The Synthesis of Ipsenol and Ipsdienol: A Review (1968–2020)

José Marco-Contelles*^[a]

This article is dedicated to the late professor Kenji Mori who deceased in 2019 for his outstanding contributions to the synthesis of biologically active natural products, in particular, pheromones

Abstract: Herein I present a review on the synthesis of ipsenol and ipsdienol, two aggregation pheromones of bark beetles, isolated from different species of genus *Ips*, and serious pests of conifer forests. I have covered the literature for around fifty years, since 1968 to 2020. This account has been divided in different sections and sub-sections, including a general and brief outlook on their isolation, structure and biological activity, to continue with the reported synthesis of racemic ipsenol and ipsdienol, including my own contribution to topic, and the presentation of reports describing the synthesis of enantiomerically pure ipsenol and ipsdienol. Particular attention has been devoted to identify and highlight racemic or enantiomerically pure “isoprene synthons”, and isoprenylation methods employed in the synthesis of ipsenol and ipsdienol, of general interest for related terpene derivatives synthesis.

Keywords: 2-(Bromomethyl)buta-1,3-diene, 1,4-Dibromo-2-(bromomethyl)but-2-ene, Ipsenol, Ipsdienol, Isoprenylation reactions

1. Introduction

I must confess that the first impetus to write the present, first review on the synthesis of natural products ipsenol and ipsdienol, came from my personal interest in the analysis of how the first publication of my scientific career, in 1982,^[1] reporting the synthesis of ipsenol and ipsdienol, has been cited and/or the results applied in other independent laboratories.

Thus, I decided to retrieve and carefully check all the available references for the synthesis of ipsenol and ipsdienol. The result of this analysis is the present review, covering the synthesis of ipsenol and ipsdienol since 1968 to 2020. I have divided it in different sections and sub-sections, starting from a general and brief outlook on the isolation, structure and biological activity associated to these natural products, to continue with the account of the reported synthesis of racemic

ipsenol and ipsdienol, including first a summary of my own contribution to topic,^[1] reporting how many times it has been *really* cited, and how it has been valued and, in the event, checked by other authors, continuing with the presentation of reports describing the synthesis of enantiomerically pure (EP) ipsenol and ipsdienol. Due to their close structural and functional relationship, most of the retrieved articles have described the synthesis of both compounds in the same publication, but a significant number of them describe the synthesis of ipsenol or ipsdienol. To simplify the account and to take into account this fact, this is why I have included in the synthesis of the racemic ipsenol and ipsdienol three different sub-sections to summarize reports describing the synthesis of both compounds or one of them.

These pheromones have attracted the interest scientists from diverse areas of research, such as the biology, natural product chemistry and organic chemistry/synthesis. Thus, I'm confident that this account could be of interest for people reading this *Journal*.

[a] Prof. J. Marco-Contelles

Laboratory of Medicinal Chemistry (IQOG, CSIC), Juan de la Cierva 3; 28006-Madrid, Spain.

E-mail: jlmarco@iqog.csic.es

2. General Aspects of Ipsenol and Ipsdienol

Diverse species of bark beetles, such as those of the genus,^[2] are significant pests to ponderosa pine forests.^[3–6] Silverstein and co-workers isolated and characterized ipsenol (**I**)^[7] (Figure 1), ipsdienol (**II**)^[8] (Figure 1) from the boring frass of male *Ips paraconfusus* Lanier. While natural ipsenol showing *S* configuration is levorotatory, natural ipsdienol with the *S* absolute configuration is dextrorotatory.^[9] Ipsenol and ipsdienol were found to be the main components of the aggregation pheromone, attracting both males and females, of a number of *Ips* species, including *Ips typographus*, an important pest to Europe spruce forests. Structures **I** and **II** (Figure 1) were advanced on the basis of their spectroscopic data,^[7] and have been later confirmed by synthesis.^[10] Field tests using EP ipsenol and ipsdienol have been carried out, and the relationship between chirality and aggregation responses have been described. It has been shown, for instance, that the five-spined engraver beetle, *Ips grandicollis*, aggregates only in response to (*S*)-ip-senol.^[9] Ipsdienol of unknown configuration and optical purity is present in the population attractant of *Ips sexdentatus*.^[9] Whereas the biological activity of the racemic mixture was inferior to the (*S*)-(–)-isomer when released in comparable quantity, the antipode proved nearly inactive.^[11] Regarding ipsdienol, there are species-specific differences in response to its enantiomers. For instance, both *Ips calligraphus* and *Ips avulsus* respond to (*R*)-**II**, while *Ips paraconfusus* is attracted by the (*S*)-enantiomer; the male *Ips pini* produces (*R*)-**II**, and this isomer inhibits the attractive pheromone response in *Ips paraconfusus*; (*S*)-**II** interrupts the response of *Ips pini* to (*R*)-**II**.^[12]

3. Synthesis of (±)-ip-senol and (±)-ip-sdienol

3.1. Author's Contribution

In 1982 García Martínez and Marco Contelles reported that the reaction of 1,4-dibromo-2-(bromomethyl)but-2-ene (**1**) with Zn, followed by treatment with 3-methylbutanal and 3-methylbut-2-enal, gave racemic ipsenol (**I**) and ipsdienol (**II**), in 64 and 50 % yields, respectively (Scheme 1).^[1]

Figure 1. Structures of (±)-ip-senol (**I**), (±)-ip-sdienol (**II**), natural (*S*)-(–)-ip-senol [(*S*)-(–)-**I**], and natural (*S*)-(+)-ip-sdienol [(*S*)-(+)-**II**].

Scheme 1. Synthesis of ipsenol (**I**) and ipsdienol (**II**) by García Martínez and Marco Contelles.^[1]

Precursor 1,4-dibromo-2-(bromomethyl)but-2-ene (**1**) was prepared here for the first time in the literature by bromination of isoprene followed by allylic radical bromination with *N*-bromosuccinimide (NBS) of the intermediate reaction products, in modest yield (38 %). The reaction of compound **1** with Zn gave the expected 1,4-dibromodehalogenated 2-(bromomethyl)buta-1,3-diene (**2**) that, *in situ*, in the presence of Zn in excess, *via* the organozinc species **III**, and reaction with 3-methylbutanal and 3-methylbut-2-enal provided ip-senol (**I**) and ipsdienol (**II**) in 24 and 19 % overall yields, respectively, low figures certainly, but clearly compensated by the simplicity of the “one-pot” process, and the ready and cheap available starting materials. As an important, but collateral result, 2-(bromomethyl)buta-1,3-diene (**2**) could be obtained in related, controlled conditions, albeit in low yield (31 %, 12 % from isoprene) (Scheme 1), most possibly due to fact that this is a very unstable compound, that decomposes on standing in hours.^[13]

In overall, the main merit of this work is that the

José Marco-Contelles obtained his PhD in 1984 (Complutense University of Madrid, Spain). Postdoctoral Fellow (1984–1986): Institut de Chimie des Substances Naturelles (France); 1986: Département de Chimie Organique, University of Geneva; (1988–1989): Department of Organic Chemistry, Duke University, Durham (USA). Invited Professor: University Pierre and Marie Curie (France), University of Picardie-Jules Verne (France), University of Okayama (Japan), and University Franche-Comté (France). He received 2002 Chemistry French-Spanish, and 2016 Lilly Outstanding OIDD Collaborator awards. Currently, he is Senior Research Scientist, at the Institute of General Organic Chemistry (CSIC). His research interests are focused on the design, synthesis and biological evaluation of new compounds for Alzheimer's disease and stroke.

organozinc species **III**, as a “isoprene synthon”, could be obtained in one step from 1,4-dibromo-2-(bromomethyl)but-2-ene (**1**), resulting in a new and simple method for the incorporation of the isoprenyl motif, very competitive respect to other reported protocols using other metalated species (potassium, boron, tin, or silicon).^[14] Molecules bearing the isoprenyl group are starting materials for the Diels-Alder reaction, and are largely present in natural products. Furthermore, direct isoprenylation using metalated species from 2-halomethyl-1,3-butadienes can only be obtained in modest yields due to their problematic, annoying, multistep protocol synthesis, being in addition very difficult to purify due to secondary, polymerization processes.^[13]

As compounds **1** and **2** are in themselves interesting synthetic intermediates, not only in the context of the present topic, in the next two sub-sections I'm going to disclose how compound **1** has been applied or cited, and the other current methods reported for the synthesis of “isoprene synthon” **2**.

3.1.1. 1,4-Dibromo-2-(bromomethyl)but-2-ene (**1**)

I have retrieved some reports where compound **1** has been used without citing the source,^[15] or applied and cited in organic synthesis.^[13,16–22]

In 1989 Witkowski and Bandermann^[16] were able to reproduce the previously reported experimental conditions^[1] for the synthesis of both compounds, **1** and **2**, this one being used in the synthesis of bifunctional initiators bearing isoprenyl motives for group transfer polymerization processes. A complete and detailed experimental conditions is available.

In 1993, first in a preliminary communication,^[18] and later as a full paper,^[19] Tokuda, Sugimoto and co-workers described a simple method for the isoprenylation of aldehydes and ketones starting from 2-bromomethyl-1,4-dibromo-2-butene (**1**), prepared by 1,4-bromination of isoprene followed by allylic bromination, following the protocol described by García Martínez and Marco Contelles,^[1] and applied this methodology to the synthesis of ipsenol (**I**) and ipsdienol (**II**). In 1997 the same group, described a new and convenient synthesis of 3-methylenepent-4-enoic acid by electrochemical carboxylation^[21] of 2-(bromomethyl)buta-1,3-diene (**2**), prepared, and reacted *in situ*, from 2-bromomethyl-1,4-dibromo-2-butene (**1**) in the presence of Zn.

The last article^[22] where 1,4-dibromo-2-(bromomethyl)but-2-ene (**1**) has been used till now, was authored by Hopf et al. in the context of their project targeted to the preparation of several cross-conjugated allenes (“allenic dendralenes”).

3.1.2. 2-(Bromomethyl)buta-1,3-diene (**2**)

The first, most cited and used method for the synthesis of 2-(bromomethyl)buta-1,3-diene (**2**) was reported by Krug and

Yen in 1956.^[23] This method consisted of the reaction of 3-methyl-2,5-dihydrothiophene (**3**) with NBS, in chloroform, to give 3-bromomethyl-2,5-dihydrothiophene 1,1-dioxide (**4**) (95%), followed by pyrolysis (30%) (Scheme 2). Intermediate 3-methyl-2,5-dihydrothiophene (**3**) was prepared from isoprene as described^[24] in 84% yield, what means that 2-(bromomethyl)buta-1,3-diene (**2**) could be isolated in 24% overall yield from isoprene. An improved protocol was proposed by Corey et al.^[25] based on the bromination of intermediate **3** using NBS in CH₂Cl₂ (DCM) to give the bromomethylsulfone **4** (66%) followed by thermolysis at low pressure (~1 mm and 170–190 °C) to form 2-(bromomethyl)buta-1,3-diene (**2**) in 60–75% yields (Scheme 2). Hegedus and Varaprath^[26] communicated that 2-(bromomethyl)-1,3-butadiene (**2**) could be synthesized in overall 53% yield from isoprene, by using a modification of the original procedure reported to proceed in only 11% yield.^[23]

In 1974, Silverstein, Katzenellenbogen et al.^[14] reported the synthesis of ipsdienol (**II**) by reaction of 2-(bromomethyl)buta-1,3-diene (**2**) with Zn followed by treatment with 3-methyl-2-butenal, in 65% yield, following the same methodology that Katzenellenbogen and Lenox have proposed for the synthesis of ipsenol (**I**).^[27] Very interestingly, the authors were unable to synthesize ipsenol (**I**) and ipsdienol (**II**) by coupling 3-methylbutanal and 3-methyl-2-butenal, respectively, with either the Grignard or the lithium reagents of 2-bromomethyl-1,3-butadiene (**2**), the use of Zn being the only successful issue.^[14] Furthermore, 2-bromomethyl-1,3-butadiene (**2**) was prepared as reported^[23] in 18% yield. Thus, an alternative, more convenient, in spite its lower overall yield (11%), was suggested based on the rearrangement of 3-methyl-3,4-oxido-1-butene (**5**), prepared from isoprene,^[28] to 2-hydroxymethyl-1,3-butadiene (**6**) using lithium diisopropylamide (LDA), followed by standard bromination (Scheme 3).

In 1991 Yadav and Ravishankar^[17] reported that they were unable to reproduce my procedure^[1] for the synthesis of 2-(bromomethyl)buta-1,3-diene (**2**), this fact prompting the

Scheme 2. Synthesis of 2-(bromomethyl)buta-1,3-diene (**2**) by Krug and Ten.^[23]

Scheme 3. Synthesis of 2-(bromomethyl)buta-1,3-diene (**2**) by Silverstein, Katzenellenbogen et al.^[14]

authors to propose an alternative approach, as shown in Scheme 4. Thus, DABCO-promoted seven days reaction of acetaldehyde with ethyl acrylate gave compound **7** in 90 % yield. Diisobutylaluminium hydride (DIBALH) reduction of ester **7** to provide diol **8** (yield not reported), followed by full bromination, afforded dibromide **9** (yield not reported), whose treatment with HMPA gave 2-(bromomethyl)buta-1,3-diene (**2**) in quantitative yield. The potential interest of this synthetic approach is seriously compromised by toxic solvents used (benzene, HMPA), and long reaction times; improved reaction conditions are thus mandatory.

In 1993 Chen and co-workers, in their new approach to the formal synthesis of (±)- α -cedrene,^[20] one of the key intermediates, 2-(phenylthiylmethyl)-1,3-butadiene, was obtained in 77 % yield from the reaction of 2-(bromomethyl)buta-1,3-diene (**2**), prepared by my procedure,^[1] as the only cited reference.

In 1994 Nájera and Sansano^[13] reported an elegant and general method for the synthesis of 2-alkyl substituted 1,3-dienes from 2-(chloromethyl)-3-tosylpropene (**10**). Among the possible target dienes, the authors described the synthesis of 2-(bromomethyl)buta-1,3-diene (**2**) and ipsenol (**I**) (Scheme 5). The reaction of 2-(chloromethyl)-3-tosylpropene (**10**) with *n*-BuLi followed by treatment with iodomethyltrimethylsilane gave the β -silyl sulfone **11** in 70 % yield. The reaction of compound **11** with NaBr afforded (3-(bromomethyl)-2-tosylbut-3-en-1-yl)trimethylsilane (**12**) in 98 % yield, that after treatment with tetrabutylammonium fluoride (TBAF) led to 2-(bromomethyl)buta-1,3-diene (**2**) in 76 %, whose physical and spectroscopic data were in full agreement with those reported by me,^[1] as kindly cited by the authors, and the only reference for compound **2**. In the same paper, a new synthesis of racemic ipsenol (**I**) was described, by reacting intermediate

Scheme 4. Synthesis of 2-(bromomethyl)buta-1,3-diene (**2**) by Yadav and Ravishankar.^[17]

Scheme 5. Synthesis of 2-(bromomethyl)buta-1,3-diene (**2**) and ipsenol (**I**) by Nájera and Sansano.^[13]

11 with Zn and 3-methylbutanal, followed by treatment with TBAF, in 83 % overall yield.

In 2000, Jing and Sheares^[29] reported a new procedure for the synthesis of 2-(bromomethyl)buta-1,3-diene (**2**) from 1,4-dibromo-2-(bromomethyl)but-2-ene (**1**) by treating it with 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU). No citation to my work^[1] or Krug's^[23] was given, although in an article^[30] published the same year by the same authors, Krug's^[23] method was applied.

In fact, and among other approaches included mine,^[1] and Yadav/Ravishankar's,^[17] Sheares' method^[29] seems preferred,^[31] and was applied by Ceschi et al.^[32] for the synthesis of 2-(bromomethyl)buta-1,3-diene (**2**). In this communication, a new synthesis of racemic ipsenol (**I**), in 91 % yield, was described by reacting the indium species generated from 2-(bromomethyl)buta-1,3-diene (**2**), with 3-methylbutanal at room temperature (rt) in THF.^[32]

To sum up, from the results shown in this section, several conclusions can be withdrawn: 1.° Marco Contelles' synthesis of ipsenol and ipsdienol^[1] has got eight citations in the current literature. 2.° The method that Tokuda, Sugimoto and co-workers^[18,19] claimed as original for isoprenylation reactions had been reported eleven years before in the same journal by García and Marco Contelles.^[1] 3.° As pointed by Tokuda, Sugimoto and co-workers,^[18,19] mine^[1] is one of the simplest methods among a number of methods including chiral synthesis of these pheromones for the synthesis of ipsenol (**I**) and ipsdienol (**II**) (Figure 1). 4.° Among the reported methods for the synthesis of 2-(bromomethyl)buta-1,3-diene (**2**) (Scheme 1), Krug's^[23] is by far the most largely used and cited, although not without inconveniences due to not easily available SO₂ reagent to prepare the key intermediate, 3-methyl-2,5-dihydrothiophene (**3**) (Scheme 2), and the low overall chemical yield.^[14] 5.° Finally, Sheares' method to prepare 2-(bromomethyl)buta-1,3-diene (**2**) by reaction of 1,4-dibromo-2-(bromomethyl)but-2-ene (**1**)^[1] (Scheme 1) with DMPU is gaining high credit in the last years.^[29]

3.2. Methods and Protocols for the Synthesis of (±)-Ipsenol and (±)-Ipsdienol

The first synthesis of ipsenol (**I**) and ipsdienol (**II**) was reported in 1968 by Silverstein and colleagues,^[10] and unequivocally confirmed the structures of these two natural products, isolated and identified by themselves two years before.^[7]

As shown in Scheme 6, deprotonation of 2-isobutyl-1,3-dithiane (**13**) or 2-isobutenyl-1,3-dithiane (**14**) with *n*-BuLi, followed by reaction with 2-(bromomethyl)buta-1,3-diene (**2**) afforded 2-methyl-6-methylene-7-octen-4-one propanedithio-ketal (**15**) or 2-methyl-6-methylene-2,7-octadien-4-one propanedithio-ketal (**16**), in 51 and 28 % yields, respectively.

Scheme 6. Synthesis of ipsenol (**I**) and ipsdienol (**II**) by Silverstein et al.^[10]

Next, the reaction of compound **15** with $\text{CdCO}_3/\text{HgCl}_2$ gave 2-methyl-6-methylene-7-octen-4-one (**17**) in 59 %, which after reduction with NaBH_4 in $\text{MeOH}/\text{H}_2\text{O}$ produced ipsenol (**I**) in 66 % yield (not shown in Scheme 6). The synthesis of ipsdienol (**II**) from analogous intermediate **14** was more complicated and proceeded in lower yield, mainly due to the complex reaction mixture that resulted upon deblocking intermediate **16** with AgNO_3 (not shown in Scheme 6); thus, the mixture containing product **18** was finally reduced with NaBH_4 in isopropanol/ H_2O to give ipsdienol (**II**) in 31 % yield (Scheme 6).^[10] Ketones 2-methyl-6-methylene-7-octen-4-one (**17**) and 2-methyl-6-methyleneocta-2,7-dien-4-one (**18**) have been also prepared by condensation of 2-(bromomethyl) buta-1,3-diene (**2**) with 3-methylbutanenitrile and 3-methylbut-2-enenitrile, in 77 and 70 % yields, respectively.^[33]

In 1976 Skatebøl and co-workers reported a new synthesis of ipsenol (**I**) and ipsdienol (**II**) in multigram scale,^[2] as the previously reported syntheses by Silverstein^[10] and Vig^[34] (see below) were not considered suitable for such scale. Thus, reaction of allenic alcohol 2,3-butadienol (**19**) with ethyl vinyl ether in the presence of $\text{Hg}(\text{CF}_3\text{CO}_2)_2$ afforded ether **20** in 69 % yield, whose pyrolysis at 390 °C in an electric oven, provided 3-methylene-4-pentenal (**21**) in 80 % yield. Final treatment of aldehyde **21** with isobutylmagnesium bromide, or isobutenylmagnesium bromide, gave ipsenol (**I**) in 62 % yield, or ipsdienol (**II**) in 52 % yield (Scheme 7).^[2]

In 1997 Clinet and Linstremelle^[35] reported a new method for the synthesis of conjugated allenic ketones and aldehydes based on the reaction of allenyl lithium species with *N,N*-dimethylamides, that was applied to the synthesis of ipsenol (**I**)

Scheme 7. Synthesis of ipsenol (**I**) and ipsdienol (**II**) by Skatebøl et al.^[2]

Scheme 8. Synthesis of ipsenol (**I**) and ipsdienol (**II**) by Clinet and Linstremelle.^[35]

and ipsdienol (**II**) (Scheme 8). Thus, the reaction of propa-1,2-dien-1-yl lithium with *N,N*,3-trimethylbutanamide (**22**), or *N,N*,3-trimethylbut-2-enamide (**23**), at low temperature, followed by mild acid hydrolysis gave allenic ketones **24** and **25**, in 70 and 83 % yields, respectively. Next, the reaction of these ketones with vinyl cuprate led to compounds **17** (95 %) and **18** (85 %)^[10] respectively, whose reduction with NaBH_4 in $\text{MeOH}/\text{H}_2\text{O}$, at 0 °C for 3 h, gave ipsenol (**I**) (95 %) and ipsdienol (**II**) (94 %), respectively.^[35]

In 1978 Bertrand and Viala reported the synthesis of ipsenol (**I**) and ipsdienol (**II**) in 60 % yields^[36] by reacting 3-methylenepent-4-enal (**21**) with isobutylmagnesium bromide, or isobutenylmagnesium bromide (Scheme 9), using the same strategy and procedure described by Skatebøl et al.,^[2] the only difference being that the French authors synthesized the key aldehyde **21** by reacting buta-2,3-dien-1-ol (**19**) with methyl orthoacetate to give the corresponding orthoester (70 %) after Claisen rearrangement, followed by reduction with DIBALH (99 %).^[36]

In 1976 Kondo and colleagues reported that the reaction of the Grignard reagent of 2-chloro-1,3-butadiene with ($\pm$)-2-isobutyloxirane (**26**) (Figure 2) gave ipsenol (**I**) and ipsdienol (**II**) in 70 % yields; no experimental details were given.^[37] This method is of interest not only in itself, but because it was later largely applied in the synthesis of optically pure ipsenol and ipsdienol using EP (*R*)- and (*S*)-2-isobutyloxiranes **26** (Figure 2).

In 1979, in a preliminary communication,^[38] followed by two full papers in 1983,^[39,40] Sakurai and colleagues identified and prepared 2-trimethylsilylmethyl-1,3-butadiene (**27**) as a new useful “isoprene synthon” of potential wide synthetic application for terpene synthesis. Based on the known reactivity of allylsilanes with electrophiles in the presence of Lewis acid catalysts, they reported a new synthesis of ipsenol (**I**) and ipsdienol (**II**).^[38,39] As shown in Scheme 10, the reaction of the Grignard reagent of chloromethyltrimeth-

Scheme 9. Synthesis of ipsenol (**I**) and ipsdienol (**II**) by Bertrand and Viala.^[36]

Figure 2. Structures of ($\pm$)-2-isobutyloxirane (**26**), (*R*)-, (*S*)-2-isobutyloxiranes **26**, 2-isobutyl-4-methylenetetrahydro-2*H*-pyran (**61**), and complex **XVI**.

Scheme 10. Synthesis of ipsenol (**I**) and ipsdienol (**II**) by Sakurai et al.^[38–40]

ylsilane and 2-chloro-1,3-butadiene in the presence of a catalytic amount of $\text{Ni}(\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2)\text{Cl}_2$ [$\text{Ni}(\text{dppp})\text{Cl}_2$] gave 2-trimethylsilyl-methyl-1,3-butadiene (**27**) in 91% yield (Scheme 10). Next, reaction of 2-trimethylsilylmethyl-1,3-butadiene (**27**) with isovaleryl chloride (or 3,3-dimethylacryloyl chloride), in the presence of TiCl_4 , afforded ketones **17** (or **18**), that after reduction with DIBALH, produced ipsenol (**I**) and ipsdienol (**II**) in 62% and 73% yields, respectively. Very interestingly, the reaction of 2-trimethylsilylmethyl-1,3-butadiene (**27**) with 3-methylbutanal in the presence of TiCl_4 or AlCl_3 , also gave ipsenol (**I**), but in low yield.

Years later it was reported that analogous 2-dimethylphenylsilylmethyl-1,3-butadiene reacted with 3-methylbutanal, in the presence of Et_2AlCl , to give ipsenol (**I**) in 87% yield, and that the reaction of 2-dimethylphenylsilylmethyl-1,3-butadiene with 3,3-dimethylacryloyl chloride, in the presence of AlCl_3 , in DCM, at -60°C afforded ketone **18**, that after reduction with DIBALH, produced ipsdienol (**II**) in 85% yield.^[41,42]

Finally, it is worth to note that almost simultaneously to the Hosomi's report,^[38] the same year, Wilson and co-workers^[43] (see below) described that the reaction of 1-cyclobutenylmethylolithium with Me_3SiCl in hexane at -78°C gave a mixture of 2-trimethylsilylmethylenecyclobutane and 1-trimethylsilylmethylcyclobutene in a 60/40 ratio, a mixture that after distillation at atmospheric pressure in the presence of maleic anhydride induced ring opening of 1-trimethylsilylmethylcyclobutene to 2-trimethylsilyl-methyl-1,3-butadiene (**27**) which was trapped as the Diels-Alder adduct.

In 1985, Bubnov and Etinger described the synthesis and reactivity of 2-dipropylborylmethyl-1,3-butadiene (**28a**), a new “isoprene synthon”, easily prepared by reacting 2-bromomethyl-1,3-butadiene (**2**) with hexyloxy(dipropyl) borane (Pr_2BOHex) in the presence of Al turnings activated with HgCl_2 , in 75% (Scheme 11, eq. 1).^[44] Compound **28a**, stable in an inert atmosphere, that could be stored for a long time without noticeable decomposition, exhibited the typical reactivity of allylboranes, in particular with aldehydes and ketones at low temperatures. Thus, and as shown in Scheme 11 (eq. 1), the reaction of 2-dipropylborylmethyl-1,3-butadiene (**28a**) with 3-methylbutanal and 3-methylbut-2-enal, followed by treatment with triethanolamine (TEA),

Scheme 11. Synthesis of ipsenol (**I**) and ipsdienol (**II**) by Bubnov and Etinger,^[44] and Brown and Randad.^[45]

afforded ipsenol (**I**) and ipsdienol (**II**) in 94 and 96% yields, respectively.

However, as the synthesis of 2-dipropylborylmethyl-1,3-butadiene (**28a**) involved the cumbersome preparation of Pr_2BOHex , Brown and Randad^[45] designed and carried out the synthesis of an alternative “boron-isoprene synthon” such as (1*S*,5*S*)-9-(2-methylenebut-3-en-1-yl)-9-borabicyclo[3.3.1]nonane (B-isoprenyl-9-BBN) (**28b**) by reacting 9-methoxy-9-borabicyclo[3.3.1]nonane (B-OMe-9-BBN) with isoprenylpotassium **IV**, prepared as reported by Brandsma et al.,^[46] followed by addition of a controlled quantity of $\text{BF}_3 \cdot \text{Et}_2\text{O}$. Without isolation, reagent **28b** was converted to ipsenol (**I**) and ipsdienol (**II**) in 65% yields, after reaction with 3-methylbutanal and 3-methylbut-2-enal, respectively, followed by oxidation (Scheme 11, eq. 2).

In 1987, Brandsma and co-workers reported the reaction of dilithiated isopropenylacetylene [$\text{LiC}\equiv\text{CC}(\text{=CH}_2)\text{CH}_2\text{Li}$] with diverse electrophilic reagents (“ E^+ ”) to give compounds $\text{HC}\equiv\text{CC}(\text{=CH}_2)\text{CH}_2\text{E}$.^[47] Thus the reaction of 2-methylbut-1-en-3-yne with $n\text{-BuLi}/\text{tert-BuOK}$ followed by treatment with 3-methylbutanal and 3-methylbut-2-enal provided alcohols **29/30** in 63 and 76% yields, respectively, that after reduction with activated Zn by treatment with $\text{BrCH}_2\text{CH}_2\text{Br}/\text{LiCuBr}_2$, in EtOH/THF , afforded ipsenol (**I**) and ipsdienol (**II**) in 55% overall yields, respectively (Scheme 12, eq. 1). The same group has described that the direct treatment of isoprene with $n\text{-BuLi}/\text{tert-BuOK}$, in the presence of tetramethylpiperidine in THF, provided potassium “isoprene synthon” species **IV**, that reacted with electrophiles to afford dienes in good chemical yields.^[46] Brandsma et al. have also reported that the metalation of isoprene could be carried out with a 50% excess of potassium diisopropylamide (KDA), prepared *in situ* by adding diisopropylamine to the couple $n\text{-BuLi}/\text{tert-BuOK}$, at -70°C in THF, and that the resulting potassium species **IV** reacted with 3-methylbutanal and 3-methylbut-2-enal to give ipsenol (**I**) and ipsdienol (**II**) in 19 and 21% yields, respectively (Scheme 12, eq. 2).^[48]

Scheme 12. Synthesis of ipsenol (**I**) and ipsdienol (**II**) by Brandsma et al.^[46–48]

In 1987 Semmelhack and Fewkes described that the $(\eta^4\text{-isoprene})\text{Fe}(\text{CO})_3$ complex can be deprotonated with LDA, and that the resulting coordinated isoprene anion **V** is a new “isoprene synthon” that reacts with electrophiles at low temperature.^[49] This reactivity was used with success for the synthesis of the iron complexes of the sex pheromones **31/32** in 36 and 49% yields, that after treatment with H_2O_2 liberated the ligands affording ipsenol (**I**) and ipsdienol (**II**) in 81 and 91% yields, respectively (Scheme 13).^[49]

In 1999 Kulinkovich and co-workers described a new synthesis of ipsenol (**I**) and ipsdienol (**II**)^[50] starting with 2-(2,2-diethoxyethyl)-1-methyl-1-cyclopropanol (**33**), prepared by reaction of $n\text{-BuMgBr}/\text{Et}_2\text{O}$ with a mixture of vinylacetic aldehyde diethyl acetal, and ethyl acetate, in the presence of $\text{Ti}(\text{O-}i\text{-Pr})_4$. As shown in Scheme 14, the regioselective two-

Scheme 13. Synthesis of ipsenol (**I**) and ipsdienol (**II**) by Semmelhack and Fewkes.^[49]

Scheme 14. Synthesis of ipsenol (**I**) and ipsdienol (**II**) by Kulinkovich et al.^[50]

step sequence of bromination-dehydrobromination of compound **33** afforded 3-(2,2-diethoxyethyl)-3-buten-2-one (**34**) in 91% yield. Next, the reduction of compound **34**, followed by mesylation and elimination, gave 2-(2,2-diethoxyethyl)-1,3-butadiene (**35**) in 55% yield. Final acid hydrolysis afforded 3-methylenepent-4-enal (**21**) that, without purification, was reacted with $i\text{BuMgBr}$ in ethyl ether, at 0°C , or with 2-methyl-1-propenylmagnesium bromide in THF, at -15°C , to give ipsenol (**I**) and ipsdienol (**II**) in 52 and 44% yields, respectively, from intermediate **35**.^[50]

The same group, following a similar strategy of bromination-dehydrobromination on 1-(2-chloroethyl)cyclopropanol prepared key intermediate 2-(bromomethyl)-4-chlorobut-1-ene (**36**) (Scheme 15), whose reaction with Zn gave the allylic organozinc species that after treatment with 3-methylbutanal and 3-methylbut-2-enal gave alcohols **37** and **38** in 73 and 76% yields, respectively (Scheme 15). Next, 8-chloro-2-methyl-6-methylenooct-4-ol (**37**) was transformed into its OTHP derivative, that after reaction with KOH/EtOH and hydrolysis of the acetal group produced ipsenol (**I**) in 57% overall yield from **37** (Scheme 15). Following a similar protocol, 8-chloro-2-methyl-6-methylenooct-2-en-4-ol (**38**) gave ipsdienol (**II**) in 60% overall yield (Scheme 15).^[51]

3.3. Methods and Protocols for the Synthesis of (±)-Ipsenol

In 1970 Vig's approach to ipsenol (**I**),^[34] the key intermediate 5-methyl-3,3-ethylenedioxy-hexanal (**40**) was synthesized from ethyl 5-methyl-3-oxohexanoate (**39**),^[52] after reaction with ethylene glycol in the presence of $p\text{-TsOH}$, followed by reduction of the resulting ester with LAH to provide the corresponding alcohol, which was oxidized with CrO_3/py in 60% overall yield from compound **39** (Scheme 16). Next, reaction of aldehyde **40** with $\text{CH}_2=\text{CHMgBr}$ gave an allylic alcohol that was oxidized with Jones's reagent to give α,β -unsaturated ketone **41** in 40% yield. Wittig reaction with $\text{CH}_2=\text{PPh}_3$ provided a diene **42** (72%) whose acid hydrolysis under mild acid conditions afforded 2-methyl-6-methylene-7-

Scheme 15. Synthesis of ipsenol (**I**) and ipsdienol (**II**) by Matyushenkov and Kulinkovich.^[51]

Scheme 16. Synthesis of ipsenol (**I**) by Vig et al.^[34]

octen-4-one (**17**) in 63 % yield, that after reduction with NaBH_4 afforded ipsenol (**I**).^[34]

In 1975, in a preliminary communication,^[54] and in 1979 in a full paper,^[43] Wilson and co-workers developed the concept of cyclobutene derivatives as isoprene equivalents, applying them to terpene synthesis. They found that metalation of methylenecyclobutane with the *n*-BuLi/*N,N,N,N*-tetramethyl ethylenediamine (TMEDA) complex, in hexane, gave 1-cyclobutenylmethylolithium species **VI**, whose reaction with electrophiles resulted in mixtures of compounds of type **VII** and **VIII**, in ratios depending of the structure of the reagent (Scheme 17). As expected, under these reaction conditions, the use of 3-methylbutanal as electrophile, at rt, gave a mixture of isomers (3:7), from where the desired, but minor 1-(cyclobut-1-en-1-yl)-3-methylbutan-2-ol (**43**) could be easily separated from the undesired major isomer by chromatography, and isolated in 30 % yield; final heating at 150 °C converted compound **43** into ipsenol (**I**). In a subsequent development from the same group,^[43] this synthetic

strategy was used to convert 1-cyclobutenylmethylolithium (**VI**) into the “isoprene synthon” 2-trimethylsilylmethyl-1,3-butadiene (**27**)^[38] (Scheme 10), and trimethylstannylisoprene (**48**), a new “isoprene synthon” (Scheme 17, eq. 1). Then, under the same reaction conditions, species **VI** and Me_3SiCl gave a 6/4 ratio of compounds **44/45** in 77 % yield. This mixture when distilled at atmospheric pressure in the presence of maleic anhydride to induce ring opening of **45** to **27**, which was trapped as the Diels-Alder adduct, pure **44** being obtained in this manner (Scheme 17, eq. 2). Similarly, when the 6/4 ratio of compounds **44/45** was thermolyzed through a hot tube at ~400 °C, the reaction product was a 6:4 mixture of **27/44** (Scheme 17, eq. 2), compound **27** being the result of partial allylic isomerization followed by cyclobutene ring opening. Finally, compound **44** reacted with 3-methylbutanal/ TiCl_4 to yield cyclobutene **44**, which was thermolyzed to ipsenol (**I**) (Scheme 17, eq. 2).^[43] Finally, in the same article, it was reported that the reaction of a hexane solution of ClSnMe_3 with **VI** at 0 °C gave a mixture of **46/47** (2/8) (55 %), that could be thermolyzed at 350 °C to yield only **48** (61 %) (Scheme 17, eq. 3),^[43] possibly due to the fact that allylic stannanes undergo even more ready [1,3]-sigmatropic isomerizations.

In an almost simultaneous and independent development, Sakurai and colleagues described the synthesis of 2-trimethylstannylmethyl-1,3-butadiene (**48**) from the Grignard reagent of chloromethyltrimethylstannane and 2-chloro-1,3-butadiene (Scheme 10), in the presence of a catalytic amount of dichlorobis(diphenylphosphino)propanenickel,^[55] following the same procedure employed for the preparation of the corresponding silyl derivative **27** (Scheme 10).^[38] As expected, and due to the fact that the double bond in allylstannanes is more nucleophilic than that of allylsilanes, 2-trimethylstannylmethyl-1,3-butadiene (**48**) was coupled with 3-methylbutanal, in the presence of $\text{BF}_3 \cdot \text{OEt}_2$, in DCM, at -78 °C, to provide ipsenol (**I**) in 40 % yield^[53] (Scheme 17, eq. 3).

In 1977 Haslouin and Rouessac reported a new synthesis of ipsenol (**I**).^[56] As shown in Scheme 18, Diels-Alder reaction of itaconic anhydride with cyclopentadiene gave adduct **49** in 80 % yield, that after reduction with NaBH_4 in DMF, regioselectively afforded lactone **50** in 55 % yield. Next, DIBALH reduction of **50** to provide lactol **51**, followed by treatment with *i*-butylmagnesium bromide afforded diol **52**. In the next step, treatment of compound **52** with PDC/DCM regioselectively oxidized the primary alcohol to the aldehyde to give a lactol that *in situ* was oxidized to lactone **53** in 50 % yield. The final steps of the sequence consisted of: (a) DIBALH reduction to give **54** (95 %), (b) Wittig reaction to furnish **55** (66 % yield) and (c) quantitative thermal retro Diels-Alder reaction of product **55** to afford ipsenol (**I**).^[56]

In 1979 Cazes et al. proposed a new “isoprene synthon” based on the chemistry and reactivity of sulfoxides,^[57] that they

Scheme 17. Synthesis of ipsenol (**I**) by Wilson et al.,^[43] and by Sakurai et al.^[53]

Scheme 18. Synthesis of ipsenol (**I**) by Haslouin and Rouessac.^[56]

applied to a new synthesis of ipsenol (**I**). As shown in Scheme 19, their approach was based on (4-(phenylthio)but-1-en-2-yl)lithium (**IX**) species, easily prepared from tosylhydrazone **56**, and converted through a series of standard transformations into key intermediate (3-(chloromethyl)but-3-en-1-yl)(phenyl)sulfane (**57**), that after Grignard reagent formation and coupling with 3-methylbutanal gave 2-methyl-6-methylene-8-(phenylthio)octan-4-ol (**58**) in 48 % yield. Finally, sulfoxide formation to give **59** followed by its thermal elimination afforded ipsenol (**I**).^[57]

In 1980, first in a preliminary communication,^[58] and later in full paper,^[59] Snider and Rodini described that the ene-reaction of 3-methylbutanal with isoprene, catalyzed by Me_2AlCl , resulted in a one-step synthesis of ipsenol, albeit in poor yield (16 %).

Scheme 19. Synthesis of ipsenol (**I**) by Cazes et al.^[57]

Scheme 20. Synthesis of ipsenol (**I**) by Halazy and Krief.^[60]

The same year Halazy and Krief^[60] proposed and developed a new “isoprene synthon” based on the reactivity of (1-(methylselanyl)cyclobutyl)lithium species **X** (Scheme 20), easily prepared from cyclobutane-1,1-diylbis(methylselane) by treatment with *n*-BuLi, and its reactivity with suitable electrophiles to give adducts **XI**, precursors for cyclobutenes **XII** and 1,3-dienes **XIII** (Scheme 20). A practical application is shown in the synthesis of ipsenol (**I**), by reacting species **X** with 2-isobutyloxirane (**26**) to give 3-methyl-1-(1-(methylselanyl)cyclobutyl)butan-2-ol (**60**) that was easily transformed into known 1-(cyclobut-1-en-1-yl)-3-methylbutan-2-ol (**43**)^[54] (Scheme 17), and whose thermolysis quantitatively provided the final target (Scheme 20).^[60]

In 1982 Hegedus and Varaprath^[26] communicated that (π -2-vinylallyl)nickel bromide complex, prepared by the reaction of 2-(bromomethyl)-1,3-butadiene (**2**) with bis(cyclooctadiene)-nickel in benzene at 0 °C, in 74 % isolated yield, reacted with 3-methylbutanal, in DMF, at 40 °C to give ipsenol (**I**) in 56 % yield.^[26]

In 1985 Margot and Schlosser found that 4-methylene-tetrahydropyrans bearing an alkyl substituent at the 2-position, on treatment with LDA/*tert*-BuOK in THF at -78 °C, gave β -methylene, δ -unsaturated alcohols. Thus, for 2-isobutyl-4-methylenetetrahydro-2*H*-pyran (**61**) (Figure 2) the reaction provided ipsenol (**I**) in 83 % yield.^[61]

In 1989 Nomoto and Takayama^[62] described that 3-bromomethyl-2,5-dihydrothiophene 1,1-dioxide (**4**) on treatment with bases quantitatively afforded 3-methylene-2,3-dihydrothiophene 1,1-dioxide (**62**), a synthetic intermediate that was successfully used for the synthesis of ipsenol (**I**) after reaction with 3-methyl-1-nitrobutane, in the presence of 1,1,3,3-tetramethylguanidine (TMG), to give 3-(3-methyl-1-nitrobutyl)-2,5-dihydrothiophene 1,1-dioxide (**63**), followed by oxidation to convert the nitro group into the corresponding ketone, reduction with NaBH_4 and thermolysis (Scheme 21).

In 1993 Masuyama and co-workers reported the carbonyl allylation of 2-(bromomethyl)buta-1,3-diene (**6**) with 3-methylbutanal, using the $\text{PdCl}_2(\text{PhCN})_2\text{-SnCl}_2$ complex, at rt in THF- H_2O , to produce ipsenol (**I**) in 56 % yield^[63] (Scheme 22).

A very elegant and efficient approach to ipsenol (**I**) was communicated by Fukushima et al.^[64] *via* $\text{Pd}/\text{Et}_3\text{B}$ catalyzed ene-type reaction of 3-methylbutanal with isoprene, by using

Scheme 21. Synthesis of ipsenol (**I**) by Nomoto and Takayama.^[62]

Scheme 22. Synthesis of ipsdienol (I) by Masuyama et al.,^[63] and Fukushima et al.^[64]

$\text{Pd}(\text{OAc})_2$ (10 mol %), Xantphos (10 mol %), and triethylborane, at rt under a nitrogen atmosphere^[64] (Scheme 22).

3.4. Methods and Protocols for the Synthesis of (±)-Ipsdienol

One of the first synthesis of ipsdienol (II) was reported by Mori in 1974 from readily available monoterpene myrcene, bearing the whole structure and functionality of ipsdienol (II), except the hydroxyl group at C4.^[65] To incorporate the hydroxyl group at its correct position, as shown in Scheme 23, myrcene was oxidized with MCPBA to give epoxide **64** in 85%, that after treatment with $(\text{PhSe})_2$, NaBH_4 in EtOH at reflux, followed by reaction with H_2O_2 , gave allylic alcohol **65** in 72% yield, ready for the allylic rearrangement to give ipsdienol (II). However, the process was more complicated than expected, and proceeded by reacting alcohol **65** with thionyl chloride plus acetylation to afford a 1:3 mixture of acetates **66** and **67** in 72% yield, that was submitted to LAH

Scheme 23. Synthesis of ipsdienol (II) by Mori.^[65]

Scheme 24. Photooxygenation of myrcene and synthesis of ipsdienol (II) by Norin et al.^[66]

reduction to furnish an unseparable 1:3 mixture of alcohols **65** and **II** in 72% yield, that after acetylation (Ac_2O , py) resulted in a mixture of unreacted tertiary alcohol **65** and acetate **67**, that were separated, pure acetate **67** being converted to ipsdienol (II) by reaction with LAH.

Swedish authors have reported that the direct photooxygenation of myrcene in the presence of Rose bengal, and continuous reduction with tetrabutylammonium borohydride of the hydroperoxides as they formed, gave alcohols **65** and **68** in modest yields^[67] (Scheme 24). They also made the interesting observation that treatment of the trienol **65** with cat. $\text{HClO}_4/\text{AcOH}$ yielded ipsdienyl acetate **67** which on hydrolysis gave ipsdienol (II) in 83% overall yield. Furthermore, the oxidation of (*E*)-2-methyl-6-methylenoocta-3,7-dien-2-ol (**65**) with PCC/py-HCl gave 2-methyl-6-methylenoocta-2,7-dien-4-one (**18**, 43%) and traces of 2-(3-(2-methylenebut-3-en-1-yl)oxiran-2-yl)propan-2-ol (**69**)^[66] (Scheme 24).

The reaction of 3-methylbut-3-en-1-yl acetate (**70**) with senecioic anhydride (**71**), in the presence of $\text{BF}_3\text{--Et}_2\text{O}$, gave a mixture of ketones **72** (70%), **73** (21%), and **74** (8%) in 76% total yield (Scheme 25). Pyrolysis of ketone **72** gave mircenone **18**, which on reduction with LAH afforded ipsdienol (II) (no reported yield)^[68] (Scheme 25).

First, as a preliminary communication^[69] and later, as a full paper,^[70] Masaki and co-workers described a new synthesis of ipsdienol (II), starting from myrcene, in 25% overall yield, as shown in Scheme 26, employing also the chemistry of sulfoxides, as Cazes et al. have previously reported.^[57] The reaction of myrcene with PhSCl in DCM at 0 °C gave compound **75**, which on treatment with NaOAc in AcOH at 20 °C for 1 h led to the regiospecific formation of the tertiary

Scheme 25. Synthesis of ipsdienol (II) by Garbers and Scott.^[68]

Scheme 26. Synthesis of ipsdienol (II) by Masaki et al.^[69,70]

acetoxysulfide **76**. This compound was transformed into *trans*-allylic acetate **66** by oxidation with $\text{H}_2\text{O}_2/\text{AcOH}$, followed by thermal elimination of sulphenic acid from the intermediary sulfoxide, in toluene under reflux, in the presence of sodium bicarbonate. The tertiary allylic acetate **66** was stirred in $\text{Et}_2\text{O}-\text{AcOH}$ in the presence of *p*-TsOH/ H_2O at 0°C for 1 h to give the rearranged allylic isomeric acetate **67**, which after reaction with $\text{EtOH}/\text{H}_2\text{O}/\text{KOH}$ at 20°C for 3 h, provided ipsdienol (**II**) (Scheme 26).

In a further development of their synthesis of ipsenol (**I**) based on the Me_2AlCl catalyzed ene reaction of isoprene and 3-methylbutanal, Snider has found that reaction of isoprene with dimethylacryloyl chloride gave a complex mixture, whose reduction with NaBH_4 and purification gave ipsdienol (**II**) in 12 % yield.^[71]

4. Synthesis of Enantiomerically Pure Ipsenol and Ipsdienol

The synthesis of the four EP forms of ipsenol and ipsdienol allowed the authors to unequivocally assign the structure and absolute configuration of the isolated natural products, as well as to afford convenient amounts of them, in order to test their biological activities, and define structure activity relationships based on the stereochemistry of these natural products (see above). Mori was who first synthesized both of these pheromones in EP form and assigned their absolute configurations at the only stereocenter. Our presentation will show first his reports on this topic.^[72] For *de novo* biosynthesis and *in vitro* production of the aggregation pheromone components ipsenol and ipsdienol, the interested reader is directed to the specialized articles.^[73–75]

4.1. (S)-(-)-Ipsenol

Mori reported the synthesis of (S)-(-)-ipsenol [(S)-(**I**)] (Figure 1) in three articles^[76–78] using the “chiron approach” from readily available chiral precursors. In the first two^[76,77] (S)-(+)-leucine was transformed into (S)-2-isobutyloxirane [(S)-**26**, 26 % yield], that afforded (S)-(**I**), establishing as *S* the absolute configuration of the naturally occurring (-)-ipsenol (**I**) $[\alpha]_{20}^{\text{D}} -17.5^\circ$ (*c* 1 %, EtOH)}. As shown in Scheme 27, reaction of epoxide (S)-**26** with diethyl malonate in NaOEt/EtOH , followed by the usual work-up, gave the expected α -carboxy- γ -lactone that was treated with $\text{CH}_2\text{O}/\text{H}_2\text{O}/\text{Et}_3\text{NH}$ to

Scheme 27. First synthesis of (S)-(-)-ipsenol (**I**) by Mori.^[76,77]

give (S)-5-isobutyl-3-methylenedihydrofuran-2(3*H*)-one (**77**). Next, lactone **77** was treated with $\text{C}_6\text{H}_5\text{SeNa}$ to protect the *exo*-double bond, followed by reaction with DIBALH to yield a lactol, that after Wittig reaction with $\text{Ph}_3\text{P}=\text{CH}_2$ produced not only the one-carbon homologated product, but the simultaneous liberation of the “protected” double bond, affording (S)-(-)-**I** $[\alpha]_{25}^{\text{D}} -16.5^\circ$ (*c* 1.47 %, EtOH)}. Finally, it is important to note that the synthesis of (S)-(-)-ipsenol [(S)-(**I**)], as shown in Scheme 27, was previously analyzed by Mori by synthesizing and transforming racemic lactone **77** from methyl isobutyl ketone.^[77] Several years later Mori reported a second and shorter synthesis of (S)-(-)-ipsenol [(S)-(**I**)] by reacting the Grignard reagent of 2-chloro-1,3-butadiene with epoxide (S)-**26** (Figure 2).^[78] To sum up, Mori’s first synthesis of (S)-(-)-ipsenol, starting from (S)-(+)-leucine, was both lengthy, and cumbersome, the chemical (5 %) and optical yields (80 %) being very low,^[76,77] although in the modified procedure to obtain optically pure it was significantly improved (>99 % ee), the overall yield still remained low.^[78]

In 1976 Skattebøl and co-workers^[2] reported that by reacting aldehyde **21** with the lithium reagent derived from each of iso-butylmagnesium bromide (Scheme 7) using equimolar amounts of (+)-(2*S*,3*S*)-*N,N,N,N*-tetramethyl-2,3-dimethoxybutan-1,4-diamine, as chelating agent “...ipsenol (**1**) and ipsdienol (**2**) were obtained. On the basis of the rotation values reported by Silverstein et al.^{1,2} for the naturally occurring substances the optical yield for **1** was 6.3 % and for **2** 10.5 % ...”^[2] To sum up, very poor enantiomeric excesses (ee), no apparent absolute configuration assigned to the major enantiomer, and no experimental details.

In 1986 Yamamoto and co-workers described an asymmetric synthesis of (-)-ipsenol by using chiral allenyl boronic esters^[79] (Scheme 28). Thus, the boron reagent **79** prepared from allenylboronic acid (**78**) and D-(-)-bis(2,4-dimethyl-3-pentyl) tartrate (D-DMPT), in toluene, was treated with 3-methylbutanal for 20 h at -78°C , to give (S)-6-methylhept-1-yn-4-ol (**80**) (78 % yield, >99 % ee). Propargylic alcohol **80** was then transformed into the 2-brominated alcohol **81** (92 % yield) by reaction with B-bromo-borabicyclo[3.3.1]nonane

Scheme 28. Synthesis of (S)-(-)-ipsenol (**I**) by Yamamoto et al.^[79]

(B-Br-9-BBN) in DCM (50 mL) at 0 °C for 3 h. Next, this alcohol was exposed to dihydropyran in the presence of *p*-TsOH (cat.) in DCM, at 0 °C for 1.5 h, followed by reaction with CH₂=CHMgBr and Pd(PH₃)₄ (cat.) in benzene at rt for 2 h, affording diene **82** in 96% yield that, upon treatment with *p*-TsOH in MeOH, was mildly transformed into (*S*)-(-)-(**I**), whose spectroscopic data and optical rotation were identical with those reported for natural ipsenol,^[8] the optical purity shown to be >99% ee by GC analysis of the

corresponding α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester.^[79]

In 1990, first in a preliminary communication^[9] and later as a full paper,^[45] Brown and Randad described the application of EP B-2'-isoprenyldiisopinocampheylboranes (+)-(**83**) and (-)-(**83**) (Figure 3), prepared from (a)-(+)-pinene and (a)-(-)-pinene, respectively, as “chiral boro-isoprene synthons” for the synthesis of the enantiomers of ipsenol and ipsdienol.

As shown in Scheme 29 (eq. 1), the reaction of methylenebut-3-en-1-ylpotassium (**IV**) with B-methoxydiisopino B'-methoxydiisopinocampheylborane (¹Ipc₂BOMe) gave B-2'-isoprenyldiisopinocampheylborane (-)-(**83**) [¹Ipc₂BIpn (-)-(**83**)] that, after treatment with 3-methylbutanal, followed by non-oxidative work-up by addition acetaldehyde and diethanolamine (DEA), afforded natural (*S*)-(-)-ipenol (**I**) { $[\alpha]_{23}^D -17.67^\circ$ (*c* 1%, EtOH)} in 96% ee and 65% yield.^[9,45]

In 1990 Oertle and co-workers^[80] described the synthesis of (*S*)-(-)-ipenol (**I**) using as key chiral intermediate (*S*)-3-hydroxy-5-methylhexanoic acid (**84**) (Scheme 30), obtained by lithium dicyclohexylamide (LDCHA) promoted asymmetric aldol reaction of *tert*-butyl acetate and 3-methylbutanal, in the presence of chiral Ti-complex **XIV**, followed by TBAF hydrolysis and treatment with NaOH, in 38% overall yield and >99% ee.^[80] Next, total persilylation and basic hydrolysis gave (*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-methylhexanoic acid (**85**) in 98% yield, that after acid chloride formation using 1-chloro-*N,N,N*,2-trimethylprop-1-enylamine (CTPEA), followed by stepwise reaction with Me₃SiCH₂MgCl, CH₂=CHMgCl, and AcONa/AcOH provided (*S*)-*tert*-butyldimethyl((2-methyl-6-methyleneoct-7-en-4-yl)oxy)silane (**86**) in 46%, that after desilylation reaction with TBAF afforded EP (*S*)-(**I**).^[80]

In 1990 Imai and Nishida reported the TiCl₄-promoted ring-opening reaction of (*R*)-epichlorohydrin (**87**) with 2,3-butadienyltrimethylsilane (**88**) to afford EP (*S*)-(-)-ipenol in a three step synthesis.^[81] As shown in Scheme 31, the resulting adduct **89** was obtained in 39% yield, converted into the corresponding epoxide with retention of the absolute config-

Figure 3. Racemic “isoprene synthons” used for the “5 + 5” strategy for the synthesis of ipsenol (**I**) and ipsdienol (**II**), and chiral “boro-isoprene synthons” for the synthesis of EP ipsenol (**I**) and ipsdienol (**II**).

Scheme 29. Synthesis of EP ipsenol (**I**) and ipsdienol (**II**) by Brown and Randad.^[9,45]

Scheme 30. Synthesis of (*S*)-(-)-ipenol (**I**) by Oertle et al.^[80]

Scheme 31. Synthesis of (*S*)-(-)-ipenol (**I**) by Imai and Nishida.^[81]

uration at the stereocenter, and treated with iso-propylmagnesium bromide to afford the expected target in 41 % yield. Note that precursor 2,3-butadienyltrimethylsilane (**88**) is and works as a new synthetic equivalent of the Grignard reagent of 2-chloro-1,3-butadiene that has been used in the synthesis of ipenol and ipsdienol (see Scheme 10).^[37–40,78]

In 1992 Trost and Rodríguez communicated a new synthesis of (*S*)-(-)-ipenol (**I**) from (*S*)-lactic acid using the chiron approach,^[82] the key step being the TiCl_4 -mediated aldol reaction of enol silyl ether of ketone **90** [prepared by reacting (*S*)-lactic acid with pivaloyl chloride, followed by treatment with MeMgBr] and 3-methylbutanal to give the desired aldol adduct **91** (Scheme 32) in 84 % yield in 89:11 ratio. Wittig olefination ($\text{CH}_2=\text{PPh}_3$) gave a 62 % yield of pivalate **92** in a 95:5 ratio. Finally, pivalate elimination in **92** was accomplished by treating it with complex hexakis(*tert*-butylisocyanide)molybdenum to give a 66 % isolated yield of (*S*)-(-)-**I**. To sum up, natural (*S*)-(-)-ipenol was obtained in 21 % overall yield in six steps.

In 1995 Nishigaichi and co-workers reported a new synthesis of (*S*)-(-)-ipenol (**I**) starting from tributylstannylmethyl-3-buten-2-ol (**93**, 92 % ee).^[83] As shown in Scheme 33, *O*-methylation of compound **93** followed by reaction with 3-methylbutanal, in the presence of *i*- PrOTiCl_3 (DCM, -78 to 0°C), gave a mixture of the *syn*- and *anti*-(4*S*,7*S*)-7-methoxy-2-methyl-6-methyleneoctan-4-ol (**94**) products in 91:9 ratio. Compound **94** structure and functionality was similar to the analogous **92** (Scheme 32) reported by Trost and Rodríguez.^[82] Final elimination or the methoxy group leading to ipenol was again problematic as it was with the pivalate (see above), but it was successfully carried

Scheme 32. Synthesis of (*S*)-(-)-ipenol (**I**) by Trost and Rodríguez.^[82]

Scheme 33. Synthesis of (*S*)-(-)-ipenol (**I**) by Nishigaichi et al.^[83]

out by treating compound **94** with Ac_2O and subsequent Pd(II) -catalyzed reaction to give an acetate intermediate, whose hydrolysis of the acetate readily afforded (*S*)-(-)-ipenol (**I**) in 33 % yield and 70 % ee. Following a similar protocol as reported for the synthesis of (*S*)-(-)-ipenol (**I**), Nishigaichi and co-workers have also described the synthesis of (*R*)-(+)-ipenol (**I**) in a lower 42 % ee (see below).^[83]

In 1997 Yamamoto et al. described the synthesis of both enantiomers of ipenol and ipsdienol from chiral boron synthons derived from *D*-DMPT and *L*-DMPT.^[84] As shown in Scheme 34 (eq. 1), the reaction of (2-bromoallyl) diisopropoxyborane (**95**)^[85] with *D*-DMPT for 1 h at 60°C provided reagent (*S,S*)-**96**, that by reaction with 3-methylbutanal, at -78°C , in toluene, in the presence of molecular sieves 4A, gave (*S*)-2-bromo-6-methylhept-1-en-4-ol [(*S*)-**81**] in 83 % yield, identical to the compound prepared by Yamamoto et al.^[79] (Scheme 28) by an analogous procedure, and whose conversion to ipenol proceeded by the known protocol based on the Pd -catalyzed cross-coupling reaction with $\text{CH}_2=\text{CHMgBr}$, without protection of the secondary alcohol, to give (*S*)-(-)-ipenol (**I**) in 82 % yield, and 90 % ee, as determined by ^1H NMR after conversion to (*R*)-(+)-MTPA ester.

In 1999 Draillard and co-workers described the synthesis of (-)-(*S*)-ipenol and (-)-(*R*)-ipsdienol by asymmetric allylboration.^[86] For (-)-(*S*)-ipenol, the key intermediate was (*S*)-5-isobutyl-3-methylenedihydrofuran-2(3*H*)-one (**77**), previously prepared by Mori from (*S*)-leucine, and used for his synthesis of (*S*)-(-)-ipenol (**I**)^[76,77] (Scheme 27). French authors obtained it now by reaction of methyl 2-(((3*S*,4*S*,7*S*)-4,8,8-trimethyl-3*a*-phenylhexahydro-4,7-methanobenzo [*d*][1,3,2]dioxaborol-2-yl)methyl)acrylate (**97**) with 3-methylbutanal, to give methyl (*S*)-4-hydroxy-6-methyl-2-methyleneheptanoate (**98**) (81 %) followed by treatment with NaH/THF (90 %) (Scheme 35). The final steps consisted of DIBALH reduction of the lactone **77** followed by Wittig reaction to provide (*S*)-(-)-ipenol (**I**) in 50–60 % yields, and 82 % ee. Note that the precautions that Mori took in order to protect the double bond in *exo*-methylene lactone **77** for a similar transformation to yield (*S*)-(-)-ipenol (**I**) (Scheme 27) apparently seemed not necessary.

Scheme 34. Synthesis of EP ipenol (**I**) and ipsdienol (**II**) by Yamamoto et al.^[84]

Scheme 35. Synthesis of (*S*)-(-)-iposenol (**I**) and (*R*)-(-)-ipsdienol (**II**) by Draillard et al.^[86]

In 2001 List and colleagues reported a new synthesis of (*S*)-(-)-iposenol from (*S*)-4-hydroxy-6-methylheptan-2-one (**99**), obtained in the *L*-proline catalyzed aldol reaction of acetone and 3-methylbutanal, in 34% yield and 73% ee.^[87] Next, aldol **99** was protected and converted to enoltriflate **100**, whose Stille coupling with tributyl(vinyl)tin furnished known diene **86**, identical to the product prepared by Oertle et al.^[80] (Scheme 30), which after deprotection gave (*S*)-(-)-iposenol (**I**) in good overall yield (Scheme 36).

The same year Yu et al. reported a new synthesis of (*S*)-(-)-iposenol [(77% yield; 99% ee] based on the efficient (*R*)-BINOL- Ti^{IV} /*i*-PrSBEt₂ complex mediated catalytic asymmetric allylic transfer reactions of 3-methylbutanal with 2-trimethylstannylmethyl-1,3-butadiene (**48**) (Figure 3).^[88]

Nakajima's synthesis of (*S*)-(-)-iposenol (**I**)^[89] started with the coupling of trimethylsilylacetylene (**101**) with (*R*)-epichlorohydrin (**87**) to give (*R*)-1-chloro-6-(trimethylsilyl)hex-5-yn-2-ol (**102**) in 76% yield (Scheme 37), which after epoxide formation and ring opening with *i*-PrMgCl led to (*R*)-2-methyl-8-(trimethylsilyl)oct-7-yn-4-ol (**103**) in 73% yield. Next, formation of vinyl ether **104** followed by treatment with $\text{Ti}(\text{O}-i\text{-Pr})_4$ /*i*-PrMgCl, at -50°C , produced vinyl migration

Scheme 36. Synthesis of (*S*)-(-)-iposenol (**I**) by List et al.^[87]

Scheme 37. Synthesis of (*S*)-(-)-iposenol (**I**) by Nakajima et al.^[89]

affording compound **105** that after TBAF gave (*S*)-(-)-iposenol (**I**) (71%) and 98% ee, as determined by the Mosher's MTPA ester method.

Zhang and co-workers have exploited the reactivity of “boro-isoprene synthon” 4,4,5,5-tetramethyl-2-(2-methylenebut-3-en-1-yl)-1,3,2-dioxaborolane (**106**) (Figure 3) [prepared as reported by Erver and Hilt by reacting isoprenylpotassium (**IV**) (Figure 3) with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane],^[91] against 3-methylbutanal, in the presence of the BINOL-derived chiral phosphoric acid (*R*)-TRIP, to synthesize (*S*)-iposenol (**I**) (Scheme 38) in 60% yield and 50.6% ee.^[90]

4.2. (*R*)-(+)-Ipsenol

Mori reported the synthesis of (*R*)-(+)-iposenol [(*R*)-(**I**)] (Figure 4) $\{[\alpha]_{20}^{\text{D}} + 17.3^\circ$ (*c* 1.58%, EtOH)} (Figure 4)^[77] from (*R*)-(-)-leucine by a similar synthetic procedure as shown in Scheme 27. Mori reported a second and shorter synthesis of (*R*)-(+)-iposenol [(*R*)-(**I**)] by reacting the Grignard reagent of 2-chloro-1,3-butadiene with epoxide (*R*)-**26** (Figure 2).^[78]

Following the same protocol, as shown in Scheme 29 (eq. 2), Brown and Randad reported that the reaction of methylenebut-3-en-1-ylpotassium (**IV**) with *B*-*d*-methoxydiisopinocampheylborane (*d*Ipc₂BOMe) gave *B*-2'-*d*-isoprenyldiisopinocampheylborane (+)-(**83**) [*d*Ipc₂BIpn (+)-(**83**)] that, after treatment with 3-methylbutanal, followed by a non-oxidative work-up by addition acetaldehyde and DEA, afforded (*R*)-(+)-iposenol (**I**) in 93.7% ee and 60% yield.^[9,45]

Following a similar protocol as reported for the synthesis of (*S*)-(-)-iposenol (**I**), starting from tributylstannylmethyl-3-buten-2-ol (**93**), Nishigaichi and co-workers described the synthesis of (*R*)-(+)-iposenol (**I**).^[83] As shown in Scheme 39, *O*-

Scheme 38. Synthesis of (*S*)-(-)-iposenol (**I**) and (*R*)-(-)-ipsdienol (**II**) by Zhang et al.^[90]

Figure 4. Structure of (*R*)-(+)-iposenol [(*R*)-(+)-(**I**)].

Scheme 39. Synthesis of (*R*)-(+)-ipsenol (**I**) by Nishigaichi et al.^[83]

acetylation of compound **93** followed by reaction with 3-methylbutanal, in the presence of SnCl_4 , DCM, at 0°C , gave a mixture of the *syn*-(**107**) and *anti* (2*S*,5*R*)-5-hydroxy-7-methyl-3-methyleneoctan-2-yl acetate (**107**) products in 25:75 ratio. Final elimination of the acetoxy group was successfully carried out by treating compound **107** with AcCl/py , and subsequent Pd(II) -catalyzed reaction to give an acetate intermediate, whose hydrolysis of the acetate readily afforded (*R*)-(+)-ipsenol (**I**) in 48 % yield, in 42 % ee.^[83]

Yamamoto et al. reported that the reaction of (2-bromoallyl)diisopropoxyborane (**95**)^[85] with *L*-DMPT provided chiral boron reagent (*R,R*)-**96** (Scheme 34, eq. 2) that by reaction with 3-methylbutanal gave (*R*)-2-bromo-6-methylhept-1-en-4-ol [(*R*)-**81**] in 90 % yield, whose Pd -catalyzed cross-coupling reaction with $\text{CH}_2=\text{CHMgBr}$, without protection of the secondary alcohol, gave (*R*)-(+)-ipsenol (**I**) in 80 % yield, and 91 % ee.^[84]

Krische et al. have recently described highly enantioselective iridium catalyzed carbonyl isoprenylation reactions *via* hydrogen auto-transfer or 2-propanolmediated reductive coupling from primary alcohol or aldehyde reactants, respectively, and applied this method to the asymmetric total syntheses of (*R*)-(+)-ipsenol (**I**) and (+)-(*S*)-ipsdienol (**II**).^[92] Thus, as shown in Scheme 40, the reaction of 3-methylbutan-1-ol and 3-methylbutanal with *tert*-butyl (2-methylenebut-3-en-1-yl) carbonate (**108**) (Figure 3), prepared by base mediated “ring opening elimination” of isoprene oxide (**5**) (Scheme 3) followed by quenching with *Boc*-anhydride, in the presence of (**S**)-**Ir** catalyst (5 % mol), K_3PO_4 (100 % mol), in DME, 70°C , for 24 h, gave (*R*)-(+)-ipsenol (**I**) in 70 % yield, and 96 % ee, and in 86 % yield, and 95 % ee, respectively.^[92]

Scheme 40. Synthesis of (*R*)-(+)-ipsenol (**I**) and (*S*)-(+)-ipsdienol (**II**) by Krische et al.^[92]

4.3. (*S*)-(+)-Ipsdienol

Mori and co-workers have reported the synthesis of natural (*S*)-(+)-ipsdienol (**II**) from (*R*)-(+)-malic acid.^[78] The key intermediate was (*R*)-2-methyl-1-(oxiran-2-yl)propan-2-ol [(*S*)-**109**], whose reaction with the Grignard reagent of 2-chloro-1,3-butadiene followed by acetylation gave (*S*)-2-hydroxy-2-methyl-6-methyleneoct-7-en-4-yl acetate [(*S*)-**67**] in 44 %, that after dehydration of the tertiary alcohol and LAH reaction, afforded (*S*)-(+)-(**II**) $\{[\alpha]_D^{25} + 11.9^\circ$ (*c* 0.26, MeOH) (yield not provided) (Scheme 41).^[78] The authors noted that based on the report by Ohloff and Giersch describing the EP synthesis of both enantiomers of ipsdienol (see below),^[93] the optical purity of (*S*)-(+)-ipsdienol obtained by Mori was 90 %.^[78]

In 1991 Mori and Takikawa reported a second synthesis of (*S*)-(+)-**II** from (*R*)-serine^[12] from key intermediate methyl (*S*)-oxirane-2-carboxylate (*S*)-**110**, prepared as reported.^[94] Thus, the reaction of compound (*S*)-**110** with Grignard reagent of 2-chloro-1,3-butadiene, followed by silylation of the free alcohol gave methyl (*S*)-2-((*tert*-butyldimethylsilyl)oxy)-4-methylenehex-5-enoate (*S*)-**111**, that after the reduction of the carboxylic ester to the aldehyde, Wittig reaction and desilylation of intermediate (*S*)-**112**, furnished (*S*)-(+)-**II** in 16 % overall yield from (*R*)-serine. The enantiomeric purity of (*S*)-(+)-**II** was determined as ~96 % ee by the HPLC analysis of the corresponding MTPA ester, and the specific rotation $\{[\alpha]_D^{25} + 15.7^\circ$ (*c* 0.99 MeOH)} was the highest ever observed for this compound.^[12]

In 1977 Ohloff and Giersch reported the synthesis of (*S*)-(+)-ipsdienol (**II**) from (–)-verbenone.^[93] As shown in

Scheme 41. First synthesis of (*S*)-(+)-ipsdienol (**II**) by Mori et al.^[78]

Scheme 42. Second synthesis of (*S*)-(+)-ipsdienol (**II**) by Mori and Takikawa.^[12]

Scheme 43, the reaction of (–)-verbenone with NaH/THF gave (1*R*,5*R*)-6,6-dimethyl-4-methylenebicyclo[3.1.1]heptan-2-one (–)-**113** in 84% yield, that after reduction with LAH afforded selectively *cis*-alcohol (–)-**114** in 94% yield. Final, flash pyrolysis of (1*R*,2*R*,5*R*)-6,6-dimethyl-4-methylenebicyclo[3.1.1]heptan-2-ol (–)-**114** gave (*S*)-(+)-**II** $\{[\alpha]_{24}^D + 11.1^\circ$ (*c* 9.8, MeOH)}.

In 1983, Norin and co-workers^[66] described the synthesis of (*S*)-(+)-ipsdienol (**II**) by reduction of myrcenone (**18**) with reagent (–)-**XV**, prepared from (*S*)-(-)-2,2-dihydroxy-1,1'-binaphthyl, at –80 °C, in 70% chemical yield and 63% ee (Scheme 44), as determined by NMR-measurements of the distereomeric MTPA mixture.

Brown and Randad have prepared (*S*)-(+)-ipsdienol following the same protocol, as shown in Scheme 29 (eq. 2), after reaction of *B*-2'-*i*soprenyldiisopinocampheylborane (+)-(**83**) [⁴IpcBIpn (+)-(**83**)] with 3-methylbut-2-enal, followed by a non-oxidative work-up by addition acetaldehyde and DEA, afforded natural (*S*)-(+)-ipsdienol (**II**) $\{[\alpha]_{23}^D + 13.18^\circ$ (*c* 1%, EtOH)} in 96% ee, and 60% yield.^[9,45]

Scheme 43. Synthesis of (*S*)-(+)-ipsdienol (**II**) and (*R*)-(-)-ipsdienol (**II**) by Ohloff and Giersch.^[93]

Scheme 44. Synthesis of (*S*)-(+)-ipsdienol (**II**) and (*R*)-(-)-ipsdienol (**II**) by Norin et al.^[66]

Yamamoto et al. communicated^[84] the preparation of (*S*)-(+)-ipsdienol (**II**) by reacting chiral boron-synthon (*R,R*)-**96** with 3-methylbut-2-enal to afford (*S*)-2-bromo-1,5-heptadien-4-ol [(*S*)-**115**] in 93% yield and 87% ee, whose Pd-catalyzed cross-coupling reaction with CH₂=CHMgBr gave the final target in 85% yield and 86% ee (Scheme 34, eq. 2).

Krische et al. have described that the reaction of 3-methylbut-2-en-1-ol and 3-methylbut-2-enal with *tert*-butyl (2-methylenebut-3-en-1-yl) carbonate (**108**), in the presence of (**S**)-**Ir** catalyst (5% mol), K₃PO₄ (100% mol), in DME, 70 °C, for 24 h, gave (*S*)-(+)-ipsdienol (**II**) in 64% yield, and 96% ee, and in 71% yield, and 96% ee, respectively (Scheme 40).^[92]

(*S*)-(+)-Ipsdienol (**II**) was synthesized in high enantiomeric purity (> 98%) from the corresponding hydrogen phthalate of 8-chloro-2-methyl-6-methyleneoct-2-en-4-ol (**38**) (Scheme 15),^[51] whose diastereoisomeric salt with (*R*)-1-phenylethanamine was separated and isolated by crystallization, submitted to hydrolysis, and dehydrohalogenation with *tert*-BuOK.^[95] The ee value of (*S*)-(+)-**II** was determined as usual in the ¹H NMR spectrum of its MTPA ester. In a subsequent publication the same authors communicated an improved method for the dehydrohalogenation step with *tert*-BuOK that gave higher chemical yields of (*S*)-(+)-ipsdienol (**II**) without loss of ee.^[96]

4.4. (*R*)-(-)-Ipsdienol

In 1976 Mori et al. reported his first synthesis of (*R*)-(-)-ipsdienol (**II**)^[97] followed by a full paper in 1979.^[78] As shown in Scheme 45, the starting material was now (*R*)-(+)-glyceraldehyde acetonide, which was easily transformed into epoxide (*S*)-2-methyl-1-(oxiran-2-yl)propan-2-ol [(*S*)-**109**] after Wittig reaction, oxymercuration-demercuration, acetonide hydrolysis, monotosylate formation and treatment with KOH/H₂O. The next steps followed also the synthetic sequence used before to transform epoxide (*S*)-2-isobutyloxirane (*S*)-**26** (Scheme 27) into (*S*)-**I**.^[76,77] Thus, epoxide (*S*)-**109** was converted into lactone **116**, followed by a series of reactions, including an additional step for the dehydration of the tertiary alcohol with POCl₃/py, to give (*R*)-(-)-ipsdienol (**II**) $\{[\alpha]_{24}^D - 5.0^\circ$ (MeOH)} (Scheme 45). As the optical rotation of the natural ipsdienol was reported to be $\{[\alpha]_{24}^D + 10^\circ \pm 0.9^\circ$ (MeOH)},^[8] the present synthesis unambiguously established the *S*-configuration of the natural and dextro-

Scheme 45. Synthesis of (*R*)-(-)-ipsdienol (**II**) by Mori et al.^[78,97]

rotatory ipsdienol, and that the synthetic (*R*)-(-)-ipsdienol (**II**) was obtained in low optical purity, most possibly due to partial racemization in the course of the multi-step synthesis. In fact, the authors observed that based on the report by Ohloff and Giersch describing the EP synthesis of both enantiomers of ipsdienol,^[93] the optical purity of (*R*)-(-)-ipsdienol obtained by Mori was 38 %.^[78]

In 1991 Mori and Tatikawa reported a second synthesis of (*R*)-(-)-**II** from (*S*)-serine,^[12] following a similar synthetic sequence as shown in Scheme 42 for the synthesis of (*S*)-(+)-**II** from (*R*)-serine.^[12] Thus, the key intermediate methyl (*R*)-oxirane-2-carboxylate (*R*)-**110** was reacted with the Grignard reagent of 2-chloro-1,3-butadiene, followed by silylation of the free alcohol gave methyl (*S*)-2-((*tert*-butyldimethylsilyl)oxy)-4-methylenehex-5-enoate (*R*)-**111**, that after the reduction of the carboxylic ester to the aldehyde, Wittig reaction and desilylation of intermediate (*R*)-**112**, furnished (*R*)-(-)-**II**. The enantiomeric purity of (*R*)-(-)-**II** was determined as ~96 % ee by the HPLC analysis of the corresponding MTPA ester; its specific rotation $\{[\alpha]_{24}^D -15.3^\circ$ (*c* 0.99 MeOH)} was the highest ever observed.^[12]

In 1977, and as shown in Scheme 43, Ohloff and Giersch reported the transformation of (-)-verbenone into (*R*)-(-)-ipsdienol (**II**) $\{[\alpha]_{24}^D -12^\circ$ (*c* 10, MeOH)}.^[93]

In 1983, Norin and co-workers described the synthesis of (*R*)-(-)-ipsdienol (**II**) by reduction of myrcenone (**18**) with reagent (+)-**XV**, obtained from (*R*)-(+)-2,2-dihydroxy-1,1'-binaphthyl, at -80 °C (Scheme 44) in 70 % chemical yield and 63 % ee, as analyzed by NMR-measurements of the distereomeric MTPA mixture.^[66]

In 1989 Franck-Neumann and co-workers described the asymmetric synthesis of EP (*R*)-(-)-ipsdienol (**II**) by reacting EP formyl(iron)tricarbonyl complex **XVI** (Figure 2) with 2-(bromomethyl)buta-1,3-diene (**2**) (Figure 3) in the presence of Zn to give a mixture of compounds in a 9:1 ratio, that were separated.^[98] Major compound was then submitted to UV irradiation to afford (*R*)-(-)-ipsdienol (**II**), whose optical rotation $\{[\alpha]_{24}^D -13^\circ$ (MeOH)}, compared with the value reported by Ohloff and Giersch,^[93] indicated that the optical purity of the (*R*)-(-)-ipsdienol (**II**) was higher than 90 %.^[98]

(*R*)-(-)-Ipsdienol (Figure 5) has been synthesized following the same protocol, as shown in Scheme 29 (eq. 1), by reacting B-2'-*i*-isoprenyldiisopinocampheylborane (-)-(**83**) [*i*Ipc₂Blpn

Figure 5. Structure of (*R*)-(-)-ipsdienol [(*R*)-(-)-**II**].

(-)-(**83**) with 3-methylbut-2-enal, followed by a non-oxidative work-up by addition acetaldehyde and DEA, afforded (*R*)-(-)-ipsdienol (**II**) $\{[\alpha]_{23}^D -13.11^\circ$ (*c* 1 %, EtOH)} in 96 % ee and 60 % yield.^[9,45]

In 1993 Terada and co-workers proposed a new method for the synthesis of (*R*)-(-)-ipsdienol (**II**)^[99] starting from methyl (*R*)-2-hydroxy-4-(phenylselenanyl)pent-4-enoate (**117**) (Scheme 46), readily obtained in 95 % and 99 % ee, by reaction of commercial phenyl(prop-1-en-2-yl)selenane and methyl 2-oxoacetate, in the presence of catalyst (*R*)-**XVII**. Thus, treatment of compound **117** with TBDMSOTf, followed by reduction with DIBALH and Wittig reaction provided (*R*)-*tert*-butyldimethyl((6-methyl-2-(phenylselenanyl)hepta-1,5-dien-4-yl)oxy)silane (**118**) in 56 % yield, which after Ni-catalyzed reaction with vinyl magnesium bromide furnished EP (*R*)-**112** in 78 % yield, whose standard deprotection afforded (*R*)-(-)-**II** $\{[\alpha]_{23}^D -15.6^\circ$ (*c* 0.99, MeOH)} in high yield. The authors also described the same synthetic sequence, with similar high chemical yields % and % ee, by using phenyl (prop-1-en-2-yl)sulfane.^[99]

In 1995 Terada and Mikami reported the very successful chiral ene-reaction of isoprene and 2,2,2-trifluoroethyl 2-oxoacetate, catalyzed by (*R*)-**XVIII** complex, that afforded EP 2,2,2-trifluoroethyl (*R*)-2-hydroxy-4-methylenehex-5-enoate (**119**) that was smoothly converted into (*R*)-(-)-**II** $\{[\alpha]_{23}^D -15.6^\circ$ (*c* 0.99, MeOH)} after a series of simple and high yielding reactions, as shown in Scheme 47.^[100]

Yamamoto et al. have communicated the preparation of (*R*)-(-)-ipsdienol (**II**) by reacting chiral boron-synthon (*S,S*-

Scheme 46. Synthesis of (*R*)-(-)-ipsdienol (**II**) by Terada et al.^[99]

Scheme 47. Synthesis of (*R*)-(-)-ipsdienol (**II**) by Terada and Mikami.^[100]

96 with 3-methylbut-2-enal to afford (*R*)-2-bromo-1,5-heptadien-4-ol [(*R*)-**115**] in 98 % yield and 88 % ee, whose Pd-catalyzed cross-coupling reaction with $\text{CH}_2=\text{CHMgBr}$ gave the final target in 84 % yield and 87 % ee (Scheme 34, eq. 1).^[84]

In 1999 Draillard and co-workers have described the synthesis of (*R*)-(-)-ipsdienol by asymmetric allylboration,^[86] the key intermediate was (*R*)-5-isobutyl-3-methylenedihydrofuran-2(3*H*)-one (**121**), obtained by reaction of methyl 2-(((3*A,S*,4*S*,7*S*)-4,8,8-trimethyl-3*a*-phenylhexahydro-4,7-methanobenzo[*d*][1,3,2]dioxaborol-2-yl)methyl)acrylate (**97**) with 3-methylbut-2-enal, to give methyl (*R*)-4-hydroxy-6-methyl-2-methyleneheptanoate (**120**) (82 %) followed by treatment with NaH/THF (93 %) (Scheme 35). The final steps consisted of DIBALH reduction of the lactone **121** followed by Wittig reaction to provide (*R*)-(-)-ipsdienol (**II**) in 50–60 % yields, and 88 % ee.

In 2001 Yu et al. reported a new synthesis of (*R*)-(-)-ipsdienol [(68 % yield; 93 % ee) by reacting 3-methylbut-2-enal with 2-trimethylstannylmethyl-1,3-butadiene (**48**) (Figure 3) in the presence of (*R*)-BINOL- Ti^{IV} /*i*-PrSBET₂ complex.^[88]

(*R*)-(-)-Ipsdienol (**II**) was prepared in high enantiomeric purity (>98 %) from the corresponding hydrogen phthalate of 8-chloro-2-methyl-6-methyleneoct-2-en-4-ol (**38**) (Scheme 15),^[51] whose diastereoisomeric salt with (*R*)-1-phenylethanamine was separated by crystallization, and submitted to hydrolysis, and dehydrohalogenation with *tert*-BuOK.^[95] The ee value of (*R*)-(-)-**II** were determined as usual in the ¹H NMR spectrum of its MTPA derivative.

Zhang has described the reaction of 4,4,5,5-tetramethyl-2-(2-methylenebut-3-en-1-yl)-1,3,2-dioxaborolane (**106**) (Figure 3) with 3-methylbut-2-enal, in the presence of the BINOL-derived chiral phosphoric acid (*R*)-TRIP, to synthesize (*R*)-(-)-ipsdienol (**II**) (Scheme 38) in 75 % yield and 85.6 % ee.^[90]

5. Conclusions and Outlook

In this account I have reviewed the synthesis of ipsenol and ipsdienol, two aggregation pheromones of bark beetles, isolated from species of genus *Ips*, and serious pests of conifer forests. I have covered the literature from 1968 to 2020. I have shown and commented the reported synthesis of racemic ipsenol and ipsdienol, including a summary of my own contribution to topic, continuing with the presentation of reports describing the synthesis of enantiomerically pure ipsenol and ipsdienol. Particular attention has been devoted to identify and highlight the “isoprene synthons”, and isoprenylation methods.

Regarding the reported synthesis of racemic ipsenol (**I**) and ipsdienol (**II**), I have found 19, 15, and 7 articles describing

the synthesis of both compounds, ipsenol (**I**), and ipsdienol (**II**), respectively. This means 41 publications at least dedicated to the racemic synthesis of these two natural products. Among these methods, and in particular for ipsdienol (**II**), myrcene has been the obvious and consequently, preferred starting material of choice, as it has been used in most of the reported synthesis of racemic ipsdienol (**II**).^[65,66,69,70] Note also that among these methods, the most attractive, shortest and convergent seem those based on the “5 + 5” strategy, by coupling “isoprene synthons” with 3-methylbutanal and 3-methylbut-2-enal, allowing the synthesis of both ipsenol (**I**), and ipsdienol (**II**), maximizing efforts and economies. Not surprisingly, a number of “isoprene synthons” have been proposed (Figure 3). Obviously, isoprene itself is the first to be cited, but unfortunately Snider’s approaches using Al-based Lewis catalyzed ene-type reaction with the aldehyde counterparts were not satisfactory.^[58,59,71] It has been only recently when Fukushima et al. found a very smart solution by using Pd/Et₃B catalyzed ene-type reaction of 3-methylbutanal with isoprene (Scheme 22).^[64] Older and first “isoprene synthons” were based on the organozinc species **III** (Scheme 1, Figure 3), prepared from 1,4-dibromo-2-(bromomethyl)but-2-ene (**1**)^[1] or from 2-(bromomethyl)buta-1,3-diene (**2**),^[1,14,27] that gave the desired compounds in modest yields, but from cheap and easily available starting materials. (2-Methylenebut-3-en-1-yl) potassium species **IV** (Scheme 12, eq. 2) was described by Brandsma et al.^[46–48] to efficiently react with 3-methylbutanal and 3-methylbut-2-enal yielding ipsenol (**I**) and ipsdienol (**II**) synthesis. Semmelhack and Fewkes described that (η^4 -isoprene)Fe(CO)₃ complex can be deprotonated with LDA, and that the resulting coordinated isoprene anion **V** (Scheme 13, Figure 3) is a new “isoprene synthon” that efficiently reacts with electrophiles at low temperature.^[49] Related 2-(bromomethyl)buta-1,3-diene (**6**) (Figure 3) has been reported to react with 3-methylbutanal, using the $\text{PdCl}_2(\text{PhCN})_2\text{-SnCl}_2$ complex to produce ipsenol (**I**) in 56 % yield^[63] (Scheme 22). Very attractive “isoprene synthons” for ipsenol (**I**) and ipsdienol (**II**) synthesis have been also: (a) 2-trimethylsilylmethyl-1,3-butadiene (**27**) (Figure 3), proposed by Wilson^[43] and Sakurai^[38–40] in the TiCl_4 -mediated coupling with the acid chlorides of the aldehyde counterparts, and (b) 2-trimethylstannylmethyl-1,3-butadiene (**48**), proposed by Wilson,^[43] and Sakurai,^[53] by coupling it with 3-methylbutanal, in the presence of TiCl_4 or $\text{BF}_3\cdot\text{OEt}_2$. Special mention deserves 2-dipropylborylmethyl-1,3-butadiene (**28a**) (Figure 3), described by Bubnov and Etinger,^[44] and B-isoprenyl-9-BBN (**28b**), described by Brown and Randad,^[45] as a new “boro-isoprene synthons” that cleanly and in high yield afforded ipsenol (**I**) and ipsdienol (**II**) when treated with 3-methylbutanal and 3-methylbut-2-enal, respectively.

Finally, I have described and commented the diverse reported synthesis of the four EP forms of ipsenol and

ipsdienol from a total of 25 articles, 9 covering both compounds in the same manuscript, 9 only for ipsenol and 7 for ipsdienol. The different synthesis comprise the “chiron approach” from readily available EP natural products, or typical asymmetric synthesis using chiral promoters or catalysts.

Among the former, I have to highlight the pioneer work on this topic carried out by Mori and co-workers, who published two preliminary communications^[76,97] and three full papers^[12,77,78] covering the synthesis of the enantiomers of (*S*)-ipsenol (**I**) [from (*S*)-leucine], (*R*)-ipsenol (**I**) [from (*R*)-leucine], (*S*)-ipsdienol (**II**) [from (*R*)-L-malic acid, and (*R*)-serine] and (*R*)-ipsdienol (**II**) [from D-glyceraldehyde, and (*S*)-serine]. Similarly, Trost and Rodríguez efficient synthesis of (*S*)-(-)-ipsenol (**I**) from (*S*)-lactic acid.^[82] (*R*)-Epichlorohydrin (**87**) has been twice the chiral precursor of choice for the synthesis of (*S*)-(-)-ipsenol (**I**): in Nakajima's starting with the coupling of trimethylsilylacetylene (**101**),^[89] and in Imai and Nishida TiCl₄-promoted ring-opening reaction with 2,3-butadienyltrimethylsilane (**88**).^[81] (*S*)-(+)-ipsdienol (**II**) and (*R*)-(-)-ipsdienol (**II**) were prepared by Ohloff and Giersch from natural (-)/(+)-verbenones.^[93]

Among the asymmetric synthesis of ipsenol (**I**) and ipsdienol (**II**) using chiral promoters, the use of chiral “boroisoprene synthons” shown in Figure 3 are particularly relevant. This is the case of Yamamoto asymmetric synthesis of (*S*)-(-)-ipsenol (**I**) by using chiral allenyl boronic ester **79** prepared from allenylboronic acid (**78**) and D-(-)-*bis*(2,4-dimethyl-3-pentyl) tartrate.^[79] Or the contributions by Brown and Randad who described the application of EP B-2'-isoprenyldiisopinocampheylboranes (+)-(**83**) and (-)-(**83**) (Figure 3), prepared from (a)-(+)-pinene and (a)-(-)-pinene, respectively, for the synthesis of the enantiomers of ipsenol and ipsdienol.^[9,45] Tartaric acid chiral boron reagents (*R,R*)-**96** (Figure 3), synthesized by reacting (2-bromoallyl)diisopropoxyborane (**95**) with *L*-DMPT, have been used in the preparation of (*R*)-(+)-ipsenol (**I**) and (*S*)-(+)-ipsdienol,^[85] whereas (*S,S*)-**96** (Figure 3) have been applied in the synthesis of (*R*)-(-)-ipsdienol (**II**).^[84]

Finally, a number of synthesis of EP ipsenol and ipsdienol have been carried out by using chiral catalysts mediated aldol or ene-reactions, such as the asymmetric aldol reaction of *tert*-butyl acetate and 3-methylbutanal, in the presence of chiral BINOL complexes, such as Ti-complex **XIV** (Scheme 30), affording an EP intermediate employed in the preparation of (*S*)-(-)-ipsenol (**I**) by Oertle and co-workers.^[80] Or the really efficient and very successful chiral ene-reaction of isoprene and 2,2,2-trifluoroethyl 2-oxoacetate, catalyzed by (*R*)-**XVIII** complex (Scheme 47), reported by Terada and Mikami for the synthesis of (*R*)-(-)-ipsdienol (**II**).^[100]

To conclude it is important to highlight how such small compounds bearing only one stereocenter have attracted the

attention of a great number of laboratories implementing diverse synthetic approaches, serving in addition to propose and advance different “isoprene synthons”, and isoprenylation methods of general interest for the synthesis of related terpene derivatives.

List of Abbreviations

B-isoprenyl-9-BBN	(1 <i>S</i> ,5 <i>S</i>)-9-(2-Methylenebut-3-en-1-yl)-9-borabicyclo[3.3.1]nonane B-OMe-9-BBN: 9-Methoxy-9-borabicyclo [3.3.1] nonane
CTPEA	1-Chloro- <i>N,N</i> ,2-trimethylprop-1-enyl-amine
DCM	CH ₂ Cl ₂
D-DMPT	D-(-)- <i>Bis</i> (2,4-dimethyl-3-pentyl) tartrate
DEA	Diethanolamine
DIBALH	Diisobutylaluminium hydride
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone
EP	Enantiomerically pure
Ipc ₂ BOMe	B-2'-Isoprenyldiisopinocampheylborane
KDA	Potassium diisopropylamide
LDA	Lithium diisopropylamide
LDCHA	Lithium dicyclohexylamide
MTPA	α -Methoxy- α -trifluoromethylphenylacetic acid
NBS	<i>N</i> -Bromosuccinimide
Ni(dppp)Cl ₂	Ni(Ph ₂ P(CH ₂) ₃ PPh ₂)Cl ₂
Pr ₂ BOHex	Hexyloxy(dipropyl)borane
TBAF	Tetrabutylammonium fluoride
TEA	Triethanolamine
TMEDA	<i>N,N,N',N'</i> -Tetramethyl ethylenediamine
TMG	1,1,3,3-Tetramethylguanidine

References

- [1] A. García Martínez, J. L. Marco Contelles, *Synthesis* **1982**, 742–744.
- [2] S. Karlsen, P. Froeyen, L. Skattebøl, *Acta Chem. Scand. Ser. B* **1976**, B30, 664–668.
- [3] S. J. Seybold, *Annu. Rev. Entomol.* **2003**, 48, 425–453.
- [4] X.-l. Sun, Q.-y. Yang, J. D. Sweeney, C.-q. Gao, *J. For. Res.* **2005**, 17, 65–70.
- [5] S. J. Seybold, D. P. W. Huber, J. C. Lee, A. D. Graves, J. Bohlmann, *Phytochem. Rev.* **2006**, 5, 143–178.
- [6] G. J. Blomquist, R. Figueroa-Terán, M. Aw, M.-M. Song, A. Gorzalski, N. L. Abbott, E. Chang, C. Tittiger, *Insect Biochem. Mol. Biol.* **2010**, 40, 699–712.

- [7] R. M. Silverstein, J. O. Rodin, D. L. Woon, L. E. Browne, *Tetrahedron* **1966**, *22*, 1929–1936.
- [8] R. M. Silverstein, J. O. Rodin, D. L. Woon, *Science* **1966**, *154*, 509–510.
- [9] H. C. Brown, R. S. Randad, *Tetrahedron Lett.* **1990**, *31*, 455–458.
- [10] C. A. Reece, J. O. Rodin, R. G. Brown, W. G. Duncan, R. M. Silverstein, *Tetrahedron* **1968**, *24*, 4249–4256.
- [11] J. P. Vité, R. Hedden, K. Mori, *Naturwissenschaften* **1976**, *63*, 43–44.
- [12] K. Mori, H. Takikawa, *Tetrahedron* **1991**, *47*, 2163–2168.
- [13] C. Nájera, J. M. Sansano, *Tetrahedron* **1994**, *50*, 5829–5844.
- [14] R. G. Riley, R. M. Silverstein, J. A. Katzenellenbogen, R. S. Lenox, *J. Org. Chem.* **1974**, *39*, 1957–1958.
- [15] S. Kobayashi, H. Uyama, US 5164477, **1992**.
- [16] R. Witkowski, F. Bandermann, *Makromol. Chem.* **1989**, *190*, 2173–2182.
- [17] J. S. Yadav, R. Ravishankar, *Tetrahedron Lett.* **1991**, *32*, 2629–2632.
- [18] M. Tokuda, N. Mimura, T. Karasawa, H. Fujita, H. Sugimoto, *Tetrahedron Lett.* **1993**, *34*, 7607–7610.
- [19] M. Tokuda, N. Mimura, K. Yoshioka, T. Karasawa, H. Fujita, H. Sugimoto, *Synthesis* **1993**, 1086–1088.
- [20] Y. J. Chen, C. M. Chen, W. Y. Lin, *Tetrahedron Lett.* **1993**, *34*, 2961–2962.
- [21] M. Tokuda, A. Yoshikawa, H. Sugimoto, H. Senboku, *Synthesis* **1997**, 1143–1145.
- [22] F. Lehrich, H. Hopf, J. Grunenberg, *Eur. J. Org. Chem.* **2011**, *14*, 2705–2718.
- [23] R. C. Krug, T. F. Yen, *J. Org. Chem.* **1956**, *21*, 1082–1086.
- [24] R. L. Frank, R. P. Seven, *Org. Synth. 1955 Collect. Vol. 3*, 499–550 (Wiley, New York).
- [25] E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, R. E. K. Winter, *J. Am. Chem. Soc.* **1968**, *90*, 3245–3247.
- [26] L. S. Hegedus, S. Varaprath, *Organometallics* **1982**, *1*, 259–263.
- [27] J. A. Katzenellenbogen, R. S. Lenox, *J. Org. Chem.* **1973**, *38*, 326–335.
- [28] E. J. Reist, I. G. Junga, B. R. Baker, *J. Org. Chem.* **1960**, *25*, 1673–1674.
- [29] Y. Jing, V. V. Sheares, *Macromolecules* **2000**, *33*, 6255–6261.
- [30] V. V. Sheares, L. Wu, Y. Li, K. Emmick, *J. Polym. Sci. Part A* **2000**, *38*, 4070–4080.
- [31] K. Takenaka, Y. Akagawa, H. Takeshita, M. Miya, T. Shiomi, *Polym. J.* **2009**, *41*, 106–107.
- [32] M. A. Ceschi, C. Petzhold, R. A. Schenato, *J. Braz. Chem. Soc.* **2003**, *14*, 759–763.
- [33] G. Rousseau, J. Drouin, *Tetrahedron* **1983**, *39*, 2307–2310.
- [34] O. P. Vig, R. C. Anand, G. L. Kad, J. M. Sehgal, *J. Indian Chem. Soc.* **1970**, *47*, 999–1005.
- [35] J. C. Clinet, G. Linstumelle, *New J. Chem.* **1977**, *1*, 373–374.
- [36] M. Bertrand, J. Viala, *Tetrahedron Lett.* **1978**, *29*, 2575–2578.
- [37] K. Kondo, S. Dobashi, M. Matsumoto, *Chem. Lett.* **1976**, 1077–1088.
- [38] A. Hosomi, M. Saito, H. Sakurai, *Tetrahedron Lett.* **1979**, *5*, 429–432.
- [39] A. Hosomi, Y. Araki, H. Sakurai, *J. Org. Chem.* **1983**, *48*, 3122–3125.
- [40] H. Sakurai, A. Hosomi, M. Saito, K. Sasaki, H. Iguchi, J. Sasaki, Y. Araki, *Tetrahedron* **1983**, *39*, 883–894.
- [41] A. Barbero, C. García, F. J. Pulido, *Synlett* **2001**, 824–826.
- [42] F. J. Pulido, A. Barbero, C. García, *Tetrahedron* **2009**, *65*, 5535–5540.
- [43] S. R. Wilson, L. R. Phillips, K. J. Natalie Jr., *J. Am. Chem. Soc.* **1979**, *101*, 3340–3344.
- [44] Y. N. Bubnov, M. Y. Etinger, *Tetrahedron Lett.* **1985**, *26*, 2797–2800.
- [45] H. C. Brown, R. S. Randad, *Tetrahedron* **1990**, *46*, 4463–4472.
- [46] P. A. A. Klusener, H. H. Hommes, H. D. Verkruijsse, L. Brandsma, *Chem. Commun.* **1985**, 1677–1678.
- [47] P. A. A. Klusener, W. Kulik, L. Brandsma, *J. Org. Chem.* **1987**, *52*, 5261–5266.
- [48] P. A. A. Klusener, L. Tip, L. Brandsma, *Tetrahedron* **1991**, *47*, 2041–2064.
- [49] M. F. Semmelhack, E. J. Fewkes, *Tetrahedron Lett.* **1987**, *28*, 1497–1500.
- [50] T. A. Chevchouk, V. E. Isakov, O. G. Kulinkovich, *Tetrahedron* **1999**, *55*, 13205–13210.
- [51] E. A. Matyushenkov, O. G. Kulinkovich, *Russ. J. Org. Chem.* **2006**, *42*, 491–495.
- [52] S. B. Soloway, F. B. LaForge, *J. Am. Chem. Soc.* **1947**, *69*, 2677–2678.
- [53] A. Hosomi, H. Iguchi, M. Endo, H. Sakurai, *Chem. Lett.* **1979**, 977–980.
- [54] S. R. Wilson, L. R. Phillips, *Tetrahedron Lett.* **1975**, 3047–3050.
- [55] A. Hosomi, M. Saito, H. Sakurai, *Tetrahedron Lett.* **1980**, *21*, 355–358.
- [56] J. Haslouin, F. Rouessac, *Bull. Soc. Chim. Fr.* **1977**, 1242–1244.
- [57] B. Cazes, E. Guittet, S. Julia, O. Ruel, *J. Organomet. Chem.* **1979**, *177*, 67–74.
- [58] B. B. Snider, D. J. Rodini, *Tetrahedron Lett.* **1980**, *21*, 1815–1818.
- [59] B. B. Snider, D. J. Rodini, C. Kirk, R. Cordova, *J. Am. Chem. Soc.* **1982**, *104*, 555–563.
- [60] S. Halazy, A. Krief, *Tetrahedron Lett.* **1980**, *21*, 1997–2000.
- [61] C. Margot, M. Schlosser, *Tetrahedron Lett.* **1985**, *26*, 1035–1038.
- [62] T. Nomoto, H. Takayama, *J. Chem. Soc. Chem. Commun.* **1989**, 295–297.
- [63] Y. Masuyama, M. Fuse, Y. Kurusu, *Chem. Lett.* **1993**, 1199–1202.
- [64] M. Fukushima, D. Takushima, M. Kimura, *J. Am. Chem. Soc.* **2010**, *132*, 16346–16348.
- [65] K. Mori, *Agric. Biol. Chem.* **1974**, *38*, 2045–2047.
- [66] P. Baekstroem, F. Bjoerkling, H. E. Hoegberg, T. Norin, *Acta Chem. Scand. Ser. B* **1983**, *B37*, 1–5.
- [67] P. Baekstrom, S. Okecha, N. DeSilva, D. Wijekoon, T. Norin, *Acta Chem. Scand.* **1982**, *36B*, 31–36.

- [68] C. F. Garbers, F. Scott, *Tetrahedron Lett.* **1976**, 1625–1628.
- [69] Y. Masaki, K. Hashimoto, K. Sakuma, K. Kaji, *J. Chem. Soc. Chem. Commun.* **1979**, 855–856.
- [70] Y. Masaki, K. Hashimoto, K. Sakuma, K. Kaji, *J. Chem. Soc. Perkin Trans. 1* **1984**, 1289–1295.
- [71] B. B. Snider, A. C. Jackson, *J. Org. Chem.* **1982**, 47, 5393–5395.
- [72] K. Mori, *Advances in Asymmetric Synthesis*, ed. A. Hassner, JAI, London **1995**; vol. 1, p. 21.
- [73] S. J. Seybold, D. R. Quilici, J. A. Tillman, D. Vanderwel, D. L. Wood, G. J. Blomquist, *PNAS* **1995**, 92, 8393–8397.
- [74] P. Ivarsson, G. J. Blomquist, S. J. Seybold, *Naturwissenschaften* **1997**, 84, 454–457.
- [75] P. Ivarsson, C. Tittiger, C. Blomquist, C. E. Borgeson, S. J. Seybold, G. J. Blomquist, H.-E. Hoegberg, *Naturwissenschaften* **1998**, 85, 507–511.
- [76] K. Mori, *Tetrahedron Lett.* **1975**, 2187–2190.
- [77] K. Mori, *Tetrahedron* **1976**, 32, 1101–1106.
- [78] K. Mori, T. Takigawa, T. Matsuo, *Tetrahedron* **1979**, 35, 933–940.
- [79] N. Ikeda, I. Arai, H. Yamamoto, *J. Am. Chem. Soc.* **1986**, 108, 483–486.
- [80] K. Oertle, H. Beyeler, R. O. Duthaler, W. Lottenbach, M. Riediker, E. Steiner, *Helv. Chim. Acta* **1990**, 73, 353–358.
- [81] T. Imai, S. Nishida, *J. Org. Chem.* **1990**, 55, 4849–4852.
- [82] B. M. Trost, M. S. Rodríguez, *Tetrahedron Lett.* **1992**, 33, 4675–4678.
- [83] Y. Nishigaichi, H. Kuramoto, A. Takuwa, *Tetrahedron Lett.* **1995**, 36, 3353–3356.
- [84] Y. Yamamoto, S. Hara, A. Suzuki, *Synth. Commun.* **1997**, 27, 1029–1036.
- [85] S. Hara, Y. Yamamoto, A. Fujita, A. Suzuki, *Synlett* **1994**, 639–640.
- [86] K. Draillard, J. Lebreton, J. Villiéras, *Tetrahedron: Asymmetry* **1999**, 10, 4281–4284.
- [87] B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, 3, 573–575.
- [88] C.-M. Yu, M. Jeon, J.-Y. Lee, J. Jeon, *Eur. J. Org. Chem.* **2001**, 1143–1148.
- [89] R. Nakajima, H. Urabe, F. Sato, *Chem. Lett.* **2002**, 4–5.
- [90] Y.-L. Zhang, B.-J. He, Y.-W. Xie, Y.-H. Wang, Y.-L. Wang, Y.-C. Shen, Y.-Y. Huang, *Adv. Synth. Catal.* **2019**, 361, 3074–3079.
- [91] F. Erver, G. Hilt, *Org. Lett.* **2011**, 13, 5700–5703.
- [92] M. Xiang, G. Luo, Y. Wang, M. J. Krische, *Chem. Commun.* **2019**, 55, 981–984.
- [93] G. Ohloff, W. Giersch, *Helv. Chim. Acta* **1977**, 60, 1496–1500.
- [94] M. Larchevêque, Y. Petit, *Bull. Soc. Chim. Fr.* **1989**, 130–139.
- [95] V. N. Kovalenko, E. A. Matyushenkov, E. A. Russ, *J. Org. Chem.* **2012**, 48, 1168–1172.
- [96] V. N. Kovalenko, K. N. Prokhorevich, *Russ. J. Org. Chem.* **2016**, 52, 757–758.
- [97] K. Mori, *Tetrahedron Lett.* **1976**, 19, 1609–1612.
- [98] M. Franck-Neumann, D. Martina, M. P. Heitz, *Tetrahedron Lett.* **1989**, 30, 6679–6682.
- [99] M. Terada, S. Matsukawa, K. Mikami, *J. Chem. Soc. Chem. Commun.* **1993**, 327–328.
- [100] M. Terada, K. Mikami, *J. Chem. Soc. Chem. Commun.* **1995**, 2391–2392.

Manuscript received: November 20, 2020

Revised manuscript received: January 20, 2021

Version of record online: February 4, 2021