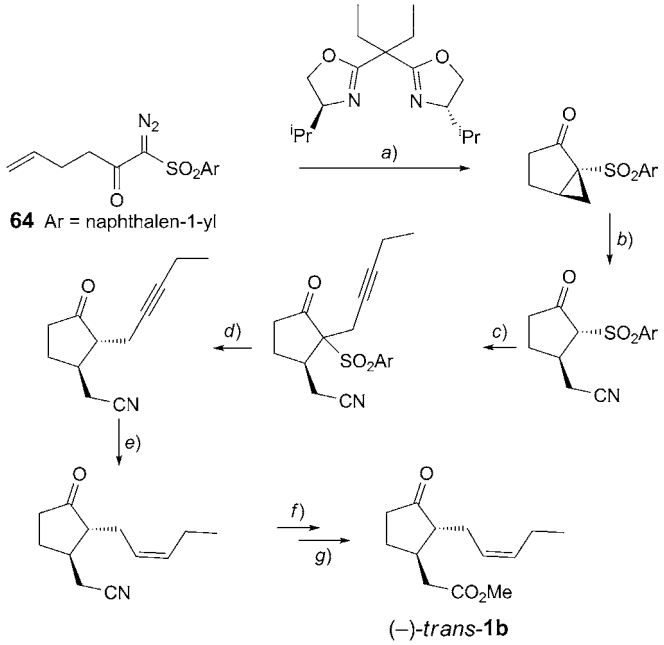
Another academic approach reported by *K. Inomata* and co-workers [108], is based on the availability of lactone (−)-**65** [109], which, after diisobutylaluminium hydride (DIBAL) reduction at −78°, was subjected to a four-fold excess of *Grignard* reagent at the same temperature, thus affording diol **66**. Catalytic re-oxidation with a perruthenate furnished lactone **67** in moderate yield. This nevertheless yielded, *via* a tandem

*Scheme 12*




*a*) BuLi, THF, −78°; 76–80%. *b*) $O_3$, $CH_2Cl_2$, MeOH, NaOH, −78°; 40–60%. *c*) $H_2$, *Lindlar* catalyst, MeOH; 92%.

*Scheme 13*

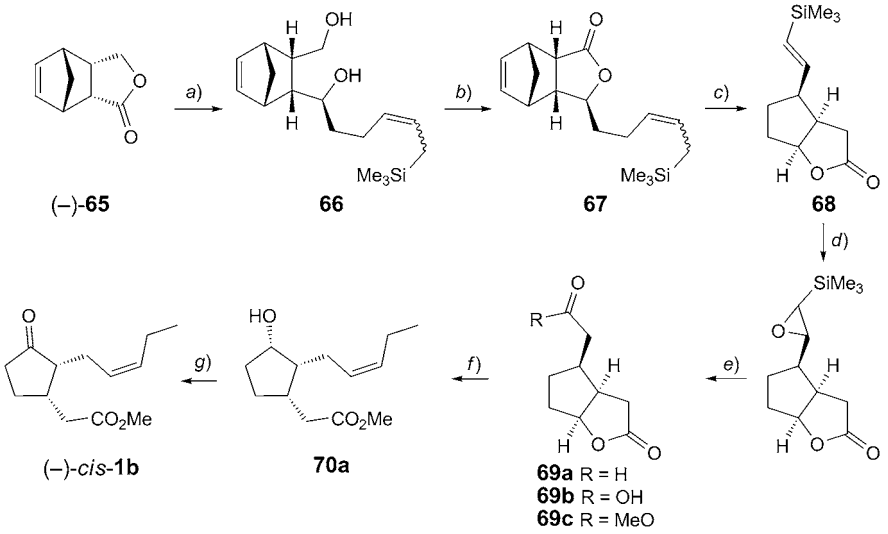



*a*) CuOTf, toluene, 50°; 93%. *b*) NaCN, DMSO, 80°; 95%. *c*) $K_2CO_3$, NaI, $BrCH_2CCEt$, DMF, 20°; 59%. *d*) $SmI_2$, THF, −78°, MeOH; 100%. *e*) $H_2$, *Lindlar* catalyst, MeOH; 90%. *f*) KOH, ethane-1,2-diol, 80°. *g*) $K_2CO_3$, MeI, acetone, 56°; 88% over two steps.

*retro-Diels–Alder*/ene reaction, the *cis*-fused bicyclic lactone **68**. Epoxidation of the latter gave, after concomitant acidic rearrangement and desilylation, an aldehyde **69a** which was further oxidized with *Jones* reagent (→**69b**). Esterification with diazo-

methane furnished **69c** as key intermediate for the *Montforts* synthesis of **70a** [110], *via* a second DIBAL reduction and *Wittig* reaction. An ultimate mild *Dess–Martin* periodinate oxidation finally furnished the undesired antipodal (−)-methyl *cis*-jasmonate ((−)-*cis*-**1b**) (*Scheme 14*).

*Scheme 14*



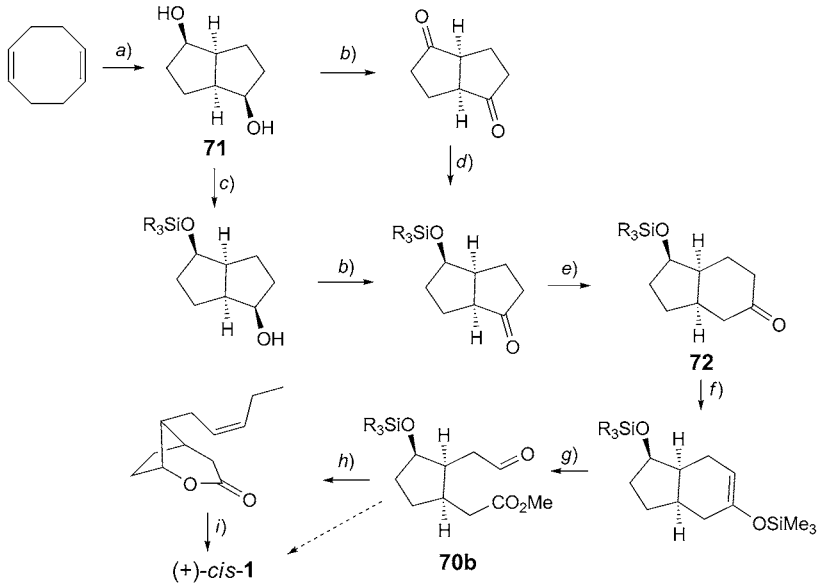

*a*) DIBAL, toluene, hexane, −78°, then $Me_3SiCH_2CH{=}CHCH_2CH_2MgBr$, THF, −78°; 79%. *b*) $(Pr_4N)RuO_4$, 4-Å molecular sieves, 4-methylmorpholine 4-oxide · $H_2O$, $CH_2Cl_2$, 0–20°; 68%. *c*) PhOPh, 258°; 75%. *d*) *m*CPBA, $CH_2Cl_2$, 0–20°; 88%. *e*) $HClO_4$, THF, $H_2O$, 0–20°, then *Jones* reagent, acetone, 0°, then $CH_2N_2$, $Et_2O$; 60%. *f*) DIBAL, THF, −78°, then $(Ph_3PPr)Br$, sodium hexamethyldisilazanide (NaHMDS), THF, −78° to r.t., then KOH, MeOH, then $CH_2N_2$, $CH_2Cl_2$; 37%; *g*) *Dess–Martin* periodinate, 4-Å molecular sieves, $CH_2Cl_2$, 0°; 94%.

Recently, a formal fifteen-step synthesis of (+)-methyl *cis*-jasmonate ((+)-*cis*-**1b**) was presented by *E. Deau*, starting from cycloocta-1,5-diene [111] (*Scheme 15*). His strategy is based on the enzymatic desymmetrization by enantioselective resolution of either a $C_2$-symmetric bicyclic dione or diol **71**, leading, by regioselective homologation, to chiral octahydro-1-(silyloxy)-5*H*-inden-5-ones of type **72** as key precursors to chiral (+)-methyl *cis*-jasmonate, finally obtained after intermediate regioselective enolization and oxidative cleavage (→ **70b**), as a 65:35 *cis*/*trans* mixture[31]). Inversion of the

[31]) Desymmetrization of the dione was performed with the horse liver alcohol dehydrogenase, while that of the diol necessitated *Pseudomonas cepacia* as lipase. Transannular bis-acetyloxylation of cycloocta-1,5-diene yielded two contiguous five-membered rings that are necessarily *cis*-fused and cannot be epimerized.

ultimate oxidation/esterification steps according to *K. Inomata* [108] or *F.-P. Montfort* [110] would eventually have been more stereoselective, by minimizing final epimerization (*Scheme 15*).

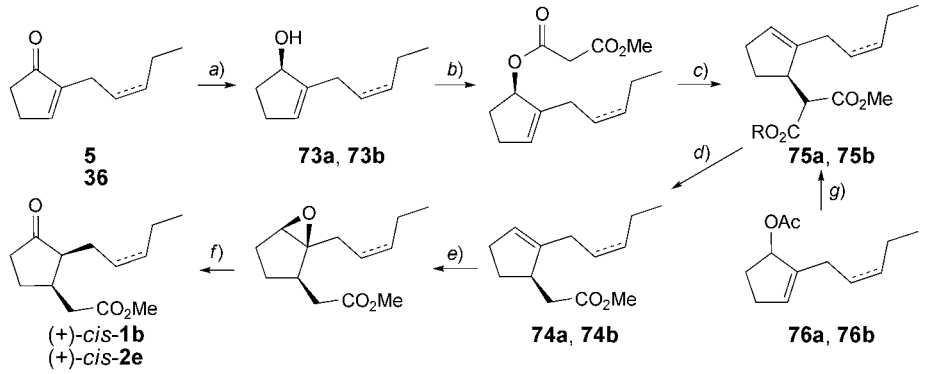
*Scheme 15*




*a*) Cat. $[Pb(OAc)_2]$, $[Pb(OAc)_4]$, AcOH, then KOH, MeOH; 74%. *b*) Pyridinium chlorochromate (PCC), $CH_2Cl_2$; 85–95%. *c*) Lipase PS, then $^t$BuPh$_2$SiCl, DMF, 0°; 45%. *d*) Horse liver alcohol dehydrogenase (HLADH), then $^t$BuMe$_2$SiOTf; 30%. *e*) $AlMe_3$, $Me_3SiCHN_2$, $CH_2Cl_2$, –78° to 20°, then AcOH, 20°; 64%. *f*) Lithium diisopropylamide (LDA), $Me_3SiCl$, THF, –78°; 94%. *g*) $O_3$, $CH_2Cl_2$, –78°, then $PPh_3$; 50%, then $Me_3SiCH_2N_2$, MeOH; 89%. *h*) $(Ph_3PPr)Br$, sodium hexamethyldisilazanide (NaHMDS), THF, 0°, then $Bu_4NF$, THF, 55°; 63%. *i*) NaOH, MeOH, 0°, then *Dess–Martin* periodinate, $CH_2Cl_2$, 20°, then $Me_3SiCHN_2$, MeOH, $Et_2O$, 0°; 69%.

Since all reported syntheses of (+)-*cis*-**1b** are tedious [108][110][112], and that furthermore the conditions of asymmetric hydrogenation developed for (+)-*cis*-*Hedione*® (= *Paradisone*®; (+)-*cis*-**2e**), failed on direct application to methyl didehydrojasmonate, due to the presence of the supplementary C=C bond in the side chain, *C. Fehr* elaborated an alternative asymmetric approach, which proved to be similarly applicable to *Paradisone*® ((+)-*cis*-**2e**) (*Scheme 16*) [113]. The chiral starting materials **73** were obtained either *via* asymmetric hydrogenation or *Corey*'s oxazaborolidine reduction of the corresponding unsaturated ketones **5** and **36** [91][92][93][114], respectively, or by kinetic enzymatic resolution, with recycling of the undesired enantiomer by acidic epimerization [115]. Chirality transfer by either *Claisen*, *Claisen–Ireland*, or *Carroll* rearrangement led *via* **75**, after appropriate decarboxylation, to the unsaturated esters **74**. The key steps were a diastereoselective *syn*-epoxidation, with a subsequent stereoselective suprafacial 1,2-H shift, to afford the *cis*-

*Scheme 16*




*a*) *Corey*'s reduction; 89%. *b*) $ClC(O)CH_2CO_2Me$, $Et_3N$, $CH_2Cl_2$; 86%, or enzymatic resolution. *c*) NaH, $Me_3SiCl$, THF, 65°; 80%. *d*) NaCl, NMP (1-methylpyrrolidin-2-one), $H_2O$, 200°; 98%. *e*) Maleic anhydride, $H_2O_2$, $CH_2Cl_2$, 20°; 86%; or $(CF_3CO)_2O$, $H_2O_2$, $CH_2Cl_2$, −50°; 83%. *f*) $AlCl_3$, $CH_2Cl_2$, 5°, then $NaHCO_3$; 81%; or $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, 5°; 80%. *g*) $[Pd(allyl)Cl]_2$, dimethyl malonate, NaH, THF, 66°; 63%.

isomers (+)-*cis*-**1b** and (+)-*cis*-**2e** in high enantiomer purity. This elegant approach represents to date the only practical access to (+)-methyl *cis*-jasmonate which avoids a *Wittig* reaction. The chiral allylic alcohol **73a** was also obtained by asymmetric hydrosilylation[32]) [116], but more practical conditions, using inexpensive polymethylhydrosiloxane (PMHS), popularized by *H. Mimoun* [117], were found at a later date [118].

Based on the *T. Kitahara* Pd-catalyzed allyl substitution [119], an alternative entry to **75a** (99% ee) was also performed under *G. Helmchen*'s asymmetric conditions, as reported from **76a** [120][33]), and analogously extended to the doubly unsaturated substrates **76b** → **75b** (98% ee) [121], in the presence of 1.4 mol-% of $[Pd(allyl)Cl]_2$ and 10 mol-% of a diphenylphosphine derived from myrtenal (=6,6-dimethylbicyclo[3.3.1]hept-2-ene-2-carboxaldehyde) [122]. These new syntheses and related products are currently being industrialized by *Firmenich's* research and development teams.

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[32]) Conditions: 2% (*S*,*S*)-Taddol-(*S*)-valine phosphazulene, 1% $[Rh(cod)Cl]_2$, 110% $Ph_2SiH_2$, THF, 20°, yield 90%, 57% ee; or 1% (*R*,*S*)-'Bu-josiphos, 0.5% $[Rh(cod)Cl]_2$, 220% $MePhSiH_2$, THF, −5°, yield 75%, 59% e.e. (cod = cycloocta-1,5-diene). When this latter josiphos ligand was applied to (+)-(*S*,*E*)- and (−)-(*R*,*E*)-3,3-dimethyl-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pent-4-en-2-one with $Ph_2SiH_2$, the stereoselectivity reached 78%, and 74% de, respectively. The selectivity diminished to 68% or 62% de with either $MePhSiH_2$, or Me-duphos, respectively (duphos = 1,1′-(1,2-phenylene)bis[phospholane]).

[33]) It is noteworthy that the absolute configuration as depicted by the German authors should be inverted.

**Isotopic and Analogous *Hedione*® and Methyl Jasmonate Derivatives.** – Several analogues of *Hedione*®[34]) or methyl jasmonate have been protected, such as *Jasmidal*® (**77**) [124], **78** [125], or **79** [126][35]), but the olfactively most similar dione analogue **80**[36]), for which all optical stereoisomers have also been described [128], is actually commercialized by *Givaudan* under the name *Magnolione*® [129] (*Scheme 17*). This analogue, whose synthesis only necessitates a replacement of dimethyl malonate by alkyl acetoacetate in the *Michael* addition, displays a more fruity and intense floral jasminic note, and increased chemical stability under harsh conditions. This actually more expensive and less biodegradable counterpart (biological oxygen demand (BOD) test, 57% average on duplicate, as compared to 85% for **2e**[37])) has been used in *Coriandre* (*Couturier*, 1973; 13%) and *Eden* (*Cacharel*, 1994; 0.7%) [32]. For another industrial application, propyl dihydrojasmonate is the active ingredient launched by *Meiji Seika Kaisha Ltd.* as an accelerator for the color development of apples [130]. Finally, the methyl didehydro-*cis*-jasmonate (+)-**81** was isolated by capillary GC by *R. Kaiser* from the widespread Asian orchid *Cymbidium goeringii* (RCHB.f.) [131], and its absolute configuration was determined by *T. Kitahara* and co-workers [132][38]).

These structural variations invited us to have a closer look at the reported direct analogues of *Hedione*® of the general formula **2** (*Scheme 17*), as summarized in *Table 2*. The most promising homologue **2i**, initially discovered by *E. Demole* in 1960, was studied in more detail amongst others by *C. Fehr*, who prepared the VHC isomer of typically floral, jasmine quality, as compared to the fattier pure *trans*-stereoisomer. Furthermore, in line with the nor-series, he found that (+)-*cis*-**2i** exhibits citrus, *Hedione*®, powerful, and fresh notes, as compared to its mirror image (−)-*cis*-**2i**, which

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34) Monomethylation of *trans*-**2**, as performed by *C. Vial* ('BuOK, THF, MeI, −20°), afforded in 97% yield a weakly flowery 3:7 *cis*/*trans* mixture lacking the typical *Hedione*® character. *cis*-Diastereoisomer: $^1$H-NMR: 0.86 (*t*, *J* = 7, 3 H); 1.02 (*s*, 3 H); 1.10–1.42 (*m*, 8 H); 1.64 (*m*, 1 H); 2.07–2.58 (*m*, 6 H); 3.71 (*s*, 3 H). $^{13}$C-NMR: 221.1 (*s*); 173.1 (*s*); 51.7 (*q*); 50.6 (*s*); 44.6 (*d*); 35.4 (*t*); 34.5 (*t*); 32.6 (*t*); 31.5 (*t*); 24.7 (*t*); 23.5 (*t*); 22.5 (*t*); 20.1 (*q*); 14.0 (*q*). MS: 240 (1, $M^+$), 209 (2), 170 (40), 149 (4), 183 (3), 128 (7), 110 (13), 97 (100), 81 (13), 69 (21), 55 (32), 41 (24). *trans*-Diastereoisomer: $^1$H-NMR: 0.85 (*s*, 3 H); 0.87 (*t*, *J* = 7, 3 H); 1.04 (*m*, 1 H); 1.13–1.39 (*m*, 6 H); 1.54 (*m*, 2 H); 2.06–2.60 (*m*, 6 H); 3.70 (*s*, 3 H). $^{13}$C-NMR: 222.1 (*s*); 173.1 (*s*); 51.8 (*q*); 51.0 (*s*); 39.2 (*d*); 37.2 (*t*); 35.8 (*t*); 35.0 (*t*); 32.4 (*t*); 25.2 (*t*); 24.1 (*t*); 22.5 (*t*); 18.0 (*q*); 14.0 (*q*). MS: 240 (1, $M^+$), 209 (1), 170 (32), 149 (3), 138 (3), 128 (8), 110 (15), 97 (100), 81 (12), 69 (19), 55 (26), 41 (19). For the corresponding methylated methyl jasmonate analogue, see [123].

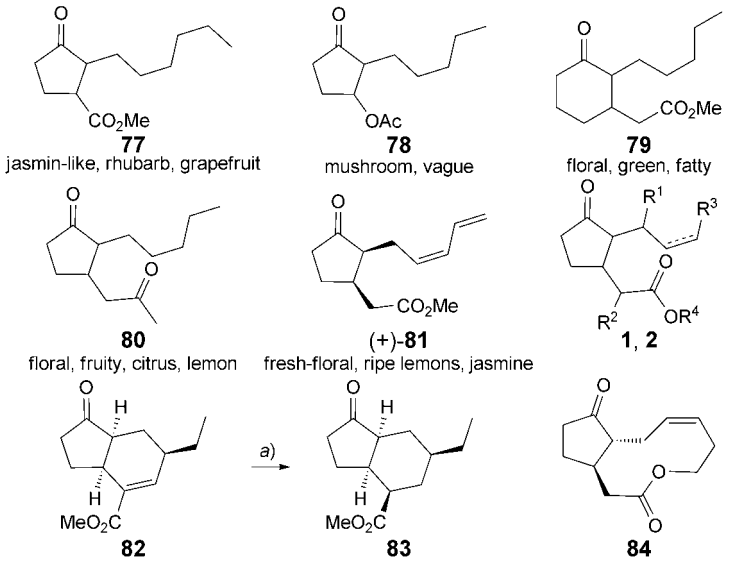
35) The corresponding unsaturated methyl jasmonate analogue is weakly floral [127].

36) The 2-[(2*Z*)-pent-2-en-1-yl] analogue [99d] exhibits weak, nicely jasmine-like, green, fruity, green apple notes.

37) I am indebted to Mr. *A. Boschung* for these measurements (after 28 d). Both ingredients were > 85% after 56 d, *Magnolione*® exhibiting a more linear kinetic as compared to the accelerated biodegradation of *Hedione*®.

38) Its racemic *trans*-stereoisomer [79][132][133], also prepared by *J. M. Lem*, is more cacao-butter-like and showed the following analytical data: $^1$H-NMR: 1.47–1.57 (*m*, 1 H); 1.92–1.98 (*m*, 1 H); 2.07–2.17 (*m*, 1 H); 2.20–2.28 (*m*, 1 H); 2.30–2.43 (*m*, 5 H); 2.63–2.71 (*m*, 1 H); 3.70 (*s*, 3 H); 5.00 (*d*, *J* = 10, 1 H); 5.11 (*d*, *J* = 16, 1 H); 5.61 (*q*, *J* = 7, 1 H); 6.04–6.12 (*m*, 1 H); 6.27 (*dt*, *J* = 10, 16, 1 H). $^{13}$C-NMR: 218.5 (*s*); 172.4 (*s*); 136.7 (*d*); 133.6 (*d*); 130.8 (*d*); 116.0 (*t*); 54.0 (*d*); 51.6 (*q*); 38.6 (*t*); 37.7 (*d*); 37.6 (*t*); 30.8 (*t*); 27.2 (*t*). MS: 222 (18, $M^+$), 204 (14), 193 (18), 149 (100), 144 (38), 130 (86), 119 (23), 107 (70), 105 (57), 91 (72), 79 (82), 67 (71), 55 (32), 41 (48).

*Scheme 17*




*a*) $H_2$, Pd/C, MeOH; 95%.

also exhales citrus, aldehydic, and jasmonic aspects, but with a more pronounced cresolic unpleasant off-note [134]. Mostly interested in SAR studies, *C. Margot* discovered that the known conformationally rigid, vaguely metallic and woody-like methyl coronafacate **82** [135] becomes woody, sesquiterpenes, and *Hedione*®-like, when hydrogenated to the main all-*cis* saturated stereoisomer **83** [136][39]), especially when heated (*Scheme 17*). Astonishingly, nobody reported on the saturated analogue of the naturally occurring odorless jasmine keto lactone **84** [137]. In the (*Z*)-configurated jasmonic unsaturated series, the practically odorless ethyl ester **1c** was earlier isolated from *Botryodiplodia theobromae* [138], a plant pathogen responsible for fungal keratisis. It is a common post-harvest fungus disease of citrus, for example. In summary, none of these analogues may, from an olfactive point of view, rival with the original (*Z*)-configurated methyl jasmonate (**1b**)[40]).

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[39]) $^1$H-NMR: 0.91 (*t*, *J* = 7, 3 H); 1.00–1.42 (*m*, 1 H); 1.19–1.37 (*m*, 3 H); 1.66–1.72 (*m*, 1 H); 1.77–1.94 (*m*, 3 H); 2.12–2.46 (*m*, 4 H); 2.59–2.80 (*m*, 2 H); 3.71 (*s*, 3 H). $^{13}$C-NMR: 219.5 (*s*); 174.6 (*s*); 51.6 (*q*); 48.9 (*d*); 42.5 (*d*); 37.2 (*d*); 37.5 (*d*); 37.0 (*t*); 29.5 (*t*); 28.6 (*t*); 28.5 (*t*); 20.7 (*t*); 11.1 (*q*). MS: 224 (50, $M^+$), 192 (21), 164 (100), 147 (60), 135 (23), 121 (25), 109 (23), 107 (25), 95 (34), 93 (31), 91 (21), 81 (29), 79 (40), 67 (33), 55 (29), 41 (22).

[40]) The isomeric methyl 3-oxo-2-[(1*E*)-pent-1-en-1-yl]cyclopentane-1-acetate [18][45][89][143b] exhibits a weak, less radiant jasmine scent with lactonic aspects. Its (2*E*)-pent-2-en-1-yl analogue (= methyl (*E*)-jasmonate) [1d][3b] is weakly floral, reminiscent of white flowers, like either the (3*E*)-pent-3-en-1-yl) analogue [1d][51c], or the pent-4-en-1-yl isomer [1d] possessing a terminal unsaturation. The methyl *trans*-2-(2-ethoxyethyl)-3-oxocyclopentaneacetate [18] possesses an odor reminiscent of cheese, curdled milk, in opposition to methyl *trans*-2-(3-methoxypropyl)-3-oxocyclopentaneacetate [18], which is weakly mushroom, *Hedione*®-like.

Table 2. *Analogues of* Hedione® (**2e**) *and Methyl Jasmonate* (**1b**). See *Scheme 17* for the general formulas **1** and **2**.

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Ref. | Odor evaluation |
|---|---|---|---|---|---|---|
| **2a**[a]) | H | H | H | Me | [21a][139] | jasmine, floral, with lemon, magnolia notes |
| **2b**[b]) | H | H | H | Et | [140] | jasmine, floral |
| **2c**[c]) | H | H | Me | Me | [126a] | floral, jasmine, *Hedione*®, weak |
| **2d**[d]) | H | H | Me | Et | [2][126a] | jasmine, fatty, rancid |
| **2e** | H | H | Et | Me | [2] | *Hedione*®, floral, jasmine, estery, citrus |
| **2f**[e]) | H | H | Et | Et | [21a][139] | floral, jasmine, *Hedione*®, weak, tenacious |
| **2g** | Me | H | Et | Me | [141] | floral, *Hedione*®, citrus |
| **2h**[f]) | H | Me | Et | Me | [39b] | vaguely jasmine |
| **2i**[g]) | H | H | Pr | Me | [21a][126a] | floral, jasmine, sweet, tenacious |
| **2j**[h]) | H | H | Pr | Et | [2][126a][142] | *Hedione*®, radiant, floral, green |
| **2k** | H | H | Bu | Me | [18] | fruity, veloutone, peach, floral, weak |
| **1a** | H | H | Me | Me | [79][143][i]) | leather, castoreum |
| **1b** | H | H | Et | Me | [2] | methyl jasmonate, jasmine, floral, radiant |
| **1c** | H | H | Et | Et | [3b][10a][138] | very weak to odorless |
| **1d** | H | H | Et | $^i$Pr | [145] | vague |
| **1e** | Me | H | Et | Me | [141] | floral, jasmine, indolic, raspberry |
| **1f** | H | H | Pr | Me | [18] | methyl jasmonate, vitamines |
| **1g** | H | H | cyclo-Pr | Me | [18] | weak |

[a]) $^1$H-NMR: 0.91 (*t*, *J* = 7, 3 H); 1.22–1,37 (*m*, 1 H); 1.40–1.50 (*m*, 1 H); 1.50–1.60 (*m*, 2 H); 1.78–1.85 (*m*, 1 H); 2.10–2.20 (*m*, 2 H); 2.20–2.30 (*m*, 2 H); 2.30–2.40 (*m*, 2 H); 2.65 (*d*, *J* = 15, 1 H); 3.70 (*s*, 3 H). $^{13}$C-NMR: 219.7 (*s*); 172.7 (*s*); 54.1 (*d*); 51.6 (*q*); 38.9 (*t*); 38.2 (*t*); 37.7 (*t*); 30.1 (*d*); 27.2 (*t*); 19.9 (*t*); 14.3 (*q*). MS: 198 (5, $M^+$), 167 (8), 156 (29), 125 (35), 83 (100), 74 (12), 55 (32), 41 (18). [b]) $^1$H-NMR: *trans:* 0.91 (*t*, *J* = 7, 3 H); 1.28 (*t*, *J* = 7, 3 H); 1.40–1.50 (*m*, 2 H); 1.52–1.57 (*m*, 2 H); 1.78–1.82 (*m*, 1 H); 2.10–2.18 (*m*, 1 H); 2.21–2.28 (*m*, 1 H); 2.30–2.38 (*m*, 3 H); 2.62 (*q*, *J* = 9, 1 H); 4.17 (*q*, *J* = 7, 2 H). $^{13}$C-NMR: 219.8 (*s*); 172.2 (*s*); 60.5 (*t*); 54.1 (*d*); 39.2 (*t*); 38.2 (*d*); 37.7 (*t*); 30.1 (*t*); 27.2 (*t*); 20.0 (*t*); 14.3 (2*q*). MS: *trans:* 212 (6, $M^+$), 170 (25), 125 (76), 96 (20), 83 (100), 55 (40), 41 (18); *cis:* 212 (5, $M^+$), 170 (28), 125 (50), 96 (22), 83 (100), 55 (40), 41 (20). [c]) $^1$H-NMR: *trans:* 0.91 (*t*, *J* = 7, 3 H); 1.16–1.26 (*m*, 1 H); 1.30–1.37 (*m*, 3 H); 1.60–1.67 (*m*, 1 H); 1.78–1.86 (*m*, 1 H); 1.97–2.13 (*m*, 2 H); 2.20–2.28 (*m*, 4 H); 2.40 (*dd*, *J* = 6, 15, 1 H); 2.79–2.87 (*m*, 1 H); 3.70 (*s*, 3 H); *cis:* 0.90 (*t*, *J* = 7, 3 H); 1.18–1.40 (*m*, 4 H); 1.47–1.59 (*m*, 2 H); 1.77–1.83 (*m*, 1 H); 2.05–2.18 (*m*, 2 H); 2.21–2.28 (*m*, 2 H); 2.30–2.40 (*m*, 2 H); 2.60–2.68 (*m*, 1 H); 3.71 (*s*, 3 H). $^{13}$C-NMR: *trans:* 219.5 (*s*); 172.6 (*s*); 54.2 (*d*); 51.6 (*q*); 38.9 (*t*); 38.1 (*d*); 37.7 (*t*); 28.8 (*t*); 27.6 (*t*); 27.2 (*t*); 23.0 (*t*); 13.9 (*q*); *cis:* 219.2 (*s*); 173.0 (*s*); 52.7 (*d*); 51.7 (*q*); 35.7 (*d*); 35.1 (*t*); 33.7 (*t*); 29.6 (*t*); 25.6 (*t*); 24.4 (*t*); 22.7 (*t*); 13.9 (*q*). MS: *trans:* 212 (5, $M^+$), 181 (7), 156 (27), 139 (30), 97 (15), 83 (100), 55 (30), 41 (22); *cis:* 212 (6, $M^+$), 181 (3), 156 (18), 139 (24), 96 (11), 83 (100), 55 (25), 41 (18). [d]) $^1$H-NMR: *trans:* 0.89 (*t*, *J* = 7, 3 H); 1.28 (*t*, *J* = 7, 3 H); 1.30–1.37 (*m*, 5 H); 1.51–1.59 (*m*, 1 H); 1.77–1.87 (*m*, 1 H); 1.98–2.15 (*m*, 2 H); 2.21–2.29 (*m*, 2 H); 2.32–2.41 (*m*, 2 H); 2.79–2.88 (*m*, 1 H); 4.16 (*q*, *J* = 7, 2 H). $^{13}$C-NMR: *trans:* 219.7 (*s*); 172.2 (*s*); 60.5 (*t*); 54.2 (*d*); 39.3 (*t*); 38.2 (*d*); 37.7 (*t*); 28.9 (*t*); 27.6 (*t*); 27.2 (*t*); 23.0 (*t*); 14.3 (*q*); 13.9 (*q*); *cis:* 219.4 (*s*); 172.5 (*s*); 60.6 (*t*); 52.7 (*d*); 35.7 (*d*); 35.2 (*t*); 34.0 (*t*); 29.6 (*t*); 25.6 (*t*); 24.4 (*t*); 22.8 (*t*); 14.3 (*q*); 13.9 (*q*). MS: *trans:* 226 (8, $M^+$), 181 (8), 170 (29), 139 (53), 96 (21), 83 (100), 55 (34), 41 (22); *cis:* 226 (9, $M^+$), 181 (4), 170 (25), 139 (41), 96 (22), 83 (100), 55 (35), 41 (24). [e]) $^1$H-NMR: *trans:* 0.88 (*t*, *J* = 7, 3 H); 1.28 (*t*, *J* = 7, 3 H); 1.22–1.44 (*m*, 8 H); 1.51–1.59 (*m*, 2 H); 1.77–1.83 (*m*, 1 H); 2.07–2.18 (*m*, 1 H); 2.19–2.28 (*m*, 1 H); 2.29–2.38 (*m*, 2 H); 2.62 (*q*, *J* = 10, 1 H); 4.16 (*q*, *J* = 7, 2 H). $^{13}$C-NMR: *trans:* 219.7 (*s*); 172.2 (*s*); 60.5 (*t*); 54.3 (*d*); 39.2 (*t*); 38.1 (*d*); 37.7 (*t*); 32.1 (*t*); 27.9 (*t*); 27.2 (*t*); 26.4 (*t*); 22.5 (*t*); 14.3 (*q*); 14.0 (*q*). MS: *trans:* 240 (9, $M^+$), 170 (42), 153 (62), 141 (10), 96 (20), 83 (100), 55 (27), 41 (25); *cis:* 240 (11, $M^+$), 170 (30), 153 (48), 141 (12), 96 (25), 83 (100), 55 (32), 41 (28). [f]) Main *trans* stereoisomer: $^1$H-NMR: 0.88 (*t*, *J* = 7, 3 H); 1.24 (*d*, *J* = 7, 3 H); 1.17–1.33 (*m*, 5 H); 1.37–1.45 (*m*, 1 H); 1.52–1.67 (*m*, 3 H); 1.87–2.01 (*m*, 1 H); 2.05–2.18 (*m*, 3 H); 2.27–2.37 (*m*, 1 H); 2.55–2.68 (*m*, 1 H);

3.69 (*s*, 3 H). $^{13}$C-NMR: 220.4 (*s*); 175.5 (*s*); 52.0 (*d*); 51.5 (*q*); 44.1 (*d*); 41.8 (*d*); 37.5 (*t*); 32.1 (*t*); 28.8 (*t*); 26.2 (*t*); 23.9 (*t*); 22.5 (*t*); 15.1 (*q*); 14.0 (*q*). MS: 240 (1, $M^+$), 170 (12), 153 (37), 97 (12), 88 (21), 83 (100), 69 (10), 55 (20), 41 (20). [g]) $^1$H-NMR: *trans:* 0.88 (*t*, *J* = 7, 3 H); 1.24–1.30 (*m*, 10 H); 1.47–1.58 (*m*, 2 H); 1.77–1.82 (*m*, 1 H); 2.07–2.18 (*m*, 1 H); 2.19–2.28 (*m*, 1 H); 2.30–2.38 (*m*, 2 H); 2.64 (*q*, *J* = 10, 1 H); 3.71 (*s*, 3 H); *cis:* 0.88 (*t*, *J* = 7, 3 H); 1.16–1.38 (*m*, 10 H); 1.57–1.65 (*m*, 1 H); 1.78–1.86 (*m*, 1 H); 1.98–2.13 (*m*, 2 H); 2.21–2.27 (*m*, 2 H); 2.40 (*dd*, *J* = 6, 16, 1 H); 2.78–2.87 (*m*, 1 H); 3.70 (*s*, 3 H). $^{13}$C-NMR: *trans:* 219.6 (*s*); 172.6 (*s*); 54.2 (*d*); 51.6 (*q*); 39.0 (*t*); 38.1 (*d*); 37.7 (*t*); 31.7 (*t*); 29.6 (*t*); 27.9 (*t*); 27.2 (*t*); 26.7 (*t*); 22.6 (*t*); 14.1 (*q*); *cis:* 219.3 (*s*); 173.0 (*s*); 52.7 (*d*); 51.7 (*q*); 35.7 (*d*); 35.1 (*t*); 33.7 (*t*); 31.6 (*t*); 29.3 (*t*); 27.4 (*t*); 25.6 (*t*); 24.7 (*t*); 22.6 (*t*); 14.1 (*q*). MS: *trans:* 240 (4, $M^+$), 167 (27), 156 (34), 83 (100), 55 (18), 41 (15); *cis:* 240 (6, $M^+$), 167 (28), 156 (30), 83 (100), 55 (18), 41 (15). [h]) $^1$H-NMR: *cis:* 0.88 (*t*, *J* = 7, 3 H); 1.27 (*t*, *J* = 7, 3 H); 1.21–1.39 (*m*, 10 H); 1.56–1.66 (*m*, 1 H); 1.78–1.87 (*m*, 1 H); 1.97–2.05 (*m*, 1 H); 2.04–2.12 (*m*, 1 H); 2.21–2.28 (*m*, 2 H); 2.38 (*dd*, *J* = 6, 17, 1 H); 2.78–2.87 (*m*, 1 H); 4.16 (*q*, *J* = 7, 2 H). $^{13}$C-NMR: *cis:* 219.4 (*s*); 172.6 (*s*); 60.6 (*t*); 52.7 (*d*); 35.7 (*d*); 35.2 (*t*); 34.0 (*t*); 31.6 (*t*); 29.4 (*t*); 27.4 (*t*); 25.6 (*t*); 24.7 (*t*); 22.6 (*t*); 14.2 (*q*); 14.1 (*q*). MS: *cis:* 254 (6, $M^+$), 170 (28), 167 (37), 96 (20), 83 (100), 55 (33), 41 (29). [i]) For an inspiring precedent to [143b], see [18][144].

Our current CEO, *Patrick Firmenich*, has challenged himself and the company to impart a distinct sustainable and green orientation to our business, by forbidding ecologically unfriendly ingredients. In concordance with the rapid evolution of legislation, such as the recent REACH directive[41]), it has become necessary to precisely know the biodegradation kinetics of large-volume ingredients and their persistence in waste or environmental waters [146]. This obligation gave the impetus to *A. Chaintreau* to develop an accurate analytical GC/MS method for quantifying trace amounts, highly diluted in $H_2O$ [147], based on $^2H_3$- to $^2H_5$-labeled internal standards [148][42]). Furthermore, for substantivity or diffusion studies on diverse materials or in complex matrices, *S. D. Escher* also synthesized [*methoxy*-$^3H_3$]-, [*methoxy*-$^{14}$C]-, and [*methoxy*-$^2H_3$]*Hedione*® [150][43]). In this context, both analogous $^2$H-labeled [100b][152], and isotopic methyl jasmonate [153] may similarly find their usefulness for wideline solid-state $^2$H-NMR or radiolabeled analyses, for example. In the latter case, the synthetic approach of *W. J. Kerr et al.* is worth mentioning (*Scheme 18*), since

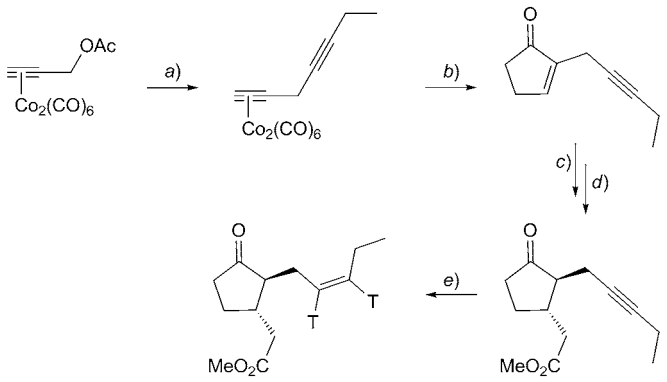
[41]) Of the European Parliament and of the Council concerning the Registration, Evaluation, Authorization, and Restriction of Chemicals (#1907/2006).

[42]) A generalized GC/MS method for bioaccumulation analysis in fish was also implemented by *O. Haefliger* on the basis of [149].

[43]) [*methoxy*-$^2H_3$]*Hedione*®: $^1$H-NMR: 0.88 (*t*, *J* = 7, 3 H); 1.20–1.32 (*m*, 6 H); 1.37–1.50 (*m*, 1 H); 1.52–1.58 (*m*, 2 H); 1.76–1.83 (*m*, 1 H); 2.05–2.18 (*m*, 1 H); 2.20–2.27 (*m*, 1 H); 2.29–2.39 (*m*, 3 H); 2.63 (*q*, *J* = 9, 1 H). $^{13}$C-NMR: 219.5 (*s*); 172.6 (*s*); 54.2 (*d*); 50.9 (*s*); 38.9 (*t*); 38.1 (*d*); 37.7 (*t*); 32.1 (*t*); 27.9 (*t*); 27.2 (*t*); 26.4 (*t*); 22.5 (*t*); 14.0 (*q*). MS: 229 ($M^+$, 7), 159 (38), 153 (32), 96 (10), 83 (100), 77 (8), 67 (10), 62 (8), 55 (20), 41 (20); typical *Hedione*-like odor. For [$^3H_3$]methyl jasmonate, see [150b]. For mechanistic, as well as epimerization kinetic studies, *V. Rautenstrauch* also hydrogenated DHH **13** with $^2H_2$ to the typically *Hedione*®-like dideuterio analogue [1,2-$^2H_2$]*Hedione*® [151]: $^1$H-NMR: *cis:* 0.88 (*t*, *J* = 7, 3 H); 1.16–1.40 (*m*, 7 H); 1.56–1.65 (*m*, 1 H); 1.77–1.85 (*m*, 1 H); 1.97–2.11 (*m*, 2 H); 2.21–2.26 (*m*, 2 H); 2.39 (*d*, *J* = 15, 1 H); 3.70 (*s*, 3 H); *trans:* 0.88 (*t*, *J* = 7, 3 H); 1.21–1.35 (*m*, 5 H); 1.36–1.56 (*m*, 4 H); 2.08–2.26 (*m*, 2 H); 2.30–2.39 (*m*, 2 H); 2.62 (*d*, *J* = 16, 1 H); 3.71 (*s*, 3 H). $^{13}$C-NMR: *cis:* 215.2 (*s*); 171.4 (*s*); 50.9 (*q*); 34.3 (*t*); 33.1 (*t*); 31.7 (*t*); 26.9 (*t*); 25.4 (*t*); 24.4 (*t*); 22.3 (*t*); 14.0 (*q*); *trans:* 219.6 (*s*); 172.6 (*s*); 51.6 (*q*); 38.9 (*t*); 37.7 (*t*); 32.1 (*t*); 27.9 (*t*); 27.1 (*t*); 26.4 (*t*); 22.5 (*t*); 14.0 (*q*).

it reminds us of the very first catalytic *Pauson–Khand* reaction reported by *V. Rautenstrauch* for the synthesis of **5** [154]. The synthesis starts from a stoichiometrically Co-complexed monoalkyne, which, after alkylation, is submitted to the *Pauson–Khand* annulation with vinyl benzoate, albeit in a poor 20% yield. The isotopes were ideally introduced during the ultimate *Lindlar*-catalyzed hydrogenation step, thus minimizing time-dependent deactivation, avoiding any possible exchange, or simple loss by saponification or transesterification.

*Scheme 18*



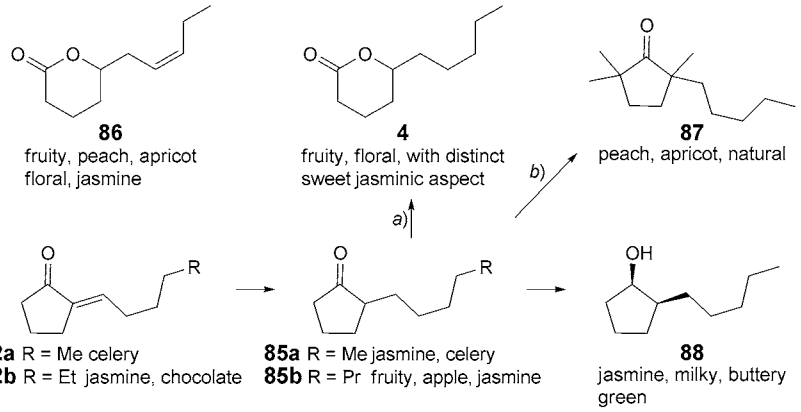

*a*) BuLi, $AlCl_3$, but-1-yne; 75%. *b*) 4-Methylmorpholine 4-oxide·$H_2O$, $H_2C$=CHOBz; 20%. *c*) $Me_2SiCH$=C(OMe)$OSiMe_3$, $TiCl_4$; 90%. *d*) $K_2CO_3$, MeOH; 95%. *e*) $T_2$ (=$^3H_2$), *Lindlar* catalyst, cyclohexane; 99%.

The *Hedione*® process with its diverse stereoisomeric and optical qualities, amongst some other large-volume compounds like macrocyclic musks, *Furaneol*®, or rose ketones [155], necessitated very important technological efforts and required the highest investment for a single ingredient. It also helped to produce several derived ingredients issued from an analogous process such as **12b**, or common intermediates such as *Delphone*® (**85a**) [156], obtained by simple hydrogenation of **12a**, or, as a saturated analogue of the natural jasmolactone (**86**) [157], δ-decalactone **4** [158], obtained by subsequent *Bayer–Villiger* oxidation, as well as *Veloutone*® (**87**) [159], obtained *via* permethylation, or *Cyclopentol*® HC (**88**), obtained by reduction [160] (*Scheme 19*). Additionally, *IFF* developed *Fleuramone*® **85b**, also called *Frutalone*® at *Polak Fructal Works*, or *Heptajasmone*® by *Soda* [161].

I do not know a single chemist in *Firmenich's* research, development, or production division, who has not invested a part of his time and efforts in this adventure. I thus beg their pardon if I could not cite all of them, because it is their work and know-how which ensure the undisputed success of these ingredients after fifty years, and long after expiration of the first patents.

I am indebted to Drs. *A. Birkbeck*, *P.-A. Blanc*, *K. Crawford*, *E. Demole*, *C. Fehr*, *D. Kastner*, *C. Margot*, *B. Maurer*, *R.* and *F. Näf*, *R. L. Snowden*, *C. Vuilleumier*, *V. Rautenstrauch*, and both of his former outstanding collaborators, *R. Challand* and *Y. Kirschmann*, as well as Mr. *C. Vial*, for fruitful discussions. Finally, the picture would not be complete without citing the continuous support of the spectroscopic team, from Drs. *B. Willhalm* to *H. Sommer*, and their faithful collaborators, *M. Abric*, *R. Brauchli*, *J.*

*Scheme 19*




*a*) $NaHCO_3$, Mg monoperoxyphthalate · 6 $H_2O$, MeOH, $H_2O$; 94%. *b*) NaH, MeI, THF, 65°; 92%.

*Porret*, and *W. Thommen*. Both the documentation and patent teams of Drs. *H. Gowal*, *C. Wiaux-Zamar*, *M. Garcia*, *R. Carina*, as well as Mrs. *B. Dumas* should not be forgotten. Finally, my thanks also go to our ingredients/marketing divisions for motivating and submitting to *Perfumer & Flavorist* a simplified less than half-length version extracted from this original technical manuscript [162].

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