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Citronellal as key compound in organic synthesis

Eder J. Lenardão,* Giancarlo V. Botteselle, Francisco de Azambuja, Gelson Perin and Raquel G. Jacob*

Instituto de Química e Geociências, LASOL, Universidade Federal de Pelotas, UFPel, PO Box 354, 96010-900 Pelotas, RS, Brazil

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Contents

1. Introduction

Citronellal (3,7-dimethyl-6-octenal, **1**, Fig. 1) is a monoterpene, predominantly formed by the secondary metabolism of plants. It is typically isolated as a non-racemic mixture of its *R* and *S* enantiomers by steam distillation or solvent extraction from the oils of *Corymbia citriodora* Hill and Johnson (former *Eucalyptus citriodora* Hook) *Cymbopogon nardus*, and Java citronella. Alternatively it is also found in more than 50 other essential oils. Along with citral, geranial, linalool, and citronellol, citronellal is one of the most important terpenes.[1] The annual production of citronella oil (which contains 40–50% of citronellal) is around 2300 metric tons. A total of 2000 tons per year of (*R*)-citronellal are produced by Takasago International Co. (the Takasago process) starting from mircene.[1b]

Keywords: Citronellal; Pheromones; Isopulegol; Asymmetric synthesis.
* Corresponding authors. Tel./fax: +55 53 3275 7354; e-mail addresses: lenardao@ufpel.edu.br; raquel.jacob@ufpel.edu.br

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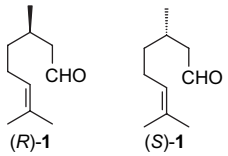


Figure 1. The enantiomers of citronellal.

Several papers describe the biotransformation of citronellal into industrially applicable compounds[2] as well as its metabolism in living organisms;[3] most importantly its reductive bioconversion into citronellol by isolated enzymes or whole cells.[2b–e] Besides their use as important commodities in the fragrance industry, citronellal and citronellol are employed as intermediates in the synthesis of several natural terpenoids such as 1-menthol, α-tocopherol, and irones.[4]

The use of renewable feedstocks, which may substitute those derived from petroleum, as well as the employment of low or non-toxic substances are currently great challenges in the chemical and pharmaceutical industries. This new trend is known as green chemistry,[5] and citronellal obtainable from renewable sources is biodegradable. As we will see in this review, it is a versatile reagent, which can be used in an efficient way to introduce a new stereogenic center in more complex structures, and a good green reagent.

This review will be limited to the description of chemical transformations of citronellal, except when biotransformation is involved as a step in a total synthesis. The use of citronellal in polymerization reactions, mechanistic and kinetics studies, and papers describing synthetic preparations where it is only an intermediate will not be considered. Papers describing preparations where citronellal is one of several substrates in a systematic study will be mentioned, but without detailed experimental conditions.

This review is divided into two parts: the first describes the use of citronellal as key intermediate or chiral source in total synthesis. The second is its use as a raw material for commodities such as isopulegol, menthol, and pharmaceuticals; including its use as an intermediate toward complex compounds with defined stereochemistry.

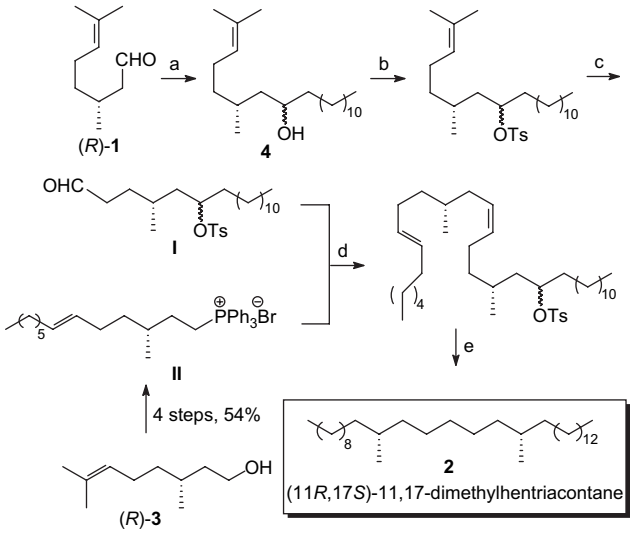
2. Citronellal in total synthesis

During the last 20 years, several total syntheses of insect pheromones and other classes of natural compounds containing a chiral methyl branched subunit have been performed starting from natural products. Citronellal is a cheap, readily available, and very versatile starting material for the asymmetric synthesis of chiral compounds.[6]

The total synthesis of natural and non-natural compounds using citronellal as a starting material can be divided into three classes: (1) synthesis of pheromones, (2) synthesis of cyclic and polycyclic compounds, and (3) synthesis of alycyclic compounds. In nearly all of these syntheses, citronellal is used to control the absolute stereochemistry at the methine position of the chiral product.

2.1. Synthesis of pheromones

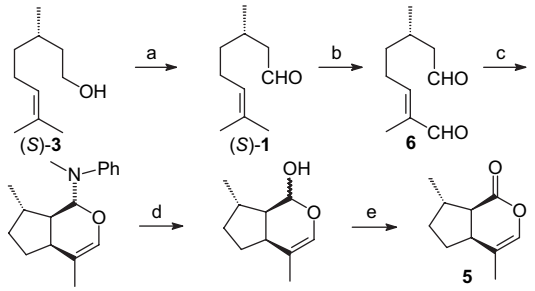
(11*R*,17*S*)-11,17-Dimethylhentriacontane (**2**), the communication pheromone of the ant *Camponotus vagus*, was obtained in high enantio- and diastereomeric purity from (*R*)-citronellal **1** via a convergent synthesis.[7] This is done in two fragments, one starting from (*R*)-citronellal (**1**, fragment **I**) and another starting from (*R*)-citronellol (**3**, fragment **II**, Scheme 1). The first step in the synthesis of fragment **I** was the addition of dodecylmagnesium bromide to **1**, affording a racemic mixture of alcohol **4** in nearly quantitative yield (97%). While maintaining the stereogenic center at carbon-3 of citronellal, tosylation and ozonolysis afford fragment **I** in 93% yield (three steps). A Wittig olefination of the aldehyde **I** with the phosphorane generated from **II** gives the desired pheromone (11*R*,17*S*)-11,17-dimethylhentriacontane (**2**) in an overall yield of 21% (six steps from (*R*)-citronellal).



Scheme 1. Reagents and conditions: (a) $CH_3(CH_2)_{11}Br$, $(CH_2Br)_2$ (10%), Mg, THF, 0.9 h, 70 °C, 97%; (b) *p*-TsCl, Py, 0–25 °C, 95%; (c) (1) O_3, CH_2Cl_2, −78 °C, Sudan Red 7B; (2) DMS, −78 to 25 °C, 98%; (d) **II**, ^{n}BuLi, THF, −78 to 25 °C, 30%; (e) (1) $LiAlH_4$, NaH; (2) H_2, Pd/C (5%), 78%.

The same strategy described in Scheme 1 was used to prepare the diastereomer of **2** (11*S*,17*R*)-11,17-dimethylhentriacontane, another communication pheromone of *C. vagus*.[8] In this case, (*S*)-citronellal and (*S*)-citronellol were used as the precursors toward fragment **I** and fragment **II**, respectively, and (11*S*,17*R*)-**2** is obtained in an overall yield of 22% (six steps from (*S*)-citronellal).

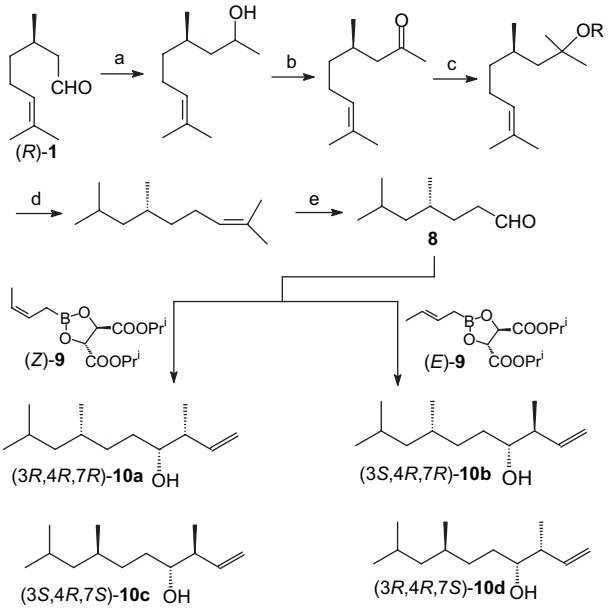
The potential use of aphid sex pheromones (cyclopentanoids) as alternative insect control methods, coupled with the need to elucidate their structure, creates the demand for a large scale, stereochemically controlled synthesis of cyclopentanoids. A synthetic approach toward these compounds through the intramolecular [4+2] cycloaddition of aldehydes into dihydropyrans was described by Schreiber (Scheme 2).[9] From this, the production of nepetalactone **5** using (*S*)-citronellal (**1**) was obtained from the oxidation of (*S*)-citronellol (**3**). When (*S*)-**1** was oxidized by selenium dioxide, 8-oxocitronellal (**6**) was obtained in 43% yield and converted, after three more steps, into **5**.



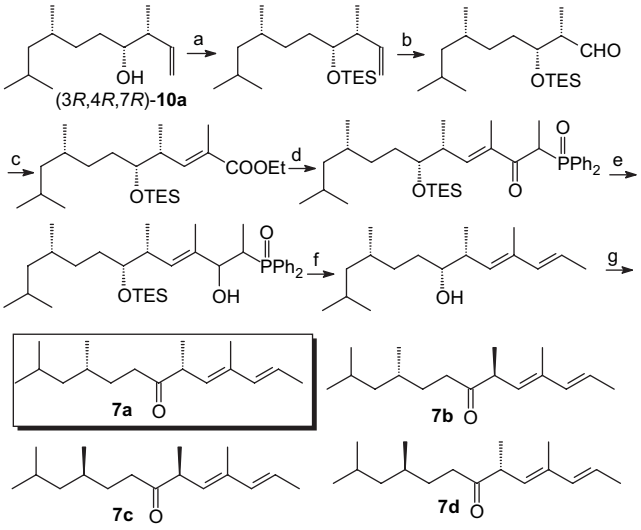
Scheme 2. Reagents and conditions: (a) Py, SO_3 complex, DMSO, Et_3N, 97%; (b) SeO_2, BuOOH, 43%; (c) MeNHPh, 4 Å sieves, 67%; (d) TsOH, THF/H_2O (1:1), 86%; (e) $AgNO_3$, Celite®, refluxing benzene, 60%.

A facile enantioselective synthesis for all four stereoisomers of (2*E*,4*E*)-4,6,10,12-tetramethyl-2,4-tridecadien-7-one (**7a–d**), the primary sex pheromone of *matsucoccus* (pine bast scale) was completed, starting from citronellal by an asymmetrical aldol reaction (Schemes 3 and 4).[10] Citronellal contributes to the final stereochemistry through its stereogenic center. This synthetic route starting from (*R*)-citronellal (**1**) afforded, after six steps, the aldehyde (*R*)-**8**. The enantiomer (*S*)-**8** was prepared in an analogous way, from (*S*)-**1**. Treatment of freshly prepared aldehyde (*R*)-**8** with the boronates (*R*,*R*)-**9**(*Z*) or (*R*,*R*)-**9**(*E*) (−78 °C, MS 4 Å, toluene, 2 h, 70% yield) yielded (3*R*,4*R*,7*R*)-**10a** and (3*S*,4*R*,7*R*)-**10b**, respectively (Scheme 3). In the same manner, the reaction of (*S*)-**8** with (*R*,*R*)-**9**(*Z*) or (*R*,*R*)-**9**(*E*), produces the other two isomers (3*S*,4*R*,7*S*)-**10c** and (3*R*,4*R*,7*S*)-**10d**, respectively. Starting from **10a–d**, all stereoisomers of **7** were obtained, as illustrated by the preparation of **7a** (Scheme 4).[10]

(5*S*,9*S*)-5,9-Dimethylheptadecane (**11a**), the main sex pheromone component of *Leucoptera malifoliella* Costa (formely *Leucoptera scitella* Zeller), 5,9-dimethylpentadecane (**11b**), a possible sex attractant of *Perileucoptera coffeella* and their respective isomers (**11c** and **11d**) were prepared

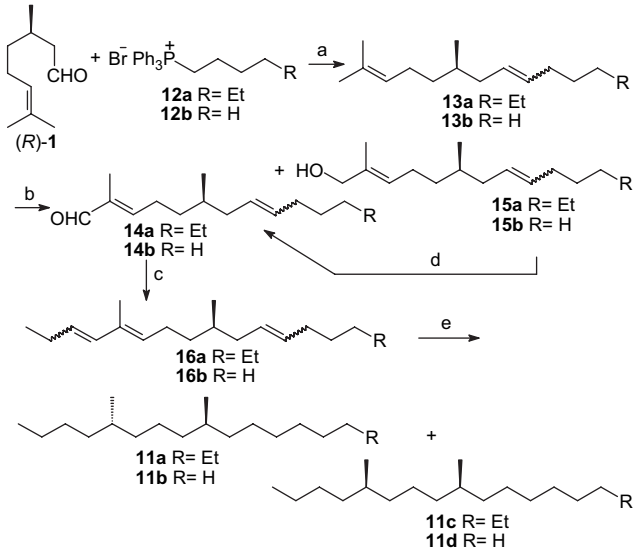


Scheme 3. Reagents and conditions: (a) (1) MeMgI, Et_2O; (2) H_3O^+, 98%; (b) PCC, CH_2Cl_2, rt, 96%; (c) (1) as in (a); (2) ^{n}BuLi, THF, −20 to 0 °C; (3) $ClPO(OEt)_2$, TMEDA, −20 °C to rt, 95%; (d) Li, $EtNH_2$, −30 °C, 100%; (e) O_3, CH_2Cl_2, −78 °C, Ph_3P. Overall yield of **10a–d** over 70% from **8**.



Scheme 4. Reagents and conditions: (a) DMF, imidazole, TES-Cl, 100%; (b) O_3, CH_2Cl_2, −78 °C, Ph_3P, rt; (c) toluene, $Ph_3P{=}C(CH_3)CO_2Et$, 80 °C, 36 h, 76% (two steps); (d) $Ph_2P(O)C_2H_5$, ^{n}BuLi, THF, −78 °C, 95%; (e) DIBAL-H, Et_2O, −78 °C, 74%; (f) NaH, DMF, 40 °C, 65%; (g) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, −78 °C, 90%.

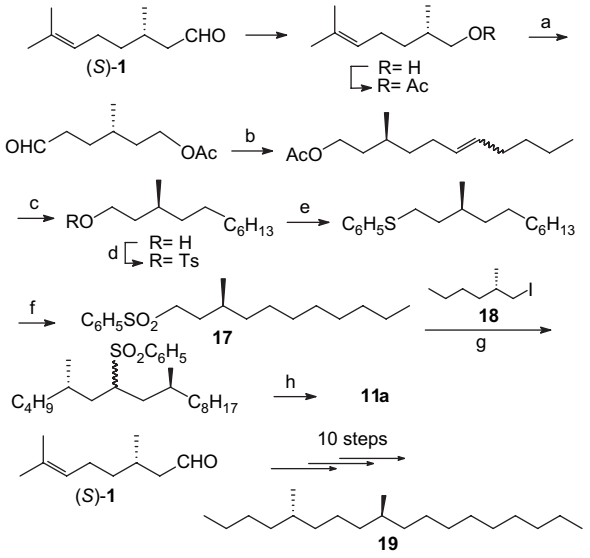
from (*R*)- and (*S*)-citronellal, respectively (**1**, Scheme 5).[11] All compounds were prepared by reacting **1** with the ylide of **12a** or **12b** to give the respective dienes **13a** and **13b**.



Scheme 5. Reagents and conditions: (a) EtONa, toluene, azeotropic removal of ethanol, then addition of **1** at −50 °C, 2 h, rt, 77%; (b) SeO_2, EtOH, reflux, 3 h, 32% for **14a** and 19% for **15a**; (c) $^n Pr(Ph)_3P^+Br^-$, EtONa, toluene, azeotropic removal of ethanol, then addition of **14a** or **14b** at 50 °C, 3 h, rt, 50% (unseparated mixture of geometrical isomers **16**); (d) PDC, CH_2Cl_2, 2 h, rt, 70%; (e) 10% Pd/C, MeOH/EtOAc, H_2, 83%.

A convergent synthesis of (5*S*,9*S*)-5,9-dimethylheptadecane **11a** was also described (Schemes 5 and 6).[12] This strategy involves two chiral building blocks, (*S*)-**1** was used in the preparation of (**17**), which was then coupled with (*S*)-2-methylhexyl iodide (**18**) (Scheme 6). The same procedure was employed to prepare (5*S*,9*S*)-**19**, a minor component in the volatile extract of female *L. malifoliella*.

With the aim to identify the female sex pheromone precursors of the pine sawfly *Microdiprian pallipes*, 16

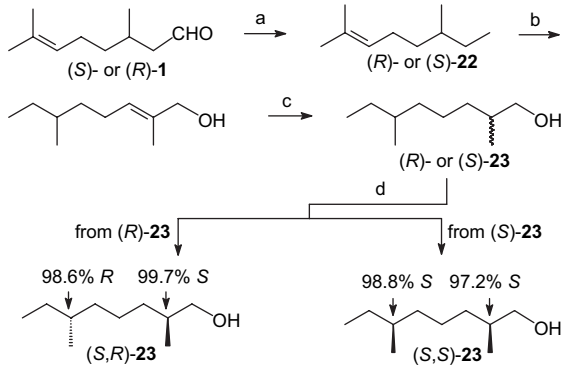


Scheme 6. Reagents and conditions: (a) (1) O_3, MeOH, −78 °C; (2) Me_2S, −10 °C, 1 h and rt, 1 h, 85%; (b) $Ph_3P{=}CHC_4H_9$, 1,2-dimethoxyethane, −60 °C, 2.5 h, 61%; (c) $LiAlH_4$, $CoCl_2$, THF, −78 °C to rt, 12 h, 85%; (d) TsCl, Py, 0–5 °C, 12 h; (e) C_6H_5SNa, MeOH, reflux, 12 h, 96%; (f) (1) MCPBA, CH_2Cl_2, 5–10 °C; (2) rt, 12 h, 96%; (g) (1) ^{n}BuLi, THF/HMPA, −65 to −30 °C, N_2; (2) −70 °C, **18** and rt, 12 h; (h) Na/Hg, rt, 40 h, 76%. (5*S*,9*S*)-Dimethylheptadecane **19** was obtained in a similar way in 24% overall yield (10 steps from (*S*)-**1**).

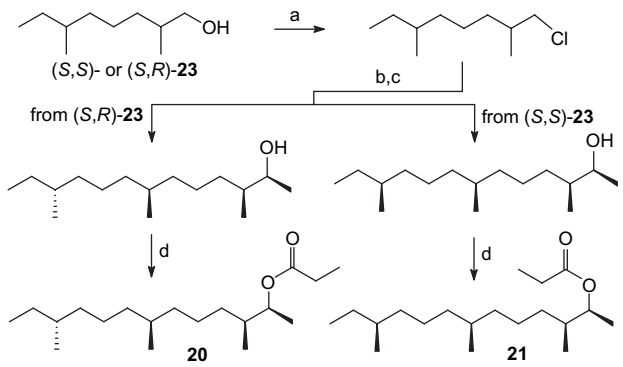
stereoisomers of 3,7,11-trimethyl-2-tridecanol were synthesized with high enantio- and diastereo-control from pure enantiomers (*R*)- and (*S*)-citronellal (**1**, Schemes 7 and 8).[13] Among the synthesized isomers, the propionate of (2*S*,3*S*,7*S*,11*R*)-3,7,11-trimethyl-2-tridecanol (**20**) and (2*S*,3*S*,7*S*,11*S*)-3,7,11-trimethyl-2-tridecanol (**21**) are present in the female of *M. pallipes*.

To prepare **20** and **21**, (*S*)- and (*R*)-citronellal (**1**) were reduced under Huang–Minhon conditions to the alkene **22**. Selenium oxidation followed by in situ reduction with $NaBH_4$ and hydrogenation with *Raney*-Ni gives a mixture of the two diastereomers of 2,6-dimethyl-1-octanol, (*R*)- and (*S*)-**23**, respectively. After enzyme-catalyzed reactions, the optically pure stereoisomers of alcohol **23** were obtained (Scheme 7).

The screwworm fly *Cochliomyia hominivorax*, a serious problem in Central and South America, utilizes several



Scheme 7. Reagents and conditions: (a) $N_2H_4{\cdot}H_2O$, KOH, diethylene glycol, 170 °C, 73% for (*R*)-**22** and 80% for (*S*)-**22**; (b) (1) ^{t}BuOOH, SeO_2, CH_2Cl_2; (2) $NaBH_4$, NaOH, MeOH, 0–30 °C, ~80%; (c) *Raney*-Ni, H_2, MeOH, 40 °C, 75%; (d) lipase-catalyzed kinetic acylation: Amano PS, $CHCl_3$, vinyl butyrate, $a_w \approx 0$, c=50–60% and then LC separation of the product and the substrate.



Scheme 8. Reagents and conditions: (a) PPh_3, CCl_4, reflux; (b) (1) Li(s), reflux, *n*-hexane; (2) addition to one of the enantiomers of *cis*-3,4-dimethyl-γ-butyrolactone at −78 °C; (3) $N_2H_4{\cdot}H_2O$, KOH, diethylene glycol, 170 °C, 1 h, then 210 °C, 3 h; (c) (1) PPh_3, $PhCO_2H$, $N_2(CO_2Et)_2$; (2) NaOH, H_2O/MeOH/dioxane; (d) 10 equiv CH_3CH_2COCl, CH_2Cl_2.

chiral acetates (**24** and **25**) and ketones (**26**, Fig. 2) as components of its female sex pheromone. The synthesis of the four stereoisomers of 6-acetoxy-19-methylnonacosane **24** was described recently by Mori and co-workers (Schemes 9 and 10).[14]

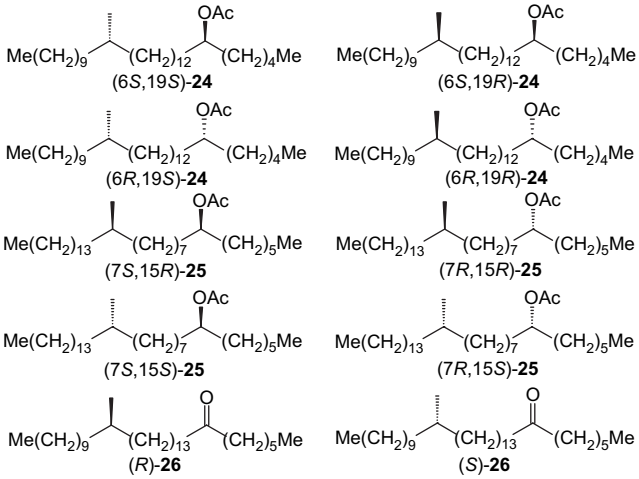
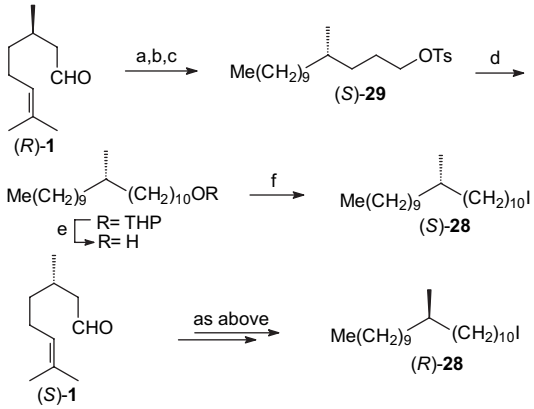
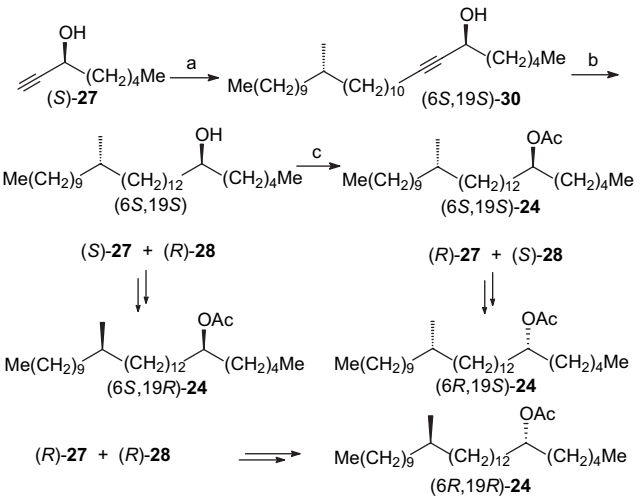


Figure 2. Components of the female sex pheromones of the screwworm fly, *Cochliomyia hominivorax*.



Scheme 9. Reagents and conditions: (a) *p*-TsCl, C_5H_5N; (b) $Me(CH_2)_7MgBr$, Li_2CuCl_4, THF; (c) (1) O_3, MeOH/CH_2Cl_2/hexane; (2) $NaBH_4$; (3) $Me(CH_2)_2MgBr$, Li_2CuCl_4, THF; (d) $THPO(CH_2)_7MgBr$, Li_2CuCl_4, THF; (e) TsOH, MeOH, 69% (steps d and e); (f) (1) TsCl, C_5H_5N; (2) NaI, DMF, 77% (two steps).



Scheme 10. Reagents and conditions: (a) 2.2 equiv ^{n}BuLi, THF/HMPA, then (*S*)-**28**, 68%; (b) H_2, PtO_2, EtOAc, 15 min, rt, 85%; (c) Ac_2O, DMAP, C_5H_5N, CH_2Cl_2, 98%.

Their synthetic strategy toward **24** involved the coupling of citronellal (**1**) and chiral propargylic alcohol **27** to yield all four isomers of 6-acetoxy-19-methylnonacosane (**24**) with notably high stereochemical control (Scheme 10).[14] The tosylate (*S*)-**29**, obtained in three steps from (*R*)-citronellal (**1**), is then converted to the methyl-branched alkyl iodide (*S*)-**28** (54% overall yield from (*S*)-**29**). Similarly, (*R*)-**28** was prepared from (*S*)-citronellal (**1**, 21% overall yield from (*R*)-**29**, Scheme 9). A substitution reaction of the chiral iodide **28** with the acetylenic anion derived from alcohol **27** afforded the key compound (6*S*,19*S*)-**30** (Scheme 10). Lastly, catalytic hydrogenation of the triple bond in **30** was achieved with PtO_2, and **24** was separated by HPLC.

Due to the very similar structures of the natural esters **24** and **25** (Fig. 2), the same approach described for **24** was employed to prepare the four isomers of 7-acetoxy-15-methylnonacosane (**25**). However, a lipase catalyzed, asymmetric acetylation was used in the acetylation step.[15] For the synthesis of the isomeric ketones **26** (Fig. 2), the intermediate (*S*)-**29** was prepared as described in Scheme 9, and after five steps, the ketone **26** was obtained with high isomeric purity.[16] For preparation of (*S*)-**26**, (*R*)-**1** was used as precursor, while (*S*)-**1** was the starting material for (*R*)-**26**.

In their studies on pheromone synthesis, Mori et al. employed both the enantiomers of citronellal in the preparation of the four stereoisomers of 3,12-dimethylheptacosane (**31**, Fig. 3), a component of the cuticular hydrocarbons with possible queen recognition properties in the ant *Diacamma* sp.[17]

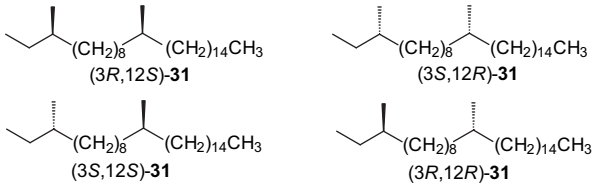
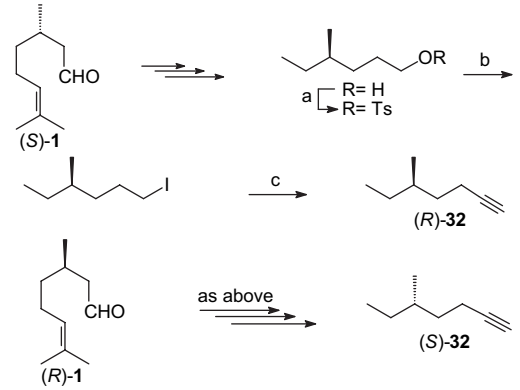
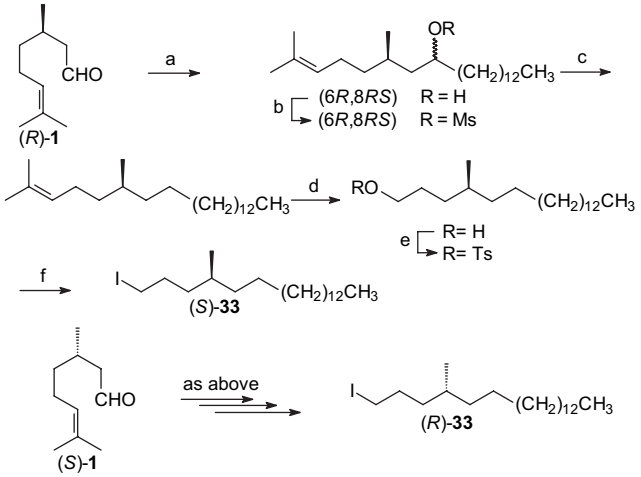


Figure 3. The four isomers of 3,12-dimethylheptacosane.

In this convergent synthesis, the authors used citronellal as a starting material for the preparation of both enantiomers of key building blocks **32** (Scheme 11) and **33** (Scheme 12). The coupling as summarized in Scheme 13 was started by choosing the appropriate enantiomer of **1**, and all four isomers of **31** were synthesized in very good yields and high stereoselectivities.

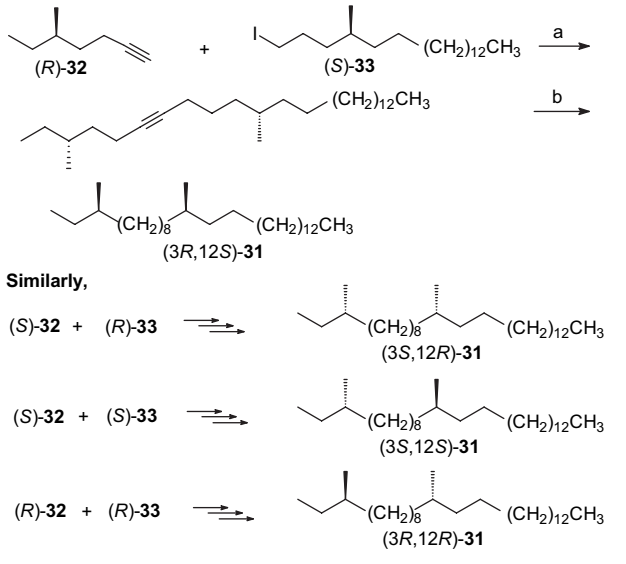


Scheme 11. Reagents and conditions: (a) TsCl, C_5H_5N, CH_2Cl_2, 4 °C, 12 h; (b) NaI, DMF, Me_2CO (81%, two steps); (c) $LiC{\equiv}CH{\cdot}H_2N(CH_2)_2NH_2$, DMSO, 60%.

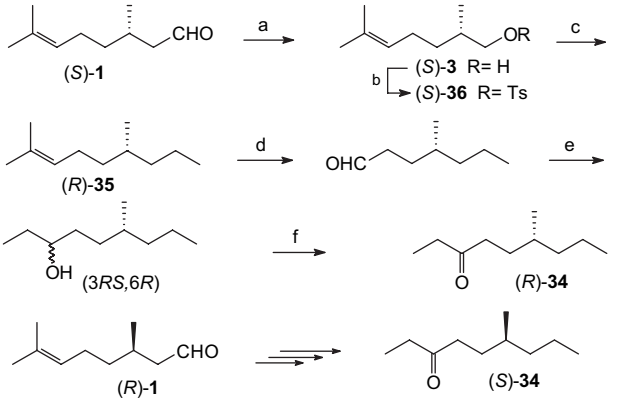


Scheme 12. Reagents and conditions: (a) $CH_3(CH_2)_{12}MgBr$, THF, 97%; (b) MsCl, C_5H_5N, CH_2Cl_2; (c) $LiB(C_2H_5)_3H$, THF, 99% (two steps); (d) (1) O_3, hexane, MeOH, CH_2Cl_2 (1:2:1); (2) $NaBH_4$, 65%; (e) TsCl, C_5H_5N, CH_2Cl_2, 4 °C, 12 h; (f) NaI, DMF, Me_2CO, 88% (two steps).

Starting from the enantiomers of citronellal, (*S*)- and (*R*)-**1**, both enantiomers of 6-methyl-3-nonanone (**34**), the female-produced sex pheromone of the caddisfly (*Hesperophylax occidentalis*) were synthesized (Scheme 14).[18] In the first step, (*S*)-citronellal (**1**) was reduced with lithium aluminum hydride to give (*S*)-citronellol (**3**). Then, the alkene (*R*)-**35** was obtained by reaction of the (*S*)-tosylate **36** with Me_2-CuLi. After ozonolysis, alkylation with ethyl magnesium bromide and oxidation with Jones reagent, the desired (*R*)-6-methyl-3-nonanone (**34**) was obtained with the same ee (97%) as the starting material. Similarly, (*R*)-citronellal (**1**) was converted to (*S*)-**34** with an overall yield (six steps from (*R*)-**1**) of 12–18%.



Scheme 13. Reagents and conditions: (a) **32**+^{n}BuLi, THF, HMPA, then **33**, 88%; (b) H_2, PtO_2, hexane, 99%.



Scheme 14. Reagents and conditions: (a) $LiAlH_4$, Et_2O, 80%; (b) TsCl, C_5H_5N; (c) Me_2CuLi, Et_2O, 65% based on **3**; (d) (1) O_3, MeOH, $NaHCO_3$; (2) Me_2S, 83%; (e) EtMgBr, Et_2O, 67%; (f) Jones CrO_3, Me_2CO, 63%.

The possible male-produced pheromones of the flea beetle *Aphthona flava*, (1*R*,2*S*)-**37**, (6*S*,7*R*)-**38**, (5*S*,5a*R*)-**39**, and (*R*)-**40** (Fig. 4) were synthesized from (*S*)-citronellal (**1**). Their enantiomers were also synthesized, starting from (*R*)-**1** (Scheme 15).[19] The absolute configuration of **37** was assigned based on stereochemical retention of the starting citronellal.

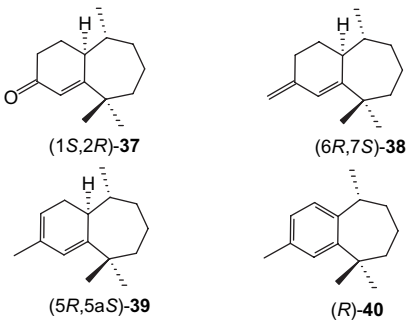
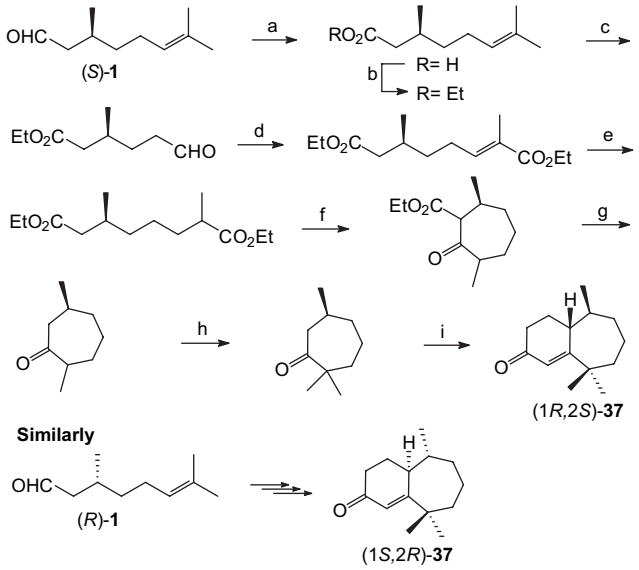


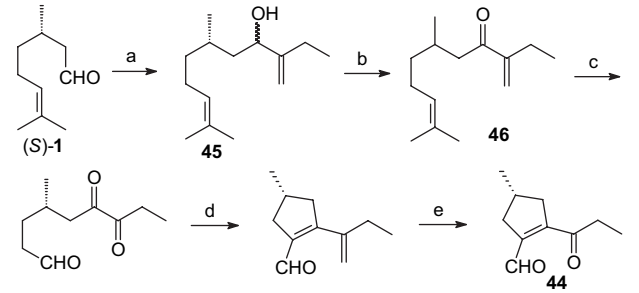
Figure 4. Structures of *Aphthona flava* himachalenes.



Scheme 15. Reagents and conditions: (a) PDC, DMF, 0 °C to rt; (b) K_2CO_3, EtI, DMF, 0 °C to rt, 74% (two steps); (c) O_3, MeOH, −78 °C, then Me_2S, 72%; (d) $(EtO)_2P(O)CHMeCO_2Et$, NaH, THF, −30 °C, 96%; (e) H_2, PtO_2, EtOAc, rt, 100%; (f) (1) ^{t}BuOK, *m*-xylene, 150 °C; (2) diluted HCl, 79%; (g) (1) NaOH, MeOH, H_2O, reflux; (2) diluted HCl, 85%; (h) ^{t}BuOK, ^{t}BuOH, MeI, 0 °C to rt, 88%; (i) (1) LDA, TMSCl, THF, −78 °C; (2) MeLi, CH_2=C(TMS)COMe, THF; (3) NaOMe, MeOH, rt, 44%.

2.2. Synthesis of cyclic and polycyclic compounds

A synthetic route to methyl-cyclopentenoids has been developed from (*S*)-citronellal (**1**) in which the chiral center is retained (Scheme 16).[20] Because they contain substituents that allow the conversion of a single enantiomer into diterpenoids of absolute configuration, these compounds are potentially valuable precursors toward several diterpenoids with a methylated cyclopentane ring as a common feature, like tigliane (**41**), lathyrane (**42**), and jatrophane (**43**, Fig. 5).



Scheme 16. Reagents and conditions: (a) 2-bromobut-1-ene, Mg, THF, 15 °C, then **1**, rt, 7 h, 100%; (b) PCC, CH_2Cl_2, sodium acetate, 2 h, 71%; (c) (1) O_3, CH_2Cl_2/EtOH, −78 °C; (2) $(CH_3)_2S$, rt, 5 h, 47%; (d) glacial acetic acid, piperidine, benzene, reflux, 20 min; (e) (1) O_3, CH_2Cl_2, −78 °C, 20 min; (2) $(CH_3)_2S$, rt, 4 h, 47%.

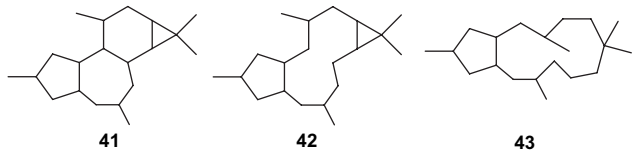
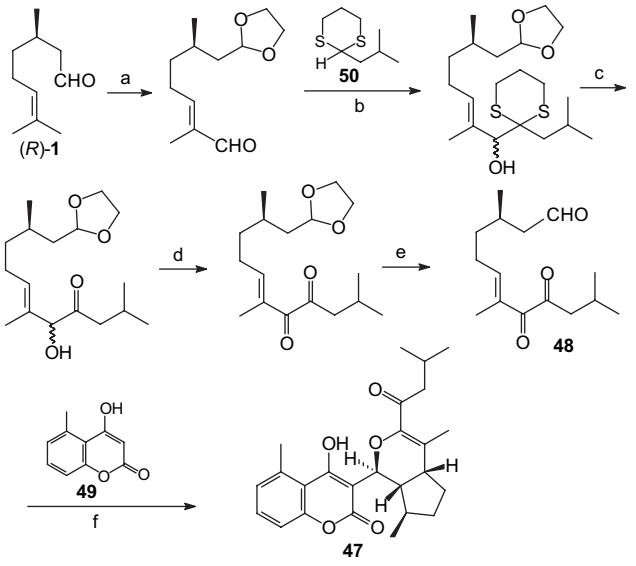


Figure 5. Methylated cyclopentane diterpenoids.

Optically active 1,2-substituted-4-methylcyclopentene **44** was prepared from (*S*)-citronellal (**1**) by treating it with a Grignard reagent derived from 2-bromobut-1-ene, which results in a mixture of diastereomeric allylic alcohols **45**. Treatment with pyridinium chlorochromate easily oxidizes these alcohols to afford the dienone **46**, which was transformed to cyclopentenoid **44** in three steps. In a similar fashion, it is possible to prepare the other enantiomer of **44**, starting from (*R*)-**1** (Scheme 16).

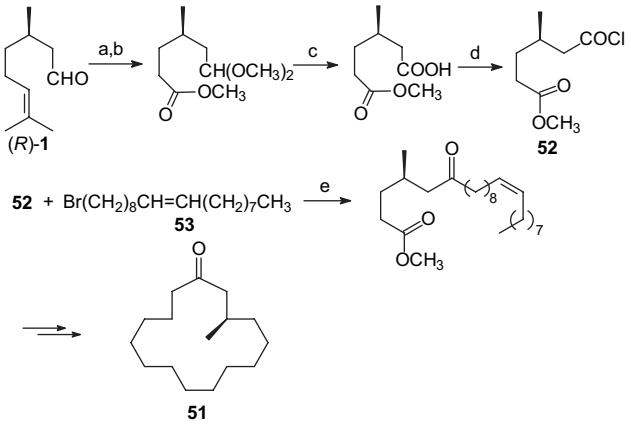
(−)-Lycoserone (**47**), a naturally occurring 4-hydroxy-5-methylcoumarine derivate is isolated from tribus plants *Multisieae* (family *Compositae*). Members of this family of structurally elaborated polycyclic compounds have mono- and sesterterpenes as side chains. With the aim to establish absolute configuration, **47** and seven other natural products have been synthesized using (3*R*,6*E*)-(+)-3,7,11-trimethyl-8,9-dioxo-6-dodecenal (**48**) and 4-hydroxy-5-methylcoumarine (**49**, Scheme 17).[21] (*R*)-Citronellal (**1**) was employed in the enantioselective preparation of **48**.



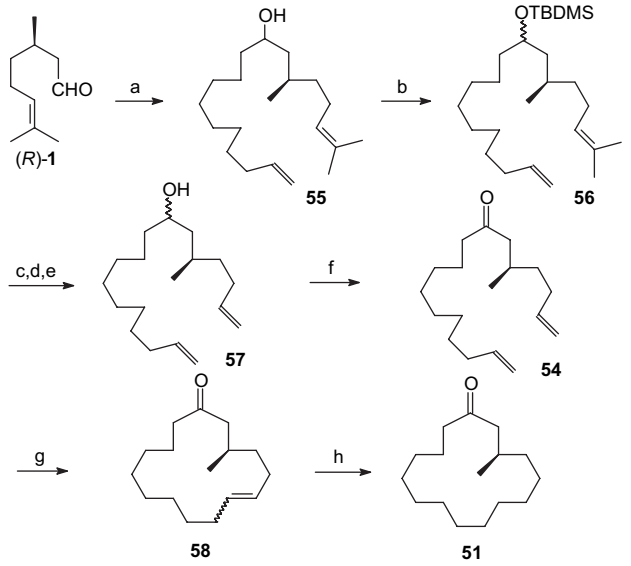
Scheme 17. Reagents and conditions: (a) (1) $HOCH_2CH_2OH$, *p*-TsOH, 90%; (2) SeO_2, 44%; (b) −78 °C, ^nBuLi, then **50**; (c) $HgCl_2$, $CaCO_3$; (d) MnO_2, CH_2Cl_2, 62%; (e) SiO_2, CH_2Cl_2, 96%; (f) $CHCl_3$, H_2O, *p*-TsOH, 44%.

(*R*)-(−)-Muscone (3-methylcyclopentadecan-1-one, **51**), a valuable perfumery ingredient, is the primary compound in musk pod. Obtained from the male musk deer *Moschus moschiferus*, it has an exotic odor and occurs rarely in nature. These factors have contributed to the development of several approaches to optically active (−)-muscone. In its first asymmetrical synthesis in 1964, (−)-muscone was obtained in 0.6% overall yield from (*R*)-citronellal (**1**) in 11 steps (Scheme 18).[22]

Recently, a simple and atom-economic approach to (−)-**51**, starting from (*R*)-citronellal (**1**), was described.[23] The key step in this synthesis was the ring closing olefin metathesis (RCM) of acyclic diolefinic substrate **54**. Initially, Grignard addition to (*R*)-**1** followed by protection (TBDMS) affords acyclic diolefinic alcohol **56** (Scheme 19). The protected alcohol **56** (TBDMS) was then converted to the terminal diolefinic alcohol **57** (three steps), and then subjected to Jones



Scheme 18. Reagents and conditions: (a) CH_3OH, NH_4Cl, rt, 65 h; (b) (1) aq $KMnO_4$, rt, 5 h; (2) CH_2N_2, 0 °C; (c) (1) dil HCl, rt, 24 h; (2) AcOH, acetone, aq $KMnO_4$, 45 min; (d) $SOCl_2$, 40 °C, 4 h; (e) (1) Mg, ether, **53**, rt, 1 h, then reflux, 1 h; (2) $CdCl_2$, reflux, 30 min; (3) **52**, benzene, reflux, 4 h.

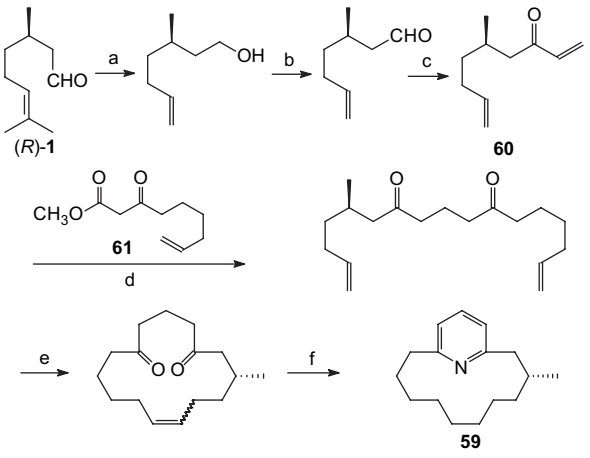


Scheme 19. Reagents and conditions: (a) 10-bromodec-1-ene, Mg, Et_2O, 16 h, 63%; (b) TBDMSCl, imidazole, DMF, 21 h, 87%; (c) O_3, CH_2Cl_2, −78 °C, Me_2S, −78 °C then rt, 12 h; (d) Ph_3PMeBr, ^nBuLi, THF, −78 °C, then rt, 4 h, 73% (two steps); (e) TBAF, THF, 24 h, 97%; (f) Jones reagent, CH_3COCH_3, 5 min, 97%; (g) 5 mmol % of bis(tricyclohexylphosphine)benzylidene ruthenium dichloride, CH_2Cl_2, 21 h, 45 °C, 78%; (h) H_2, 10% Pd/C, MeOH, 3 h, 98%.

oxidation to give the desired RCM substrate **54** in high yield. Subsequently, treatment of ketone **54** with RCM conditions and Grubb's catalyst affords the cyclic alkene **58** in 78% yield. Finally, catalytic hydrogenation of **58** over palladium on carbon provided pure (*R*)-(−)-muscone (**51**).

RCM was also employed in the total synthesis of (*R*)-(+)-muscopyridine (**59**, Scheme 20), a minor constituent of *M. moschiferus*.[24] In this convergent total synthesis, (*R*)-citronellal (**1**) is converted to the vinyl ketone **60**, then Michael addition of β-keto-ester **61** under PTC conditions (Scheme 20).

Arteannuin (**62**) is an antimalaria active compound isolated from *Artemisia annua* L., which is used in the traditional



Scheme 20. Reagents and conditions: (a) (1) $NaBH_4$, MeOH, 91%; (2) O_3, DMS, CH_2Cl_2; (3) THF, $Ph_3P{=}CH_2$, 70% (two steps); (b) $SO_3{\cdot}Py$, DMSO, Et_3N, CH_2Cl_2; (c) (1) $CH_2{=}CHMgBr$, THF, 68% (two steps); (2) TPAP, NMO, CH_2Cl_2, 70%; (d) (1) K_2CO_3, $(^nBu)_4NI$, 93%; (2) LiCl, DMPU, 120 °C, 72%; (e) bis(tricyclohexylphosphine)benzylidene ruthenium dichloride, CH_2Cl_2, 40 °C, 90%; (f) (1) Pd/C, H_2, EtOH, 98%; (2) NH_2OH/HCl, 61%.

Chinese herbal treatment of malaria (Fig. 6). Deoxyarteannuin (**63**) occurs in the same plant and was also isolated as a metabolite from the urine of patients treated with arteannuin. (+)-Deoxoartemisinin (**64**), obtained from artemisinic acid, exhibits several fold greater activity than **62** in the in vitro antimalarial assay against the chloroquine-resistant *Plasmodium falciparum* (Fig. 6). The high biological activity and novel chemical structure combined with its low yield from natural sources have stimulated several studies toward the synthesis and structure–activity relationships of **62** and its analogs. In Scheme 21, the total synthesis of the two naturally occurring sesquiterpene lactones **62** and **63**, starting from (*R*)-citronellal (**1**) is illustrated.[25]

The dihydroxy compound **65** was obtained in two steps from (*R*)-**1**[26,27] involving cyclization with $ZnBr_2$ and subsequent reaction with diborane under basic conditions.[25] After several steps, the key intermediate **66** was obtained and converted to **67** in an overall yield of 33% (four steps). Photooxidation of **67** in the presence of oxygen and Rose Bengal, followed by acid treatment afforded the trapping compound **68**, which is hydrolyzed in acidic medium to give arteannuin **62** in 28% yield (two steps). On the other hand, when **67** was hydroxylated with osmium tetroxide, followed by treatment with hydrogen sulfide, the deoxyarteannuin **63** was obtained in 45% yield (Scheme 21).[25]

A mixture of 2,3-desethano-12-deoxoartemisinin related compounds **69a** and **69b**, analogs of **64** (Fig. 6), was synthesized from (*R*)-citronellal (**1**) by a stereoselective procedure after nine steps (1.2% overall yield, Scheme 22).[28]

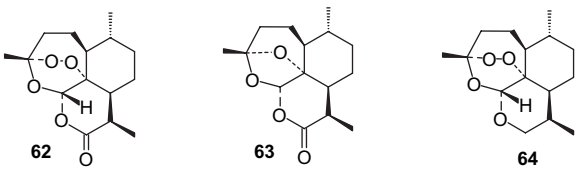
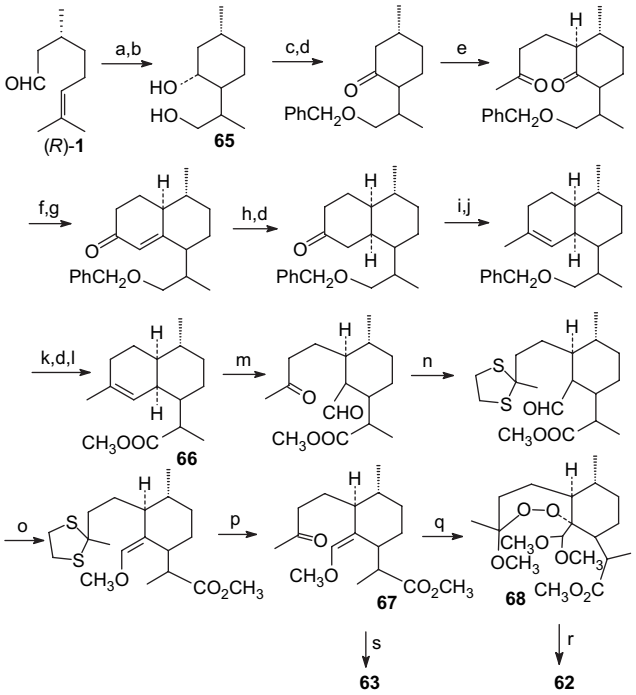
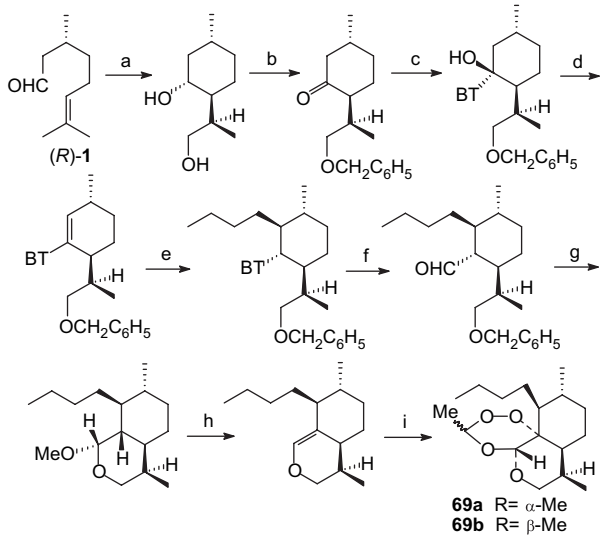


Figure 6. Arteannuin (**62**) and analog compounds.

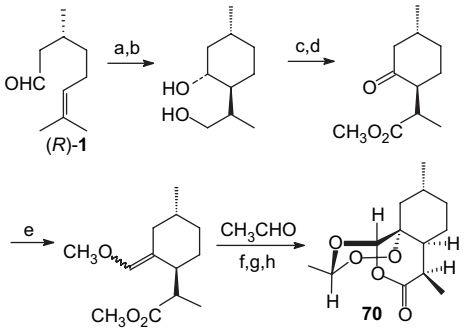


Scheme 21. Reagents and conditions: (a) $ZnBr_2$; (b) B_2H_6/H_2O_2, ^-OH; (c) $PhCH_2Cl$, NaH; (d) Jones oxidation, 51% (steps c and d); (e) LDA, $CH_2{=}C(Me_3Si)COCH_3$, 55%; (f) $Ba(OH)_2{\cdot}8H_2O$; (g) $(COOH)_2$, 62% (steps f and g); (h) $NaBH_4$ and (d), 47%; (i) CH_3MgI, 93% (isomeric ratio 1:1); (j) *p*-TsOH; (k) Na-liq. NH_3 and (d); (l) CH_2N_2, 72% (steps k, d, and l); (m) O_3, Me_2S; (n) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$; (o) $HC(OMe)_3$, *p*-TsOH, xylene, heat; (p) $HgCl_2$, aq $CaCO_3$, CH_3CN, 33% overall from compound **66**; (q) O_2, Rose Bengal, *hν*; (r) 70% $HClO_4$, 28% (steps q and r); (s) OsO_4, H_2S, 45%.

The same strategy described in Schemes 21 and 22 was employed in the stereoselective synthesis of desethanoartemisin (**70**), a potential antimalarial analog of artemisinin (Scheme 23).[29]

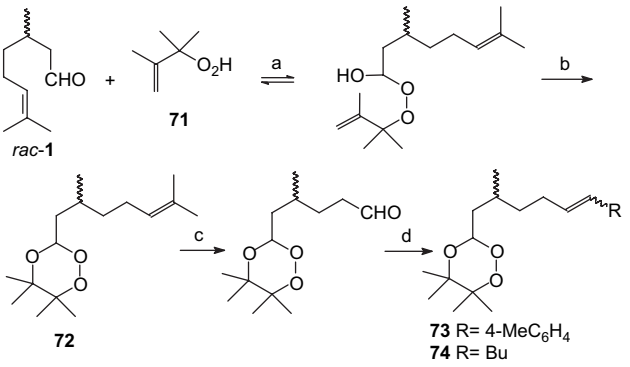


Scheme 22. Reagents and conditions: (a) (1) $ZnBr_2$, 0–5 °C, benzene; (2) B_2H_6; (3) NaOH, H_2O_2; (b) (1) $C_6H_5CH_2Cl$, NaH, 0 °C, DMF; (2) Jones oxidation, 50%; (c) benzothiazole (BT), ^{n}BuLi, −78 °C, 44%; (d) $MeO_2CN^-SO_2N^+Et_3$, benzene, 75%; (e) ^{n}BuLi, THF, −78 °C, 70%; (f) (1) $MeOSO_2F$, CH_2Cl_2, 2.5 h; (2) $NaBH_4$, EtOH, −20 °C, 30 min; (3) $AgNO_3$, 60%; (g) *p*-TsOH, $(MeO)_3CH$, xylene, reflux, 2 h, 90%; (h) 10% H_2SO_4, 130 °C, 62%; (i) Rose Bengal, MeCHO, $^1O_2$, *hν*, −78 °C, 31%.



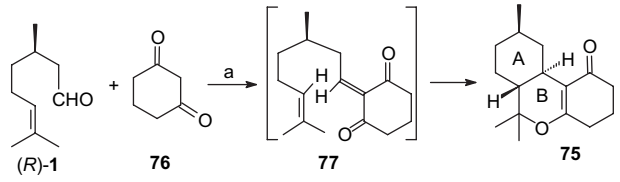
Scheme 23. Reagents and conditions: (a) $ZnBr_2$; (b) B_2H_6/H_2O_2, ^-OH; (c) Jones oxidation, (d) CH_2N_2, 85%; (e) ^nBuLi, $MeOCH_2PPh_3Cl$, 40%; (f) $^1O_2$, Rose Bengal, MeOH, *hν*, −70 to −78 °C; (g) HCl gas; (h) 60% $HClO_4$, 15%.

Thanks to the great interest of artemisinin and its peroxide analogs as antimalaria drugs, a general methodology for the synthesis of 1,2,4-trioxanes via cyclo-oxymercuriation was described (Scheme 24).[30] This method involves the use of crude hydroperoxide obtained by photooxygenation of 2,3-dimethylbut-2-ene (**71**) with citronellal. The 1,2,4-trioxane derivate of citronellal (**72**) was then converted to the alkenyl 1,2,4-trioxanes **73** and **74**.



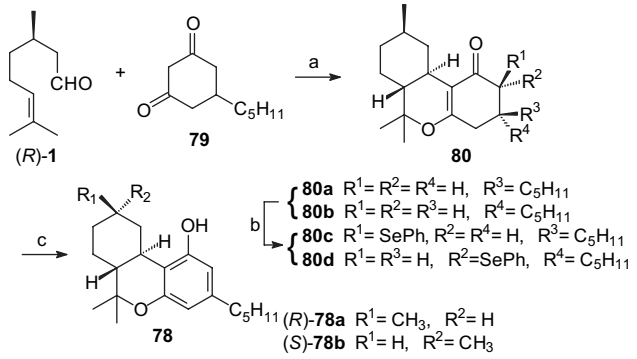
Scheme 24. Reagents and conditions: (a) cat. CF_3CO_2H; (b) (1) $Hg(OAc)_2$, 6 mol % $HClO_4$; (2) $NaBH_4$, NaOH, 85%; (c) $NaIO_4$, 1 mol % OsO_4; (d) $RCH_2PPh_3^+Br^-$, ^nBuLi.

A 100% stereocontrolled intramolecular hetero-Diels–Alder reaction of 1,3-dienes using α,β-unsaturated carbonyl compounds was described using (*R*)-citronellal (**1**) to synthesize the tricyclic dihydropyran **75** (Scheme 25).[31] Here, (*R*)-**1** was reacted with the enolate of 1,3-cyclohexanedione **76**. As no diastereomers of **75** were detected, the authors deduced that complete control by the chiral center of citronellal (**1**) is operative in the transition state of cycloaddition of **77**.



Scheme 25. Reagents and conditions: (a) MeONa, MeOH, 1 h, 0–20 °C, 33%.

The new protocol described above was employed in the highly selective synthesis of (9*R*)-hexahydrocannabinol (HHC) (**78a**, Scheme 26).[32] This non-natural HHC belongs to the psychotropic cannabinoids and is nearly as active as the natural D^8-tetrahydrocannabinol (D^8-THC, $C^8{=}C^9$), whereas the (9*S*)-epimer **78b** is 20 times less active. The cycloaddition is 100% stereocontrolled by the chiral center of citronellal (**1**).[32] Thus, condensation of (*R*)-**1** with 5-*n*-pentyl-1,3-cyclohexanedione (**79**) at 100 °C in DMF leads to a 1:2 mixture of the tricyclopyran derivatives, **80a** and **80b**, in 65% yield. The formation of the epimeric C-3 compounds has no significance for the synthesis of (9*R*)-HHC **78a**, since C-3 becomes achiral in the subsequent aromatization step. For aromatization, selenium oxide *syn*-elimination of **80c** and **80d** was employed, affording the desired (9*R*)-HHC in 70 and 56% yield, respectively. As the configuration at C-3 in the starting citronellal is maintained, (9*S*)-HHC **78b** (the enantiomer of **78a**) can be synthesized in the same way starting from (*S*)-citronellal (**1**).



Scheme 26. Reagents and conditions: (a) DMF, 100 °C, 65%; (b) LDA, PhSeCl, 65%; (c) *m*-chloroperbenzoic acid, −40 °C to 25 °C, 70% from **80c** and 56% from **80d**.

Pyridoxatin (**81**, Fig. 7) is a 1-hydroxy-2-pyridone free-radical scavenger isolated from *Acremonium* sp. BX86 and it is approximately 20 times more active as vitamin E.

When 4-hydroxy-2-pyridone **82** was reacted with **1** instead of 1,3-cyclohexanedione **79**, the pyridoxatine analogs **83** and **84** were obtained through an intramolecular Diels–Alder condensation (Scheme 27).[33] By heating a solution of (*S*)-**1** and pyridone **82** in the presence of piperidine and pyridine in EtOH for 60 h at reflux, 46% of the Diels–Alder adduct **85**, 28% of the ene adduct **86**, and 25% of Diels–Alder adduct **87** were obtained. All three products appear to arise from the proposed *o*-quinone methide intermediate **88**. The ene reaction affords **86**; inverse electron demand Diels–Alder reaction with the enone provides Diels–Alder adduct **85**, while a similar Diels–Alder reaction with enamide yields adduct **87**. *N*-Hydroxypyridones **83** and **84** are also effective free-radical inhibitors, preventing Fe^{2+} lipid peroxidation in rat

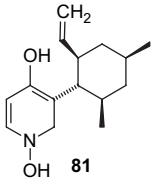
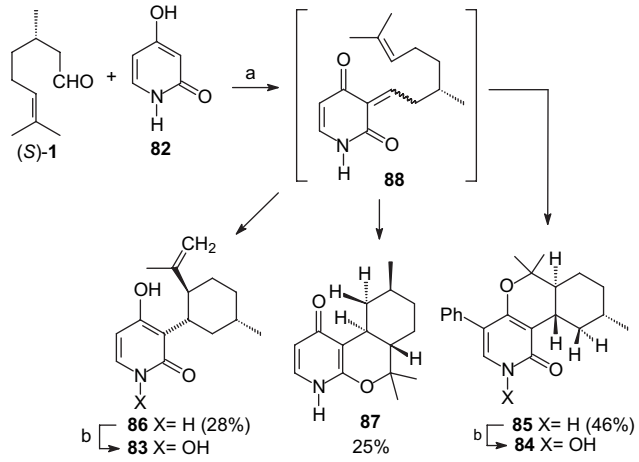


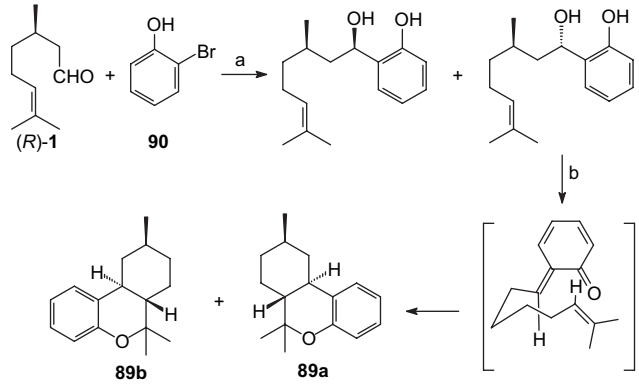
Figure 7. Pyridoxatin.

brains. The two-step sequence toward these compounds from commercially available 4-hydroxy-2-pyridone **82** and (*S*)-**1** makes these compounds very readily available (Scheme 27).



Scheme 27. Reagents and conditions: (a) (1) Py, piperidine, EtOH, reflux, 60 h; (2) $(Me_3Si)_2NH$, TMSCl; (3) MoO_5, pyridine, HMPA; (b) (1) HMDS, TMSCl; (2) $MoO_5 \cdot Py \cdot HMPA$, CH_2Cl_2, 15 h; (3) CH_2Cl_2, tetrasodium EDTA, 4 h, 48% for **83** and 54% for **84**.

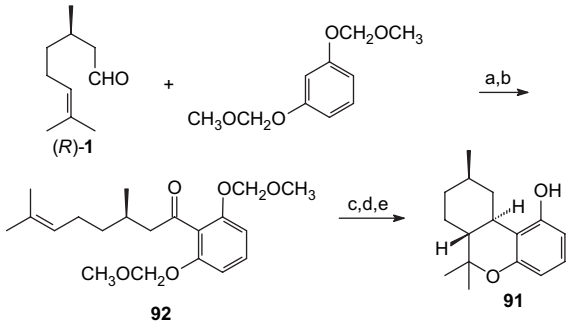
The synthesis of **89a** and **89b**, possessing the ring system and absolute configuration of naturally occurring cannabinoids, was completed by introducing the stereocenter from (*R*)- or (*S*)-citronellal (**1**).[34] The first step in the synthesis was the reaction of the dilithium salt derived from **90** with citronellal, followed by protonation with NH_4Cl (Scheme 28). A pseudoequatorial conformation adopted by C-9 methyl in the chair-like transition state accounts for the observed stereochemistry.



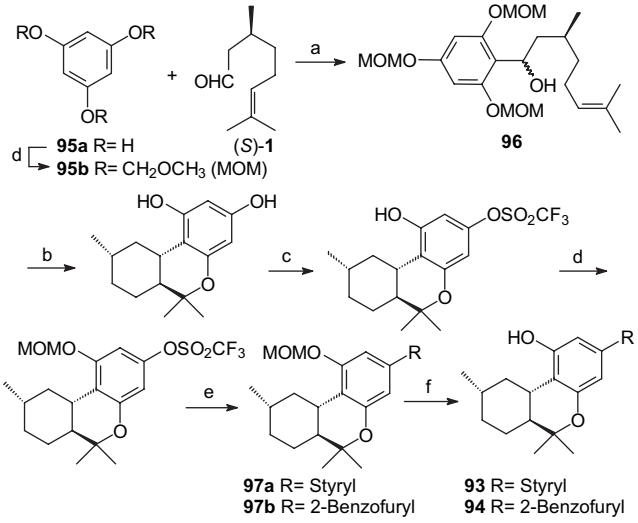
Scheme 28. Reagents and conditions: (a) Ether, −20 °C, then NH_4Cl, 94%; (b) *o*-dichlorobenzene, 180 °C, 0.25 h, 95%.

The known cannabinol analog **91** was prepared through *ortho*-metallation of 1,3-bis(*o*-methoxymethyl)resorcinol followed by condensation with (*R*)-**1**, which gave a 1:1 mixture of diastereomers of **92**. After three more steps, **91** was obtained (Scheme 29).[34] In Section 10 of this review, several different and general methods for the synthesis of other cannabinols and analogs starting from citronellal are presented.

A short and efficient synthesis of the naturally occurring antimalaria compounds machaeriols A (**93**) and B (**94**) (Scheme 30)[35] involves the condensation of phloroglucinol



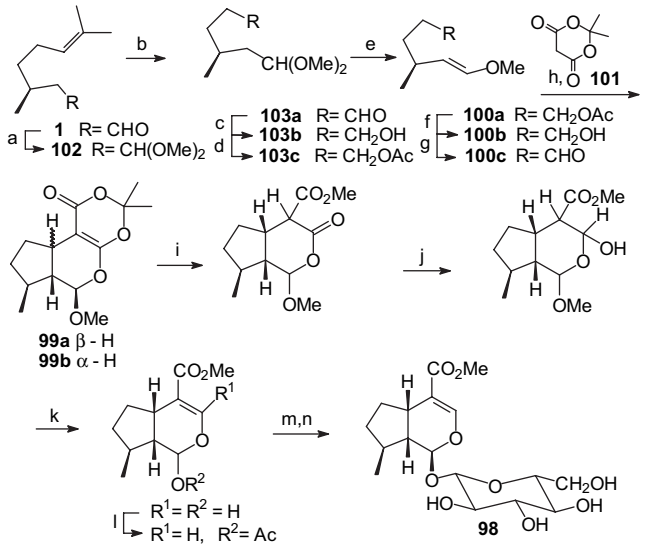
Scheme 29. Reagents and conditions: (a) ^{n}BuLi, Et_2O, 25 °C, (*R*)-**1**, 67%; (b) $CrCO_3 \cdot 2Py$, CH_2Cl_2, 25 °C, 2 h, 83%; (c) anhydrous MeOH, heat, *p*-TsOH, 91%; (d) $NaBH_4$, MeOH, 0 °C, 95%; (e) CF_3COOH, 87%.



Scheme 30. Reagents and conditions: (a) ^{n}BuLi, TMEDA, 0 °C, 30 min, 85%; (b) 4% aq HCl in MeOH, rt, 12 h, 65%; (c) $PhNTf_2$, Et_3N, CH_2Cl_2, 3 h, 74%; (d) NaH, MOMCl, THF, 30 min, 97%; (e) boronic acid (*trans*-phenyl-vinyl or 2-benzofuryl, 1.5 equiv), $Pd(PPh_3)_4$ (1 mol %)/2 M aq Na_2CO_3 (1.5 equiv)/MeOH/toluene, reflux, 2 h (**97a**, 90%; **97b**, 86%); (f) 1% aq HCl in MeOH, reflux, 30 min (**93**, 95%; **94**, 97%).

(**95a**), which was protected by *ortho*-metallation with tris-(*O*-methoxymethyl)ether (MOMO) to give **95b**, with (*S*)-citronellal (**1**). Treatment of **95b** with ^{n}butyl lithium and *N*,*N*,*N*′,*N*′-tetramethylethylene diamine (TMEDA), followed by condensation with citronellal led to **96** as a 1:1 mixture of diastereomers in 85% yield. After five steps, **96** was converted to **93** (R=styryl) and **94** (R=benzofuryl) in good yields for the individual steps. The overall yield of **93** and **94** was 33% and the configuration at C-3 of citronellal was maintained.

Deoxyloganin (**98**) is a member of the large class of natural iridoid glycosides (Scheme 31). In plants, this compound is a precursor of secologanin, which is a key intermediate for a large variety of alkaloids. The synthetic route to **98** includes **99**, which is obtained from condensation of the aldehyde (*E*)-**100c** with meldrum's acid **101**. (*S*)-Citronellal (**1**) was used to obtain **100c** through its conversion via the dimethylacetal **102** into aldehyde **103a** (Scheme 31).[36] Configuration at C-3 in citronellal was kept in the final product.



Scheme 31. Reagents and conditions: (a) $CH(OMe)_3$, K-10 montmorillonite, 10 min, 20 °C, 95%; (b) O_3 in CH_2Cl_2/MeOH, −70 °C, 25 min; (c) $NaBH_4$, 20 °C, 20 min, 65%; (d) $(MeCO)_2O$, Py, 1 h, 20 °C, 98%; (e) $KHSO_4$, 1 h, 120 °C, 6 Torr, 80%; (f) K_2CO_3/MeOH, 20 °C, 4 h; (g) $(COCl)_2$, DMSO, CH_2Cl_2, 20 min, −70 °C, Et_3N, 0 °C, 80–90%; (h) toluene ethylenediammoniumdiacetate, Na_2SO_4, 20 °C, 2 h, 52%; (i) MeOH, 1 h, 64 °C; (j) DIBAL-H, ether, 2 h, −70 °C; (k) *p*-TsOH, 1 h, 20 °C, 62%; (l) Ac_2O, Py, 95%; (m) 1-*O*-trimethylsilyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, trimethylsilyltriflate, SO_2 (l) −40 °C, 48 h, 44%; (n) NaOMe/MeOH, 20 °C, 2 h, 95%.

Many 2,2,6-trimethylcyclohexyl derivatives, such as α-ionone, irones, and α-damascone, are used as important raw materials for flavor and fragrance industries.[4] The irone containing perfums are of high quality, and four isomers (**104**–**107**) were isolated from its natural source, the orris oil (Fig. 8).[4b]

(*R*)-Citronellal (**1**) was employed as chiral precursor in the synthesis of several natural and non-natural irones derivatives.[37–41] The key intermediate in the preparation of chiral irones is a cyclocitral derivative. Thus, the high isomeric purity and versatility of aldehyde **108** was explored for preparation of the natural irones **105** and **106** and artificial irone **109a** (Scheme 32).[37] In the first step of the synthesis, (*R*)-**1** was converted to (+)-methyl citronellate (**110**). That was then methylated stepwise to afford methyl 2,2,3,7-tetramethyloct-6-enoate (**111**). The ester **111** was then submitted to hydrolysis, followed by acylation and cyclization with $SnCl_4$ to give 2,2,3-trimethyl-6-(1-chloro-1-methyl-ethyl)-cyclohexanone (**112**). After five steps, the key intermediate, 1-(2,2,3-trimethyl-6-methylenecyclohexyl)acetaldehyde (**108**) was stereoselectively obtained in very good yield. The (+)-*trans*-γ-irone (**109a**) was the main product of the elongation

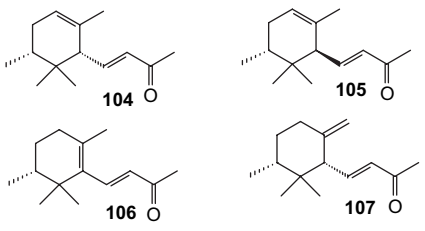
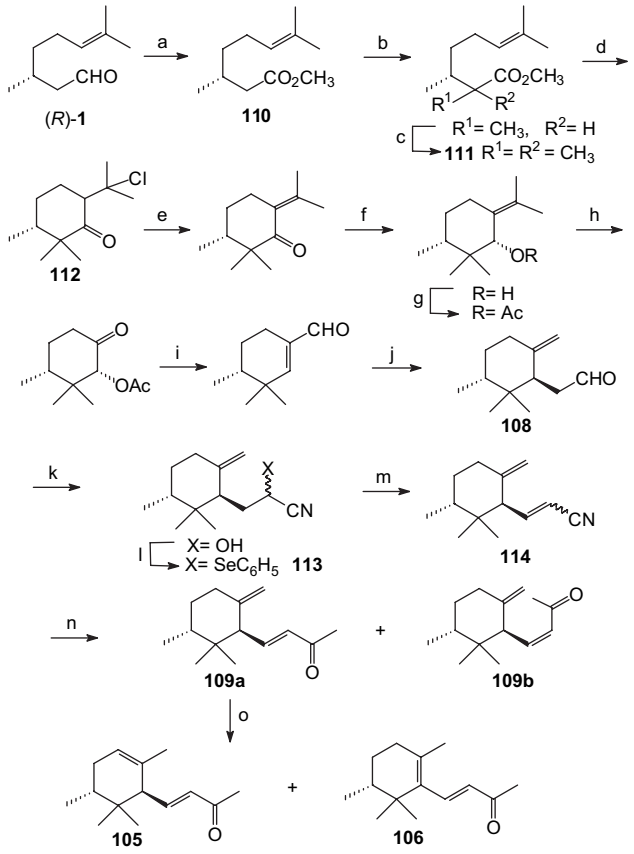


Figure 8. Irones and analogous.

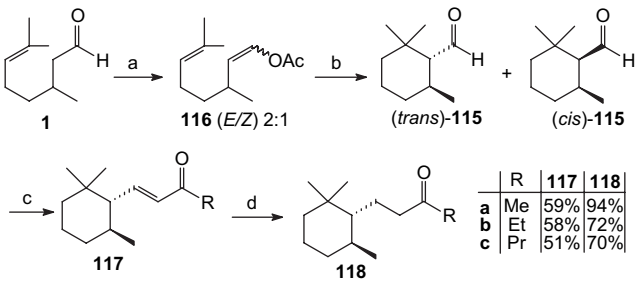


Scheme 32. Reagents and conditions: (a) (1) Jones reagent, acetone, 0 °C; (2) CH_3OH, H_2SO_4, 59–67%; (b) LDA, CH_3I, THF; −60 °C, N_2, 2 h; (c) LDA, CH_3I, THF, 0 °C, N_2, 3 h, 80%; (d) (1) KOH, EtOH, reflux, 72 h; (2) $(COCl)_2$, benzene, $SnCl_4$, CH_2Cl_2, rt, 1.5 h and then reflux, 3 h; (e) Li_2CO_3, DMA, 100 °C, 6 h; (f) $LiAlH_4$, Et_2O, 0 °C, 30 min, 100%; (g) Ac_2O, C_5H_5N, 70 °C, 8 h; (h) O_3, CH_2Cl_2, −78 °C, 91%; (i) (1) $(C_6H_5)_3P{=}CHOCH_3$, toluene, 18-crown-6, rt, 2 h; (2) $HClO_4$, then Al_2O_3, 65%; (j) (1) $LiAlH_4$, Et_2O, 0 °C, 30 min; (2) $EtOCH{=}CH_2$, $Hg(AcO)_2$ then reflux, 72 h, 61%; (k) KCN, HOAc, EtOH, 0 °C, 1 h, then rt, 2 h, 100%; (l) MsCl, C_5H_5N, 0 °C, 5 h, then C_6H_5SeNa, EtOH, rt, 2 h, 86%; (m) H_2O_2, C_5H_5N, CH_2Cl_2, rt, 2 h, 88%; (n) CH_3Li, Et_2O, −55 to 0 °C, 3 h, 63%; (o) H_3PO_4, rt, 6 h, 83%.

of the side chain in **108** (63%, 83:17 trans/cis ratio). The treatment of **109a** with phosphoric acid yielded a mixture of (−)-*trans*-α-irone (**105**) and (+)-β-irone (**106**) in a 93:7 ratio (83% yield).

An alternative procedure has also been employed for the synthesis of irone derivatives, starting from the important and versatile precursor dihydrocyclocitral **115**, a valuable compound in the perfum industry (Scheme 33).[4] Treatment of citronellal with a mixture of Ac_2O, Et_3N, and KOH gives the enol acetate **116**, which underwent acid-induced cyclization to **115**.[38] Cyclization was effectively achieved with 85% aqueous H_3PO_4 solution, yielding **115** as an 8:1 trans/cis mixture in 80% yield after distillation. This cationic olefin cyclization was employed in the synthesis of several odoriferous compounds, like the irones **117** and **118** (Scheme 33).[39]

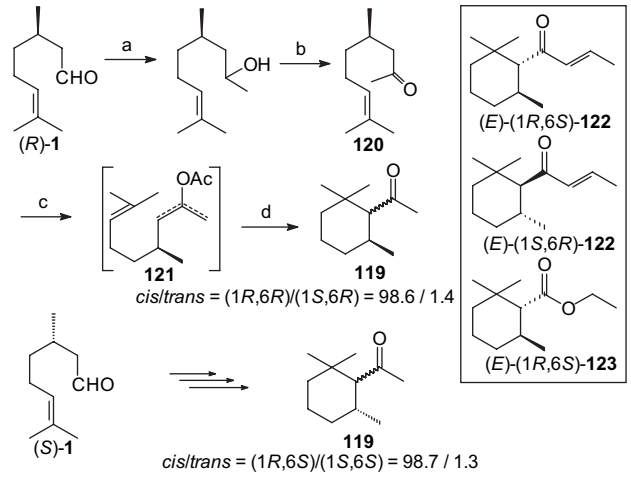
More recently, the same authors described the use of *trans*-dihydrocyclocitral (**115**), obtained as described in Scheme 33, in the synthesis of *Norlimbanol*® and several other chiral alcohol analogs[40] using (*R*)- and (*S*)-citronellal as starting materials.



Scheme 33. Reagents and conditions: (a) Et_3N, KOAc, Ac_2O, 120 °C, 6 h, 85%; (b) 85% aq H_3PO_4, toluene, 0–100 °C, 2 h, 80%; (c) R_2COMe, EtONa, EtOH, reflux; (d) H_2, 5% Pd/C, AcOEt.

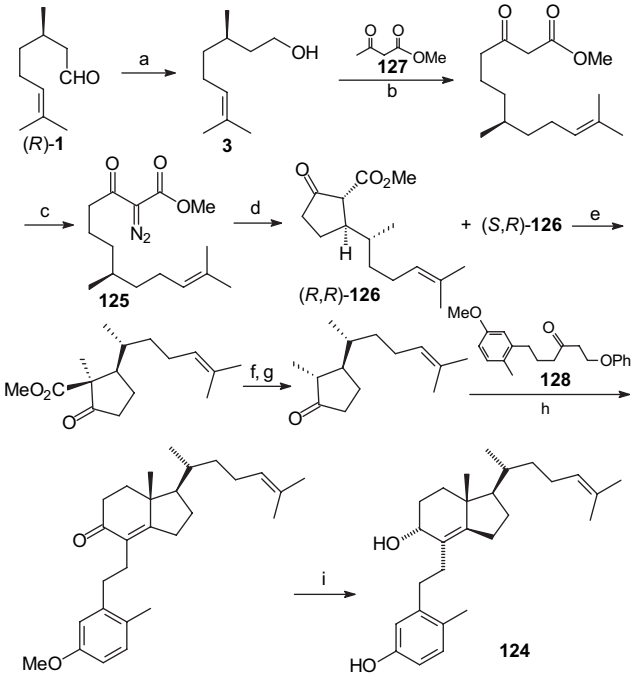
A greener and highly stereoselective methodology to access *trans*-dihydrocyclocitral (**115**) was developed, which involves MW irradiation and no solvent.[41] The first step in this new protocol is the reaction of citronellal with acetic anhydride under base catalysis. Then, *p*-toluenesulfonic acid supported on silica gel was used to perform the cyclization of intermediate enol ester **116** under MW, affording **115** in 94% yield (trans/cis ratio=97:3).

In a variant of this cyclization, the novel (1*R*,6*R*)- and (1*R*,6*S*)-2,2,6-trimethylcyclohexyl ketones **119** were obtained from (*R*)- and (*S*)-citronellal, respectively, after four steps (Scheme 34).[42] The two key steps, ketone enol acetylation and subsequent cyclization were successfully accomplished by applying the enol ester exchange method. The first step of the synthesis was the preparation of the ketone **120**, which was then converted to the respective enol acetate **121**. The cationic olefin cyclization described above afforded ketones **119** in good yields. The configuration of C-3 on citronellal was kept and it was possible to synthesize both enantiomers of **119** starting from each citronellal enantiomer. The authors have also described the preparation of two irones: (*E*)-(1*R*,6*S*)- and (*E*)-(1*S*,6*R*)-1-(2,2,6-trimethylcyclohexyl)-2-buten-1-one (**122**) and ester analog (*E*)-(1*R*,6*S*)-ethyl 2,2,6-trimethylcyclohexyl-carboxylate (**123**), starting from (1*R*,6*S*)- and (1*S*,6*R*)-**119** (Scheme 34).



Scheme 34. Reagents and conditions: (a) MeMgCl, THF, toluene, −5 °C, 1.5 h, then 40–45 °C, 7 h, 95.4%; (b) Jones reagent, acetone, 0–5 °C, 4 h, 81.7%; (c) (1) *p*-TsOH, toluene, reflux, 1 h; (2) ^{i}PrOAc, rt to 90–118 °C, 18 h, 67.8%; (d) 85% aq H_3PO_4, toluene, 95–110 °C, 24 h, 62.1%.

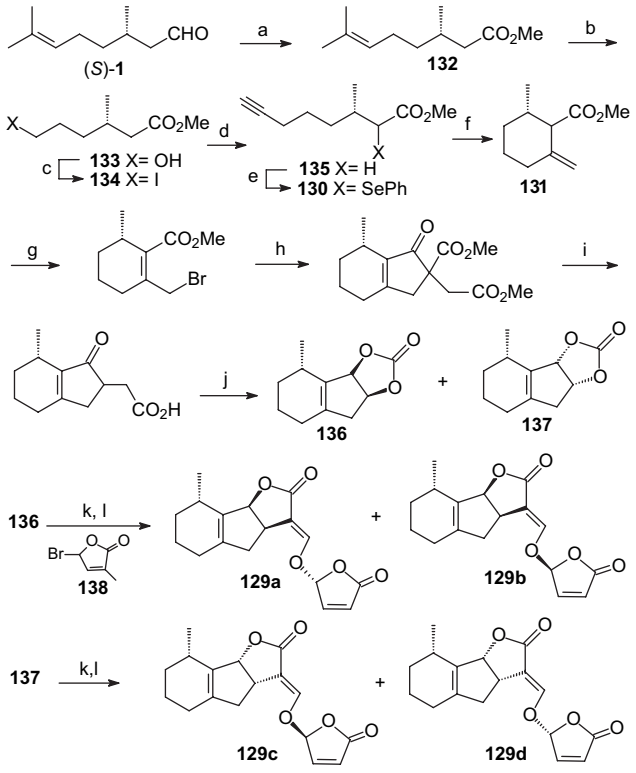
(−)-Astrogorgiadiol (**124**, Scheme 35) is a secosteroid isolated from a Japanese marine sponge of the genus *Astrogorgia* and is a naturally occurring vitamin D analog with antiproliferative properties. A synthetic route to **124** was developed starting from (*R*)-citronellal (**1**), which was converted to (*R*)-citronellol (**3**) by reduction with $LiAlH_4$. (*R*)-**3** was used as starting material to obtain the diazo compound **125** (Scheme 35).[43] The Rh-mediated cyclization of the pure enantiomer **125** proceeds with appreciable selectivity to give the β-ketoester **126**, a key intermediate in the preparation of **124**. As the C-3 configuration on **1** is kept, it is expected that both enantiomers of **126** could be prepared by this citronellal-based methodology.



Scheme 35. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C, 15 min, then reflux, 92%; (b) (1) BsCl, Et_3N; (2) **127**; (c) MsN_3/Et_3N, CH_3CN, 49% (two steps); (d) (1) Rh_2Oct_4, CH_2Cl_2, 12 h, rt; (2) Rh_2PTPA_4, 71% (two steps); (e) CH_3I, K_2CO_3, acetone, heat, 90%; (f) NaCN, HMPA; (g) KOH, MeOH, 75% (two steps); (h) NaOMe, MeOH, **128**, rt, 3 h, then reflux, 26 h, 78%; (i) enantioselective reductive sequence, 21% (three steps).

Sorgolactone (**129**, Scheme 36) is a germination stimulant for parasitic weeds isolated from *Sorghum bicolor*. With the intention to elucidate its structure, a synthetic approach for all four isomers (**129a–d**) starting from (*S*)-citronellal (**1**) was developed (Scheme 36).[44] The key step in the synthesis was the radical cyclization of **130** to **131**, affording the optically active A-ring building block. To construct the highly functionalized compound **130**, (*S*)-**1** was converted to methyl-(*S*)-citronellate (**132**) and subsequently transformed to hydroxyl ester **133**. After two steps, **133** was converted to the corresponding iodo ester **134**, followed by ethynylation to give the acetylenic ester **135** in moderate yield. To perform the cyclization, **135** was converted to the α-phenylseleno ester **130** and subsequently treated with tri-*n*-butyltin hydride and AIBN. After several steps, the isomers **136** and **137** were obtained. Starting from **136**, compounds **129a** and **129b** were obtained, while the use of **137** led to **129c** and **129d**. However, due to some differences

in the ^{1}H NMR of the naturally occurring and the synthetic product, the correct structure remains unknown.



Scheme 36. Reagents and conditions: (a) (1) Jones reagent; (2) K_2CO_3, CH_3I, 65%; (b) (1) $NaHCO_3$, MCPBA, CH_2Cl_2, 0 °C, 30 min; (2) $HIO_4\cdot 2H_2O$, THF, Et_2O, 0 °C, 30 min; (3) $NaBH_4$, MeOH, 0 °C, 1 h, 91% (three steps); (c) (1) TsCl, Py, CH_2Cl_2, 5 °C, 19 h; (2) NaI, acetone, reflux, 2 h, 82% (two steps); (d) LiCCH·EDA, THF, DMSO, 5 °C, 15 min, 37%; (e) (1) LDA (2 equiv), THF, −78 °C, 1 h, then −30 °C, 1 h; (2) PhSeBr, −78 °C, 1 h; (3) dil HCl, rt, 69%; (f) $^nBu_3SnH$, AIBN, C_6H_6, reflux, 1 h, 55%; (g) (1) $C_5H_5N\cdot HBr\cdot Br_2$, $CHCl_3$, −60 °C, 3 h, 37% from **130**; (h) (1) NaH, THF, $CH_2(CO_2Me)_2$, −10 °C, 10 min, then rt, 28 h; (2) $BrCH_2CO_2Me$, rt, 43 h, 98%; (i) 6 N HCl, glacial AcOH, reflux, 2.5 h, 96%; (j) (1) $NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH, 0 °C, then rt, 45 min; (2) MPLC separation, 21% (for **136**) and 30% (for **137**); (k) NaH, HCO_2Et, Et_2O, 100%; (l) (1) K_2CO_3, **138**, *N*-methylpyrrolidone; (2) SiO_2 chromatography, 42% of **129a**, 41% of **129b**, 33% of **129c**, and 48% of **129d**.

The marine macrolide laulimalide (Fig. 9) is a new paclitaxel (Taxol™)-like microtubule-stabilizing agent, with potentially therapeutical activities. This potent cell growth inhibitor was isolated from *Cacospongia mycofijiensis*, *Hyatella* sp., and *Fasciospongia rimosa*.[45] Its action mechanism is similar to that of taxol, but unlike taxol, it inhibits proliferation of the multidrug-resistant cell line SKVLB-1.

The synthetic potential of (*S*)-citronellal (**1**) was explored to prepare C_1–C_{14} allyl stannane fragments **140** (Scheme 37)[45]

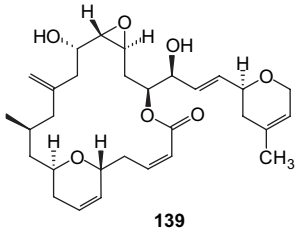
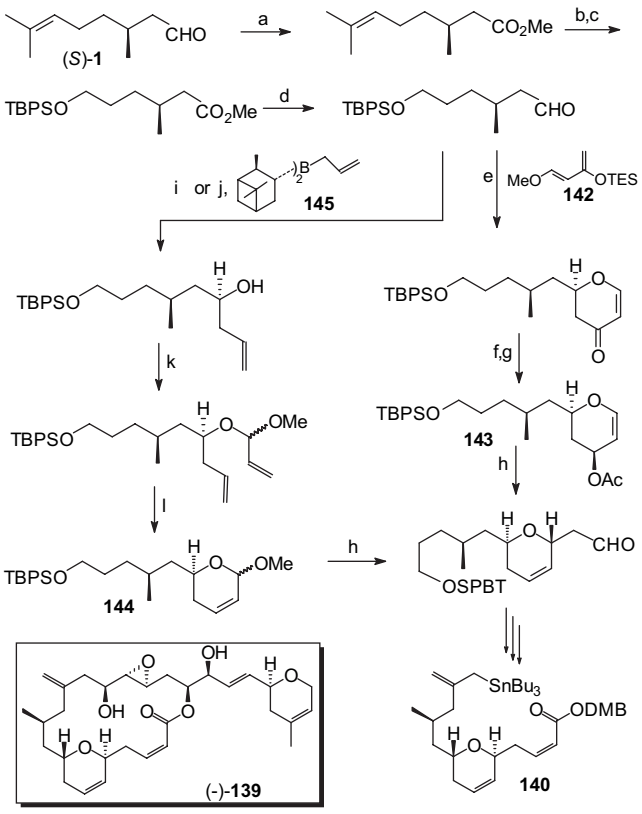


Figure 9. Laulimalide.

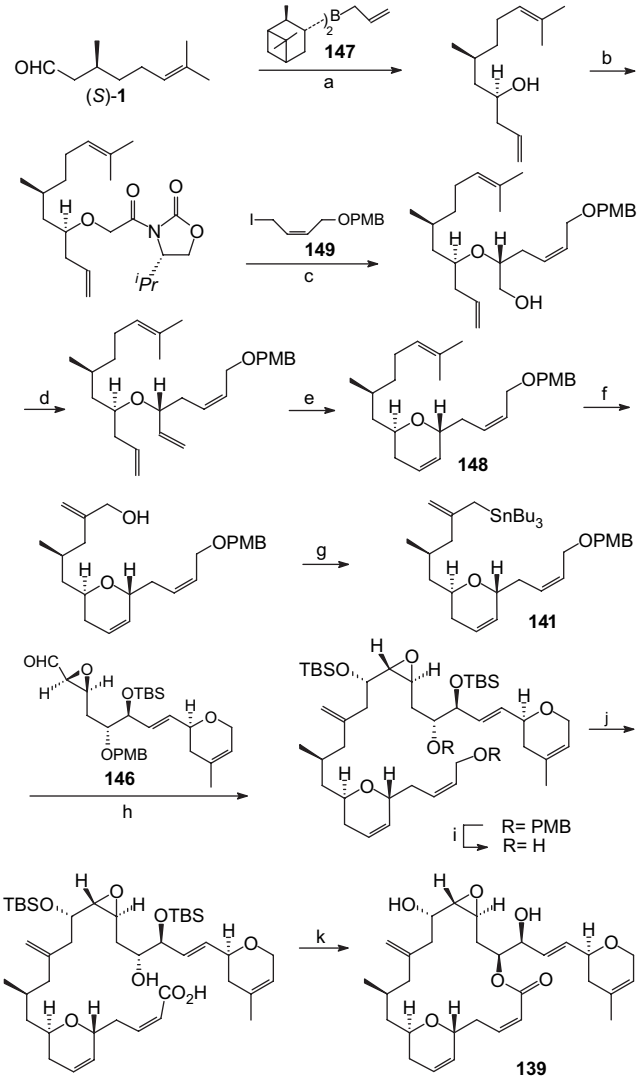


Scheme 37. Reagents and conditions: (a) PDC, MeOH, DMF, rt, 80%; (b) O_3, MeOH, −78 °C, then $NaBH_4$, 82%; (c) TBPSCl, DMAP, imidazole, DMF, rt, 10 h, 89%; (d) DIBAL-H, CH_2Cl_2, 1.5 h, 85%; (e) **142**, (*S*)-BINOL, $Ti(O^iPr)_4$, then TFA, 53%; (f) $NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH, 97%; (g) Ac_2O, $^iPrNEt_2$, DMAP, CH_2Cl_2, 96%; (h) CH_2=CHOTBS, 3.0 M $LiClO_4$, EtOAc, 86% from **143** and 78% from **144**; (i) allyltributyltin, (*S*)-BINOL, $Ti(O^iPr)_4$, 80%; (j) **145**, THF, −78 °C, 1 h, NaOH, H_2O_2, 3 h, 80%; (k) methoxyallene, $Pd(OAc)_2$, CH_3CN, reflux, 20 h, 83%; (l) 0.1 M $Cl_2(PCy_3)_2Ru$=CHPh, CH_2Cl_2, rt, 36 h, 85%.

and **141**, key intermediates in the synthesis of **139** (Scheme 38).[46] The C-9 chiral center was established using an asymmetric allylation, and the stereochemistry at C-11 came from (*S*)-**1**.

In the total synthesis of **139** starting from (*S*)-citronellal (**1**), the tributylstannane **141** reacts with aldehyde **146** in a macrolactonization step. The chiral center at C-9 was established using the chiral Brown borane **147**, while the configuration at C-11 came from (*S*)-**1**. In contrast to the procedure previously described, the chiral allylation was the first step in the synthesis of fragment **141**. Further, it should be noted that the authors used a very elegant procedure to selectively oxidize the isoprene fragment in compound **148**. Using *m*-CPBA and acidic periodate, they selectively epoxidized the unactivated isoprenic olefin, in spite of the presence of allylic heteroatoms. The critical fragment assembly between **146** and **141** was performed with good stereocontrol, and afforded a 3:1 mixture of diastereomers favoring the (−)-laulimalide (**139**) stereochemistry at C-15.

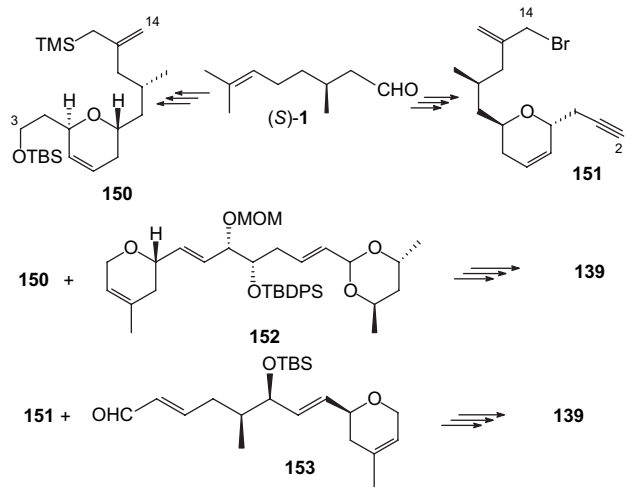
A closely related strategy starting from (*S*)-**1** was employed by Mulzer and co-workers[47] and Gallager, Jr. and co-workers[48] to prepare laulimalide and its analogs (Scheme 39).



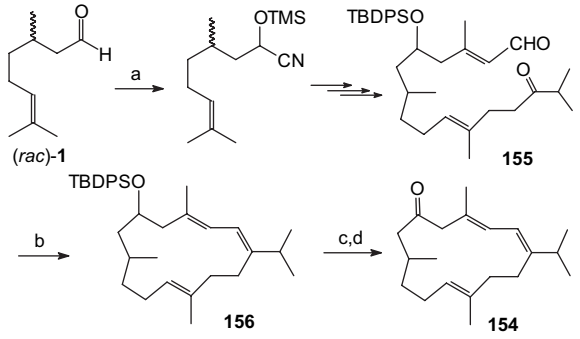
Scheme 38. Reagents and conditions: (a) (1) −78 °C, **147**, 1 h, then 25 °C; (2) 3 N NaOH, 30% H_2O_2, reflux, 1 h; (b) (1) NaH, $BrCH_2CO_2H$, THF, 97%; (2) CH_3CCOCl, Et_3N, THF, −78 to 0 °C, (*S*)-5-lithio-4-isopropyl-oxazolidin-2-one, 89%; (c) (1) $NaN(SiCH_3)_2$, THF, −78 to −45 °C, iodide **149**, 86%; (2) $LiBH_4$, MeOH, Et_2O, 0 °C; (d) (1) $(COCl)_2$, DMSO, Et_3N; (2) $(C_6H_5)_3P{=}CH_2$, 66% (three steps); (e) $(Cy_3P)_2Cl_2Ru{=}CHC_6H_5$, CH_2Cl_2, 40 °C, 85%; (f) (1) *m*-CPBA, $HClO_4$, $NaIO_4$; (2) $Me_2N{=}CH_2I^-$, 84% (two steps); (3) $NaBH_4$, $CeCl_3$, 78%; (g) (1) MsCl, Et_3N, CH_2Cl_2; (2) Bu_3SnLi, THF, 85% (two steps); (h) (1) Me_3Al, CH_2Cl_2, 3:1, 72% major isomer; (2) TBSOTf, 2,6-lutidine, 97%; (i) DDQ, H_2O, CH_2Cl_2, 90%; (j) (1) MnO_2, 91:9 *Z*/*E*; (2) $NaClO_2$, 75% (two steps); (k) (1) DEAD, $(C_6H_5)_3P$, THF, −20 °C, 46%; (2) Et_3N/3HF, CH_3CN, 75%.

Both syntheses involve a convergent protocol where the fragments C_3–C_{14} (**150**)[47] and C_2–C_{14} (**151**)[48] were coupled, respectively, with **152** and **153** affording, after a macrolactonyzation step, laulimalide and its analogs.

The first total synthesis of (1*E*,3*E*,11*E*)-cembra-1,3-11-trien-6-one (**154**), an important marine cembrane ketone isolated from *Eunciea calyclulata*, was performed starting from (*rac*)-citronellal (Scheme 40).[49] The key step in the synthesis was the intramolecular macrocyclization induced by low valent titanium on **155** to afford protected alcohol **156** that was further oxidized to **154**. The overall yield of the synthesis was of 6.6% (11 steps from citronellal).

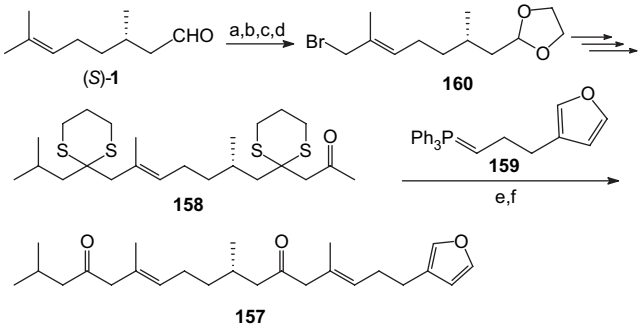


Scheme 39.



Scheme 40. Reagents and conditions: (a) Me_3SiCN, KCN/18-crown-6, 0 °C, 30 min, 100%; (b) $Zn/TiCl_4$, Py, DME, reflux, 30 h, 62%; (c) $^nBuN^+F^-$, THF, rt, 36 h, 91%; (d) PCC, silica gel, CH_2Cl_2, rt, 10 min, 90%.

A convergent synthesis of (−)-idiadione (**157**), a furanoses-terterpene isolated from marine sponge *Spongia idia*, was developed from (*S*)-citronellal (**1**) and bromoperillene (Scheme 41).[50] The optically active form of **157** was obtained after 10 steps and the absolute configuration of the natural product was determined to be 11*S*. The key step in the synthesis of **157** was the Wittig reaction between the diketone **158** and the ylide **159**, derived from bromoperillene.



Scheme 41. Reagents and conditions: (a) ethyleneglycol, benzene, *p*-TsOH, reflux; (b) SeO_2, 70%, ^{t}BuOOH, CH_2Cl_2, rt; (c) $NaBH_4$, MeOH, rt, 50% (three steps); (d) CBr_4, Ph_3P, THF, rt, 82%; (e) Wittig reagent (**159**), THF, −30 °C, 40%; (f) $HgCl_2$, $CaCO_3$, MeCN, H_2O, rt, 46%.

Integerrimine (**161**), usaramine (**162**), and swazine (**163**, Fig. 10) belonging to the pirrolizidine alkaloids group, those

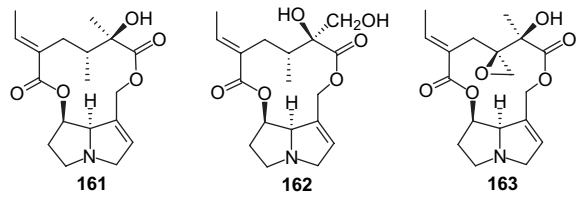
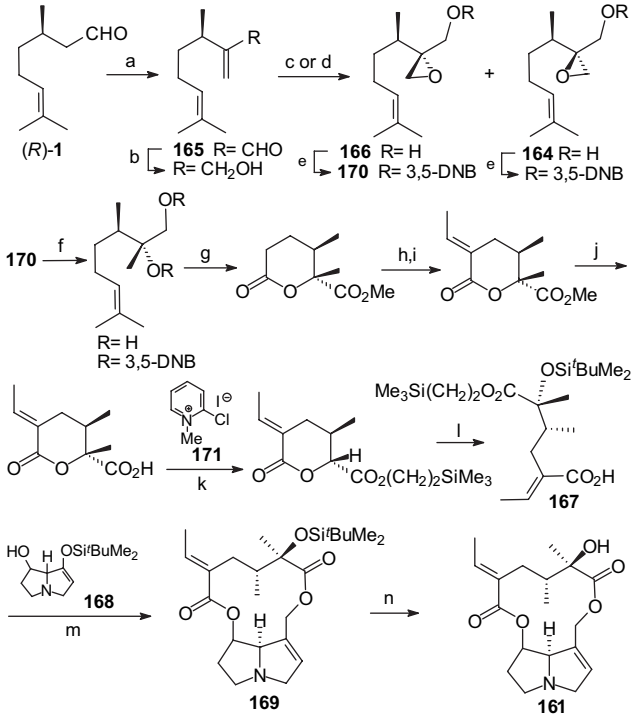


Figure 10.

are widespread in nature, especially among plants of the *Senecio* family. These macrocyclic dilactones have a high level of hepatotoxicity and possess serious risk to human and animal health, since ingestion of these alkaloids from dietary sources has proved fatal.

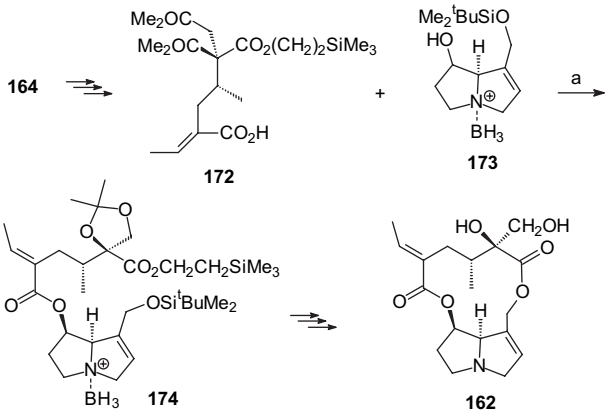
(*R*)-Citronellal (**1**) was used to prepare the epoxide **164**, a key intermediate in a synthetic route to prepare **161** and **162** (Scheme 42).[51] Alkylation of the lithium enolate derived from **1** with Eschenmoser's salt, followed by methylation of the resulting amine and subsequent treatment with aqueous $NaHCO_3$, gave **165** in 78% overall yield (Scheme 42). After several steps, epoxide **164** and its diastereomer **166** were obtained. After eight steps, the necic acid derivative **167** was



Scheme 42. Reagents and conditions: (a) LDA, $CH_2{=}N^+Me_2I^-$, MeI, THF, $NaHCO_3$, 78%; (b) $NaBH_4$, $CeCl_3$, MeOH, 95%; (c) cumene hydroperoxide, (−)-DIPT, $Ti(O^iPr)_4$; CH_2Cl_2, −5 °C, overnight, −20 °C, 1 h, 69% (43/44 ratio=3:1); (d) similar to step 'c', using (+)-DIPT, 81% (43/44 ratio=4:96); (e) 3,5-dinitrobenzoyl chloride, Py, 4 h, 98%; (f) (1) $LiAlH_4$, THF, rt, 15 h; (2) 3,5-dinitrobenzoyl chloride, Py, rt, 72 h, 65% (two steps); (g) (1) $RuCl_3{\cdot}3H_2O$, CCl_4/MeCN/H_2O, $NaIO_4$, rt, 24 h; (2) K_2CO_3, MeOH; (3) HCl; (4) $RuCl_3{\cdot}3H_2O$, HIO_6; (5) CH_2N_2, 55%; (h) (1) LDA, CH_3CHO; (2) Ac_2O, Et_3N, DMAP; (i) DBU, 50% (four steps); (j) LiOH, H_2O; (k) $Me_3Si(CH_2)_2OH$, **171**, CH_2Cl_2, 0 °C, then rt, overnight, 90%; (l) (1) LiOH, H_2O_2, THF, 0 °C, 1 h, then rt, 3 h; (2) TBDMSOTf, CH_2Cl_2, 0 °C, 1 h; (3) AcOH, THF/H_2O, rt, 8 h, 52% (three steps); (m) (1) $(EtO)_2POCl$, THF, Et_3N, 0 °C, then rt, 3 h; (2) **168**, THF, DMAP, ^{n}BuLi, 0 °C, then rt, 5 h; (3) NH_4F, MeOH, 60–65 °C, 4 h; (4) MsCl, CH_2Cl_2, Et_3N, 0 °C, 30 min; (5) $^n Bu_4NF$, MeCN, 0 °C, 30 min, 26%; (n) HF, MeCN, rt, 12 h, 67%.

obtained in high stereoisomeric purity. The acyl phosphate derived from **167** was then used for esterification of **168**, the *tert*-butyldimethylsilyl ether of retronecine, to afford the macrocyclic diester **169**, which was deprotected to give (−)-integerrimine (**161**).

The epoxide **164**, obtained according to Scheme 42, was transformed to *tert*-butyldimethylsilyl ester **172** by several steps. Coupling of **172** with the retronecine borane **173** afforded **174** that was, after several steps, transformed to (+)-usaramine (**162**, Scheme 43).

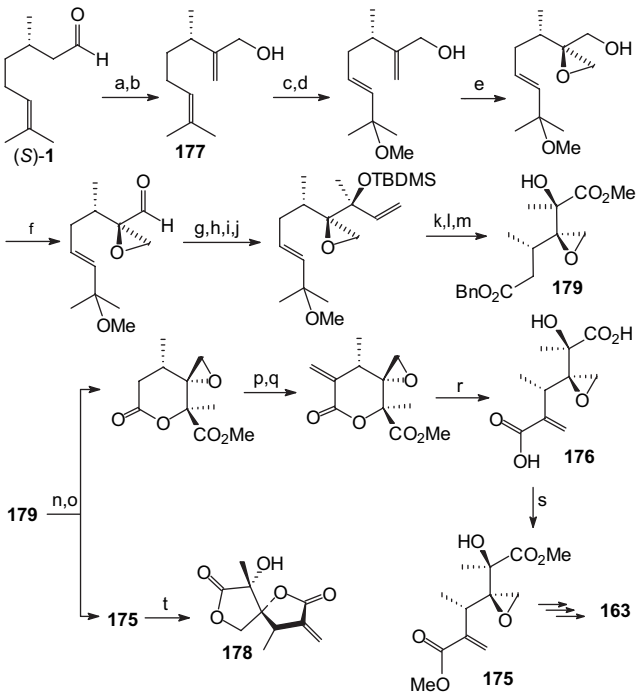


Scheme 43. Reagents and conditions: (a) (1) ^{n}BuLi, DMAP, (2) **172**, $(EtO)_2$-POCl, (3) NH_4F.

The synthesis of dimethyl swazinecate (**175**), a major component of pyrrolizidine alkaloid swazine, and of the swazinecic acid (**176**) were completed starting from (*S*)-citronellal (**1**, Scheme 44).[52] These compounds are among the more complex members of the pyrrolizidine alkaloids, and analogously to the macrocyclic lactones cited above, many of them possess toxic properties that cause serious risk to human and animal health. (*S*)-Citronellal (**1**) was converted to allylic alcohol **177**, with retention of configuration, via α-methylenation followed by Luche reduction in 87% yield (two steps). After several steps, the dimethyl swazinecate (**175**) and the swazinecic acid (**176**) were obtained. The original configuration of (*S*)-**1** at the carbon-3 was maintained in the final products. This synthesis was used to confirm the absolute stereostructure of (−)-swazine through its conversion to the spirodilactone **178** upon treatment of the synthetic dimethyl swazinecate (**175**) with hot sulfuric acid.

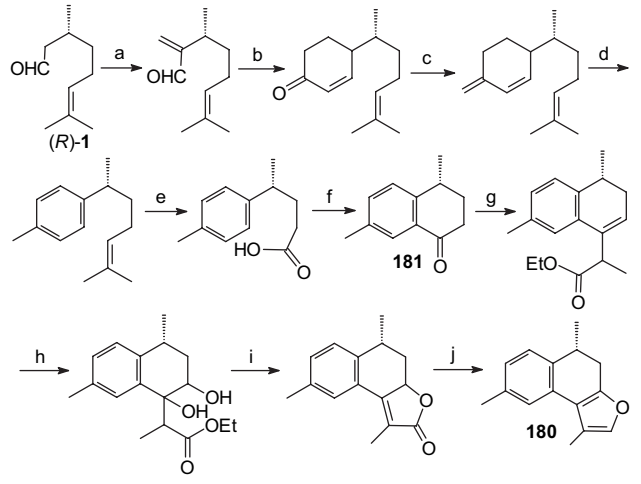
Laevigatin (**180**) is a naturally occurring terpene isolated from *Eupatorium laevigatum*, which has an unusual skeleton. The first enantiospecific synthesis of **180** was achieved starting from (*R*)-citronellal (**1**, Scheme 45).[53] Optically active α-tetralone **181**, the key intermediate, is obtained in good yield after six steps. Besides the lack of experimental details, the authors report that all the 10 reaction steps are very simple, mild, and proceed with excellent yields.

Isoiridomyrmecin (**182**) and related compounds, as iridodial (**183**), were isolated from different species of ants of the genus *Iridomyrmex* and it is probable that iridodial is the biological precursor of **182** and its epimers. A very short synthesis of both epimers of **182** was described starting from (*R*)- and (*S*)-**1** (Scheme 46).[54] Bio-assays demonstrated

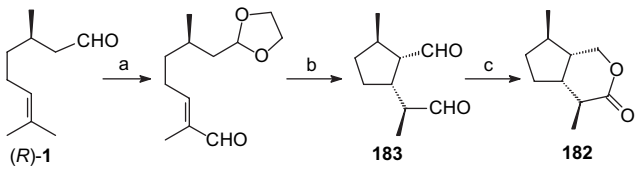


Scheme 44. Reagents and conditions: (a) LDA, $CH_2{=}N^+Me_2I^-$, MeI, $NaHCO_3$, 94%; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, 93%; (c) PhSeCl, $NaHCO_3$, THF/MeOH; (d) H_2O_2, $NaHCO_3$, THF/H_2O, 82% (two steps); (e) ^{t}BuOOH, Ti(O^iPr), (+)-DIPT, CH_2Cl_2, 92%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 95%; (g) vinylmagnesium bromide, THF, −78 °C, 72%; (h) Dess–Martin periodinane, 100%; (i) methyl magnesium bromide, Et_2O, −78 °C, 60%; (j) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, −35 °C, 76%; (k) O_3, $(CF_3CO)_2O$, BnOH/CH_2Cl_2, $NaHCO_3$, Et_3N, −78 °C; (l) $NaClO_2$, ^{t}BuOH, $Me_2C{=}$CHMe; (m) CH_2N_2, Et_2O, 65% (four steps); (n) H_2, Pd/C; (o) 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent), 99% (two steps); (p) LDA, CH_2O, 55%; (q) MsCl, Et_3N, 96%; (r) KOH, MeOH/H_2O; (s) CH_2N_2, Et_2O, 63% (two steps); (t) H_2SO_4, THF, heat.

that there is no difference in the insecticidal activity of natural iridomyrmecin and the two epimeric synthetic iridolactones **182**.

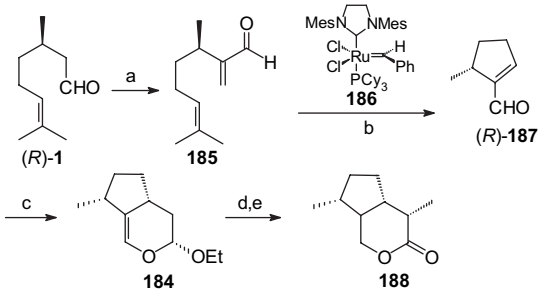


Scheme 45. Reagents and conditions: (a) HCHO, piperidine acetate reflux; (b) methylacetoacetate, MeOH, MeONa, reflux; (c) $(Ph)_3PCH_3I$, ^{n}BuLi, THF, 0 °C, 80%; (d) sulfur, DMF, reflux, 70%; (e) OsO_4 (cat.), Jones reagent, rt, 84%; (f) TFA, TFAA, 0 °C, 80%; (g) ethylbromopropionate, Zn, H^+, 78%; (h) OsO_4, NMO, CH_3CN, 80%; (i) TsOH, benzene, reflux, 73%; (j) DIBAL-H, THF, −40 °C, 77%.



Scheme 46. Reagents and conditions: (a) (1) $HOCH_2CH_2OH$, benzene, *p*-TsOH, reflux, 2 h; (2) SeO_2, EtOH, 50 °C, 2 h, then 95–100 °C, 24 h (26%, two steps); (b) (1) 50% aq AcOH, N_2, reflux; (2) 10% aq HCl, acetone, N_2, reflux; (c) (1) 2 N aq KOH, 70 °C, 1 h, (2) 8 N AcOH, 0 °C, 12.5%.

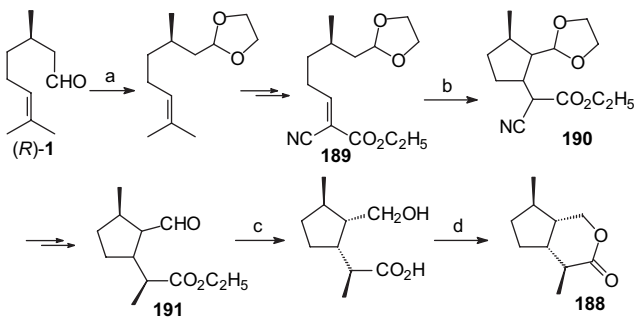
A ring closing metathesis (RCM) followed by an inverse electron demand hetero-Diels–Alder (HDA) reaction catalyzed by tridentate (Schiff base) Cr(III) complex was used in the stereoselective synthesis of the natural iridoid product **184** (Scheme 47).[55] In the first step of this elegant synthesis, (*R*)-citronellal (**1**) was used to obtain the enantio-enriched 2-methylene aldehyde **185** by a single-step route. Subsequently **185** underwent a RCM with Grubbs's catalyst (**186**) to afford the unsaturated aldehyde **187**.



Scheme 47. Reagents and conditions: (a) Eschenmoser's salt, TEA, CH_2Cl_2; (b) CH_2Cl_2, 12 h, 40 °C, **186** (5 mol %), 80%, 97.5% ee; (c) ethyl vinyl ether, (Schiff base) Cr(III) complex (5 mol %), 4 Å MS, 2 days, 85%; (d) H_2, PtO_2, EtOAc, 12 h, quant.; (e) (1) cat. *p*-TsOH, acetone/H_2O (1:1), 24 h; (2) PCC, CH_2Cl_2, 16 h, 80% (three steps).

The hetero-Diels–Alder reaction between **187** and ethyl vinyl ether promoted by a Schiff base yielded the pyran derivative **184** that was then oxidized to **188**. Since both enantiomers of citronellal are produced commercially, this represents a practical route to both enantiomers of **188**.

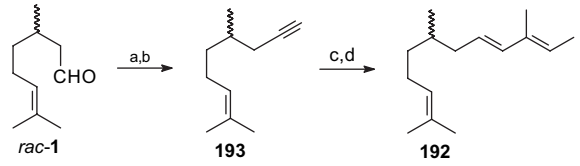
Another route to afford (+)-isoiridomyrmecin (**188**), starting from (*R*)-citronellal (**1**), was serendipitously developed by studying the transformation of ethyl-2-cyano-6-methyl-8,8-ethylenedioxyoct-2-enoate (**189**, Scheme 48).[56] During the assignment of the configuration of the cyanoacetate



Scheme 48. Reagents and conditions: (a) ethylene glycol, benzene, *p*-TsOH, reflux, 2 h; (b) *p*-TsOH, excess PhCHO, reflux, 17 h, 80%; (c) (1) $NaBH_4$, MeOH; (2) NaOH solution; (d) dil AcOH (pH 5).

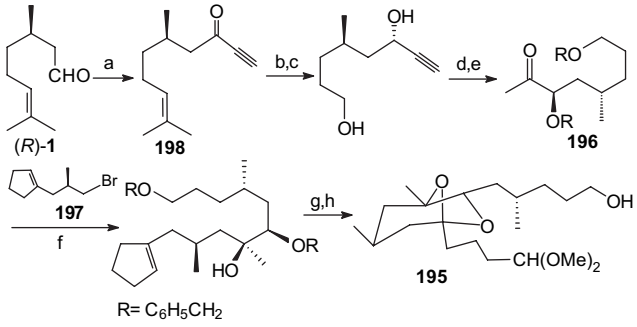
acetal **190**, the methyl α-(2-formyl-3-methylcyclopentyl)-propionate (**191**) was incidentally converted to (+)-isoiridomyrmecin (**188**).

(±)-Carrapatriene (**192**, Scheme 49) is a conjugated diene isolated from the oil of *Ocotea carrapi*, a native tree from Colombia. The oil of this plant is used in local remedies to treat a wide variety of diseases including cancer. A short and selective synthesis of its naturally occurring 2*E*-isomer was described starting from racemic citronellal (Scheme 49).[57] The synthetic strategy involved the conversion of *rac*-(**1**) to the 4,8-dimethylnon-7-en-1-yne (**193**), via a Corey–Fuchs homologation. The key step in this synthesis is the Susuki coupling of the *E*-vinyl borane derived from **193** with *E*-2-bromobut-2-ene, giving **192** in an overall yield of 36% (Scheme 49). An alternative route using Wittig reaction was also described.[57] However, here (±)-carrapatriene was obtained as an inseparable 2:1 mixture with its 2*Z*-isomer.



Scheme 49. Reagents and conditions: (a) CBr_4, PPh_3, Zn; (b) ^{n}BuLi (2.1 equiv), 64% (two steps); (c) catecholborane, THF; (d) *E*-2-bromobut-2-ene, $Pd(PPh_3)_4$ (5 mol %), NaOEt, benzene, reflux, 56% (two steps).

Palytoxin (**194**, Fig. 11) is a complex natural marine product that has a complex structure. Studying its stereochemistry, the bicyclic ketal **195** was synthesized in its optically active form starting from (*R*)-citronellal (**1**, Scheme 50).[58] The ketal **195** played a central role in the determinination of the stereochemistry of a part of palytoxin and was synthesized in eight steps from (*R*)-**1** with an overall yield of about 21%, where the key step was the reaction of **196** with the bromide **197**.



Scheme 50. Reagents and conditions: (a) acetylene, ^{n}BuLi, THF, −78 °C, followed by Jones oxidation, 74%; (b) O_3, 1.5 equiv MeOH, Sudan Red 7B, CH_2Cl_2, −78 °C, followed by treatment with $(Me)_2S$, −78 °C to rt; (c) $LiAlH_4$, (+)-Darvon alcohol, Et_2O, −78 °C, $C_6H_5CH_2Br$, NaH, THF/DMF (4:1), 0 °C to rt; (e) $HgCl_2$, H_2O/MeOH (1:250), 60 °C, 43% overall yield from **198**; (f) bromide **197**, Mg, I_2, THF, reflux, followed by addition to ketone **196** at −78 °C; (g) Li, NH_3(l), THF; (h) O_3, MeOH, −78 °C, followed by treatment with camphorsulfonic acid, $(Me)_2S$, −78 °C to rt, 85%.

Starting from (*R*)-citronellal (**1**), *trans* and *cis*-*p*-menthenolide (**199a** and **199b**) and menthofuran (**200**) were synthesized using readily available materials (Scheme 51).[59] Their terpenoid *exo*-methylene lactone and furane units are present in a vast number of natural compounds, like elemanolides and other cytotoxic sesquiterpene like *exo*-α,β-unsaturated γ-butyrolactones. The key step in the synthesis of **199** is the use of the regioselective allylic oxidation of *trans*- and *cis*-acetate **201** using *tert*-butylhydroperoxide/SeO_2 (step e, Scheme 51) followed by treatment with active MnO_2 (**202b**, step f, 65%) or Ag_2CO_3 (**202a**, step g, 48%). The menthofurane **200** was obtained from isopulegone (**203**) in 52% yield.

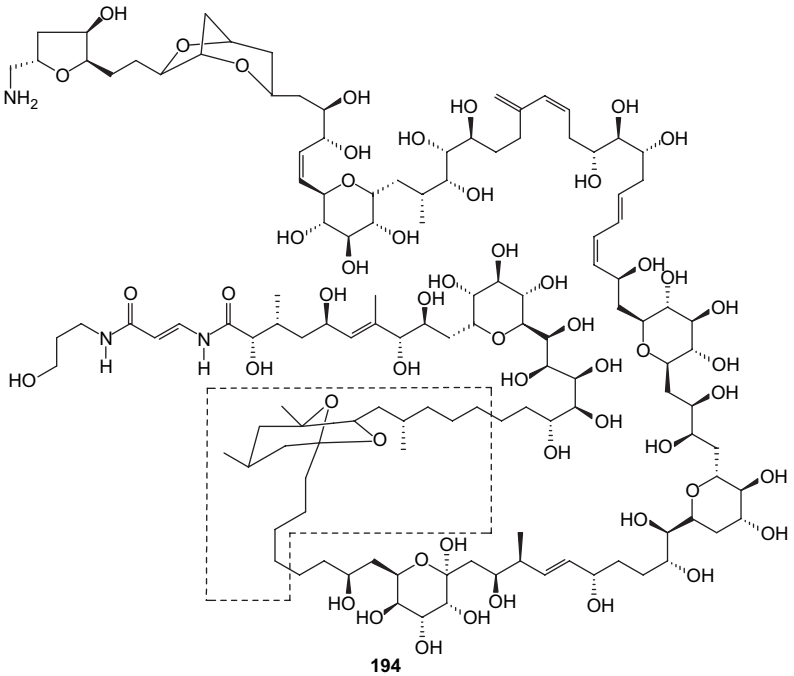
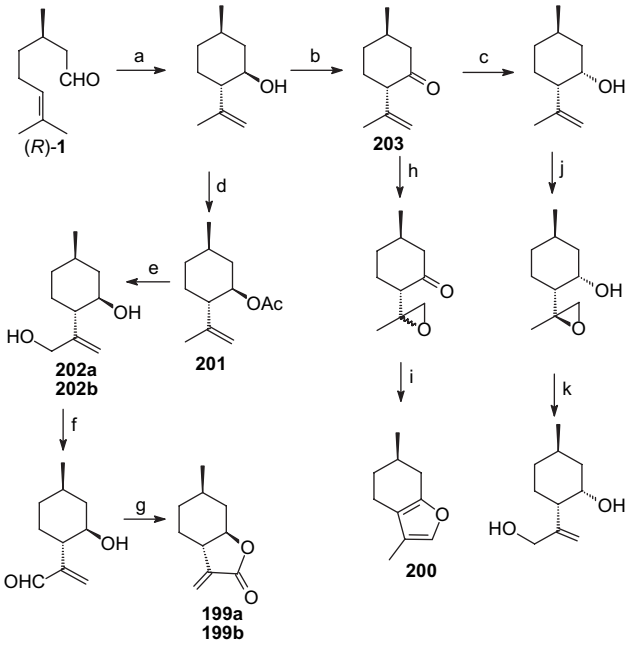


Figure 11. Palytoxin.



Scheme 51. Reagents and conditions: (a) $SnCl_4$, CH_2Cl_2, −10 °C, 30 min, 77%; (b) Jones reagent, 0 °C, 82%; (c) (1) L-Selectride, THF, −78 °C, 15 min, then rt, overnight, (2) H_2O_2, NaOH, 88%; (d) Ac_2O, Py, benzene, rt, 36 h, 65%; (e) (1) ^{t}BuOOH, SeO_2, rt, 36 h; (2) $LiAlH_4$, 0 °C, ether, then rt, overnight, 68%; (f) MnO_2, ether, rt, 2 h; (g) Ag_2CO_3, benzene, 8 h, 48%; (h) MCPBA, benzene, rt, 20 h; (i) KOH, MeOH, rt, 4 h, 52%; (j) ^{t}BuOOH, $VO(acac)_2$, benzene, rt, 4 h; (k) LDA, rt, 60 h, 65%.

Both vitamin K_1 (**204**) and natural vitamin E (**205**) have a closely related polymethyllated side chain with multiple chiral centers (Fig. 12). Pure (*R*)- and (*S*)-citronellal (**1**) were used in the enantioselective preparation of three isomers of (*E*)-vitamin K_1 (phylloquinone, Scheme 52),[60] while (*R*)-citronellal was employed to prepare (2*R*,4′*R*,8′*R*)-α-tocopherol (natural vitamin E, Scheme 53).[61] The two described syntheses of these vitamins are convergent, where citronellal was converted to a phytol derivative, prior to its reaction with the bicyclic building block present in the vitamin structures.

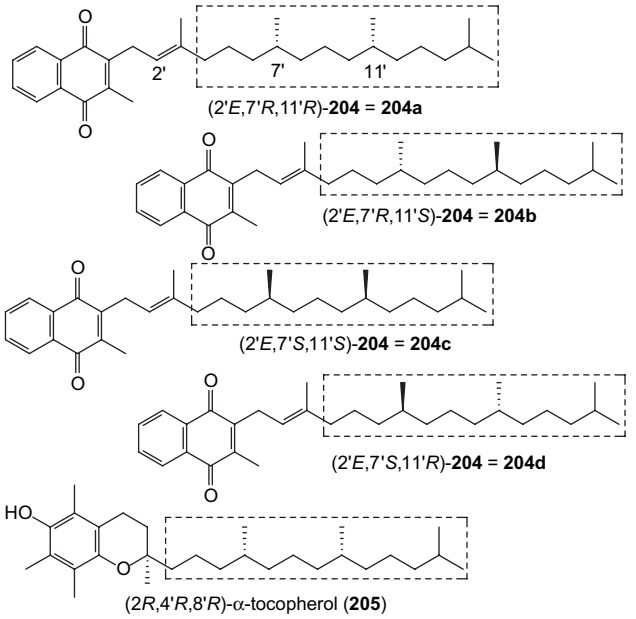
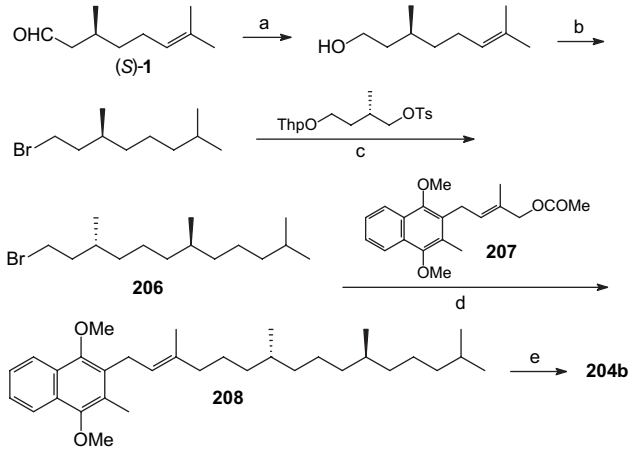
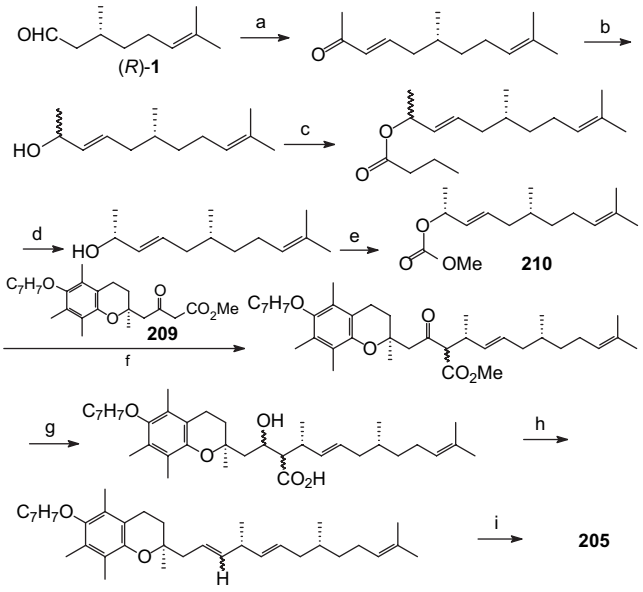


Figure 12. Structures of stereoisomers of (*E*)-vitamin K_1 (**204a–d**) and natural vitamin E (**205**) and their similar side chains.



Scheme 52. Reagents and conditions: (a) $NaBH_4$, EtOH, 0 °C, 93%; (b) (1) H_2, *Raney*-Ni, 91%; (2) NBS, PPh_3, CH_2Cl_2, 90%; (c) (1) Mg, THF, Li_2CuCl_4, 89%; (2) EtOH, Py, TsOH, 60 °C, 91%; (3) NBS, PPh_3, CH_2Cl_2, 93%; (d) Mg, THF, Li_2CuCl_4, 79%; (e) $Ce(NH_4)_2(NO_3)_6$, CH_3CN, benzene, H_2O, 77%.



Scheme 53. Reagents and conditions: (a) acetone, aq KOH, 6 h, reflux, 87%; (b) $(^iPrO)_3Al$, ^{i}PrOH, toluene, 5.5 h, 99%; (c) butyric anhydride, Py, DMAP, 5 °C, 1 h, then rt, 3 h, 94.1%; (d) hydrolase (lipase ex *P. fluorescens*); (e) (1) ^{n}BuLi, THF, 90 min; (2) methyl chloroformate, rt, overnight; (f) NaH, $Pd[P(C_6H_5)_3]_4$, THF, −78 °C to rt, 96%; (g) (1) $NaBH_4$, MeOH, 48 h, 99.9%; (2) aq NaOH, THF, MeOH, reflux, overnight, 100%; (h) di-*tert*-butyldimethylformamide acetal, toluene, 60 °C, overnight, 50%; (i) (1) 500 psi H_2, 5% Pt/C, EtOAc, rt, 4 h, 99.2%; (2) 60 psi H_2, 10% Pd/C, EtOH, THF, 4 h, 86%.

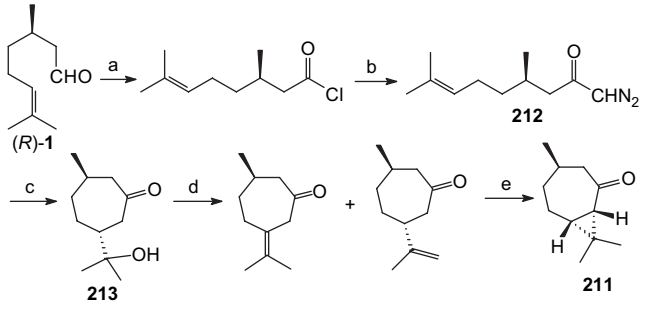
The key step in the synthesis of (2′*E*,6′*R*,11′*S*)-vitamin-K_1 was the Schlosser-type coupling between the Grignard reagent derived from bromide **206** and the allylic benzoate **207**, affording the dihydro-vitamin-K_1 (**208**). Reaction with $Ce(NH_4)_2(NO_3)_6$ converted **208** to **204b** in 77% yield.[60]

The stereoisomers **204c** and **204d** were synthesized by the same procedure described above. The naturally occurring isomer **204a** was obtained by an O-alkylation/rearrangment

procedure using natural phytol as starting material instead of bromide **206**. There are three additional procedures described to synthesize the polymethylated side chain of α-tocopherol (**205**) and vitamin K_1 (**204**).[62] In two of these syntheses, (*R*)-citronellal (**1**) was converted to phytol[62a,b] and also into (3*R*,7*R*)-3,7,11-trimethyldodecanal.[62c]

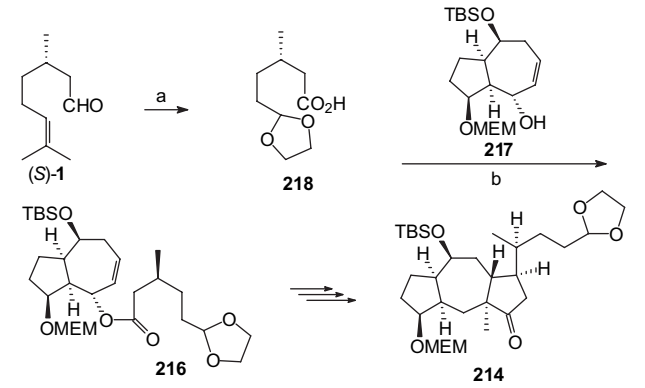
(*R*)-Citronellal (**1**) was also used in a new convergent synthesis of natural vitamin E (**205**), by reaction with methyl (*S*)-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl) acetate (**209**, Scheme 53).[61] The key step in this synthesis is a lipase catalyzed kinetic resolution to control the new chiral center at **210**, derived from *R*-(**1**).

Starting from (*R*)-citronellal (**1**), a versatile method for the synthesis of the bicyclo[5.1.0]octanone (**211**), an important sesquiterpene synthon was described (Scheme 54).[63] The key step of this preparation is an intramolecular cyclization of diazoketone **212**, obtained from **1** after three steps (48% yield), to afford the chiral cycloheptanone **213**. After an elimination–cyclopropanation sequence, **211** was obtained in 45% yield (Scheme 54).



Scheme 54. Reagents and conditions: (a) (1) Jones oxidation, 0 °C, 1 h, 80%; (2) $(COCl)_2$-Py, CH_2Cl_2, 0 °C to rt, 4 h, 90%; (b) CH_2N_2, ether, 0–5 °C, overnight, 60%; (c) (1) CF_3CO_2H, CH_2Cl_2, −20 °C, 30 min; (2) 10% KOH/MeOH, 30 min, 70%; (d) CH_3SO_2Cl, $N(C_2H_5)_3$, DMAP, CH_2Cl_2, rt, 3 h, 45%; (e) Ref. 63b.

The optically pure tricyclic compound (**214**, Scheme 55) is an advanced intermediate in the synthesis of ceroplastic acid (**215**, Fig. 13), a structurally elaborate ophiobolane sesterterpene with potent biological and phytological activities.[64]



Scheme 55. Reagents and conditions: (a) (1) $AgNO_3$, KOH; (2) O_3, DMS; (3) $(CH_2OH)_2$, 79%; (b) DCC, 4-pyrrolidinylpyridine, 72%.

In order to obtain **214**, the preparation of intermediate **216**, a bicyclic with six stereogenic centers was necessary. This

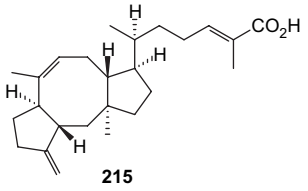


Figure 13. Ceroplastic acid (**215**).

was prepared by coupling the optically pure alcohol **217** with optically pure modified citronellic acid (**218**), obtained from (*S*)-**1** after three steps, using DCC in the presence of 4-pyrrolidinylpyridine.

Pyrrolostatin (**219a**, Fig. 14), a pyrrole isolated from *Streptomyces chrestomyceticus*, has an in vitro inhibitory activity against lipid oxidation comparable to that of the well-known antioxidant vitamin E. Natural pyrrolostatin (**219a**) contains a geranyl group at the 4-position and a carboxylic group at the 2-position, while its analog **219b** possesses a citronellyl group at the 4-position.[65]

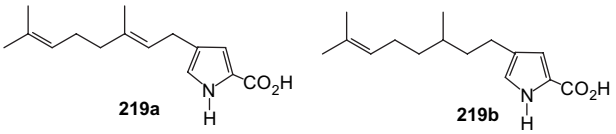
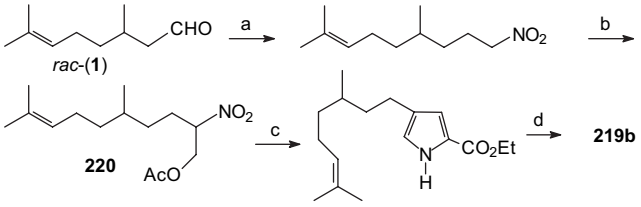


Figure 14. Pyrrolostatin (**219a**) and analog (**219b**).

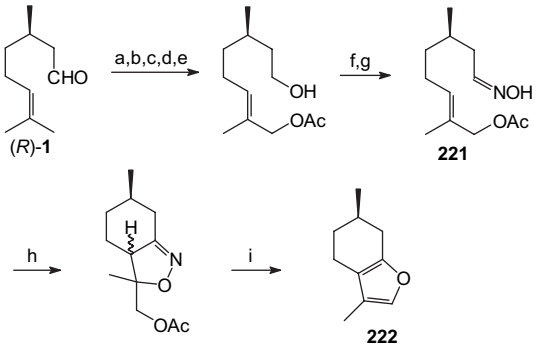
Although the synthesis of **219a** is rather difficult, its analog **219b** can be easily prepared starting from racemic citronellal (**1**, Scheme 56).[65] The key intermediate in this synthesis is the β-nitro acetate **220**, obtained in three steps from *rac*-(**1**) by a condensation–acetylation sequence in the presence of formaldehyde. In a preliminary experiment, **219b** presented a larger activity against lipid peroxidation than vitamin E and its analog **219a**.



Scheme 56. Reagents and conditions: (a) (1) CH_3NO_2, Et_3N, 24 h; (2) Ac_2O, Py, 2.5 h; (3) $NaBH_4$, DMSO, 2.5 h, 42%; (b) HCHO or CH_3CHO, base, Ac_2O, Py, 98%; (c) $CNCH_2CO_2Et$, THF/^{t}BuOH, DBU, 0 °C, 26 h, 18–61%; (d) LiOH/H_2, aq dioxane.

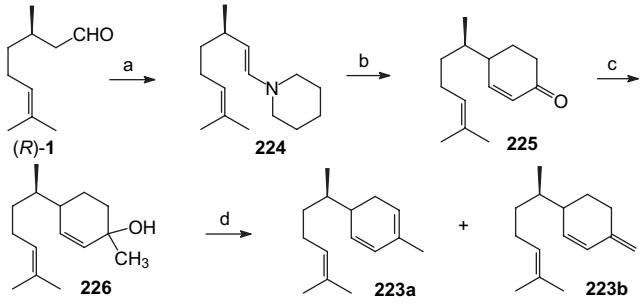
(*R*)-Citronellal (**1**) was used in the preparation of the oxime acetate **221**, a key compound in the synthesis of (+)-menthofuran (**222**). Usually obtained from peppermint oil, *Mentha piperita vulgaris* S. is important as a perfume and a synthetic intermediate in organic synthesis.[66] In this synthesis, the key step is fused furan construction based on an intramolecular nitrile oxide cycloaddition reaction with an overall yield of 31% (Scheme 57, nine steps from (*R*)-**1**).

Zingiberene (**223**), isolated from *Zingiber officinale*, is a mixture of the monocyclic sesquiterpenes **223a** and **223b**, where **223a** is the active component. A short synthesis of



Scheme 57. Reagents and conditions: (a) $NaBH_4$; (b) $^tBuMe_2SiCl$, imidazole, DMF; (c) SeO_2, ^tBuOOH; (d) Ac_2O, Py; (e) $^nBu_4NF$; (f) $(COCl)_2$, DMSO, Et_3N; (g) NH_2OH, HCl, AcONa; (h) 7% aq NaOCl, CH_2Cl_2; (i) (1) H_2, *Raney*-Ni, $(MeO)_3B$, MeOH, H_2O; (2) $LiOH·H_2O$, THF, H_2O; (3) *p*-TsOH, CH_2Cl_2.

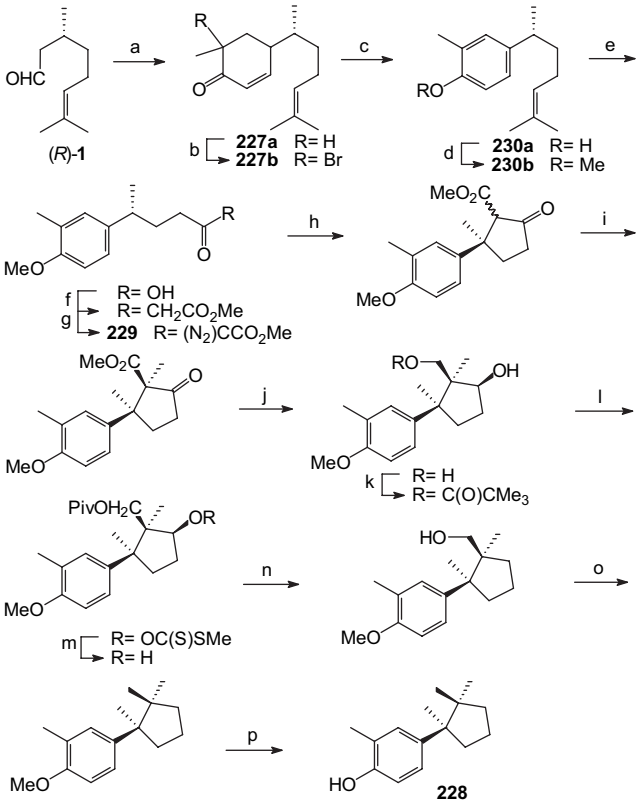
these components was described starting from (*R*)-citronellal (**1**, Scheme 58).[67] Here, the key step is Stork's enamine condensation between (*R*)-**1** and piperidine, resulting in enamine **224**. The treatment of **224** with methyl vinyl ketone followed by acetic acid yielded the α,β-unsaturated ketone **225**. After reaction of **225** with MeMgI, followed by treatment with oxalic acid, a mixture of **223a** and **223b** (**223a/223b** ratio=1.5:1) was obtained.



Scheme 58. Reagents and conditions: (a) piperidine, K_2CO_3; (b) $CH_2{=}CHCOCH_3$, acetic acid; (c) CH_3MgI; (d) oxalic acid.

The same protocol involving the chiral enone **227** and (*R*)-citronellal (**1**) was employed recently for the enantiospecific synthesis of (+)-β-herbertenol (**228**), a sesquiterpenoid isolated from *Herbertous* species and other liverworts (Scheme 59).[68] Herbertene-type sesquiterpenoids with an oxygenated aromatic six-membered ring, as in **228**, are potent antifungal, neurotrophics and lipid peroxidation inhibitors. The key step of the asymmetric synthesis of **228** is the use of Taber's protocol for the diazo decomposition of α-diazo-β-ketoester **229** by $Rh_2(OAc)_4$, to provide the five-membered ring with retention of the configuration at the chiral center (Scheme 59).

The intermediate sesquiterpenoids involved in the preparations described in Schemes 58 and 59 are closely related to several natural bisabolane sesquiterpenoids, like (−)-4-(1,5-dimethylhex-4-enyl)-2-methylphenol [(−)-**230a**].[69] A short and enantiospecific synthesis of (−)-**230a** was described starting from (*R*)-citronellal (**1**) and methyl isopropenyl ketone (**231**). This uses the same procedure described in Scheme 59, for the preparation of the enantiomer of the cyclic enone **227a**. The conversion of the phenol

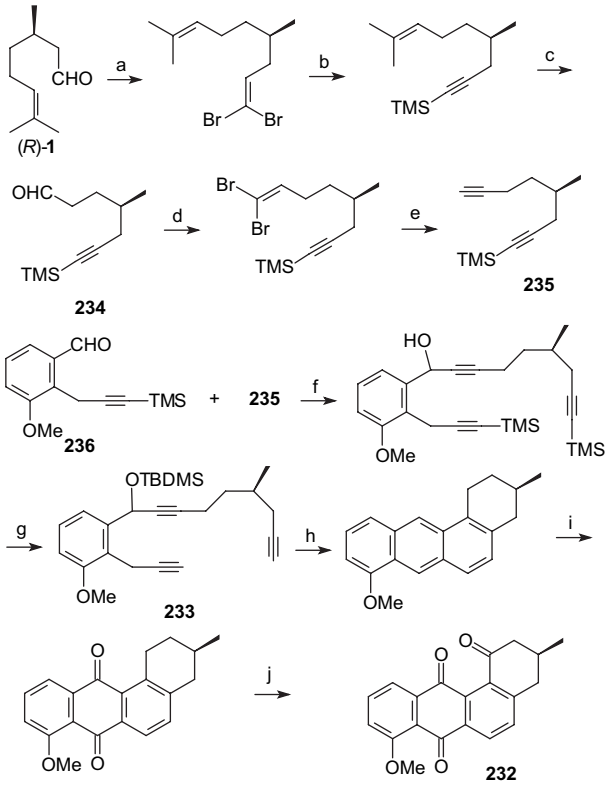


Scheme 59. Reagents and conditions: (a) (1) piperidine, K_2CO_3; (2) $CH_2{=}C(CH_3)COCH_3$ (**231**), acetic acid; (b) (1) LDA, THF, −78 °C, TMSCl; (2) NBS, THF, 0 °C, 0.5 h; (c) Li_2CO_3, LiBr, DMF, 135 °C, 4 h, 75% from **227a**; (d) K_2CO_3, Me_2SO_4, acetone, reflux, 12 h, 90%; (e) OsO_4 (cat.), Jones reagent, acetone, rt, 5 h, 80%; (f) (1) $SOCl_2$, CH_2Cl_2, reflux, 2 h; (2) Meldrum's acid, Py, CH_2Cl_2, 0 °C–rt, 2 h; (3) MeOH, reflux, 4 h, 78%; (g) Et_3N, MsN_3, CH_2Cl_2, −10 °C–rt, overnight; (h) $Rh_2(OAc)_4$ (cat.), CH_2Cl_2, rt, 40% (two steps); (i) K_2CO_3, MeI, acetone, rt, 85%; (j) $LiAlH_4$, THF, 0 °C–rt, 5h, 80%; (k) pivaloyl chloride, Et_3N, CH_2Cl_2, −10 °C to rt, 4 h, 65%; (l) NaH, CS_2, THF, 0 °C, 1.5 h, then MeI, rt, 5 h, 95%; (m) TBTH, AIBN (cat.), toluene, reflux, 2 h, 80%; (n) $LiAlH_4$, THF, rt, 2 h, 95%; (o) (1) PDC, CH_2Cl_2, 0 °C, 3 h; (2) NH_2NH_2–H_2O, diethyleneglycol, 150 °C, 4 h, 190 °C, 3 h, 73% (two steps); (p) BBr_3, CH_2Cl_2, −78 °C to rt, overnight, 93%.

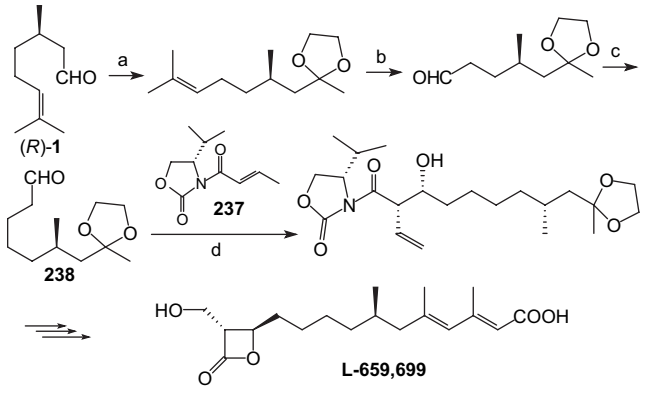
(−)-**230a** was achieved in 68% yield by $PdCl_2$ in ^tBuOH in the presence of Na_2CO_3 (4 equiv) at 80 °C.

(+)-Rubiginone B2 (**232**, Scheme 60) is an antibiotic angucylinone isolated from a strain of *Streptomyces griseorubiginosus*. It presents a potential vincristine-induced cytotoxicity against multi-drug-resistant tumor cells. A short enantioselective synthesis of (+)-**232** was reported using commercially available (*R*)-citronellal (**1**, 92% ee) as starting material (Scheme 60).[70] The key step in the synthesis was the intramolecular photocyclization of triyne **233** with 10% $CpCo(CO)_2$ in refluxing toluene under irradiation (tungsten lamp).

The naturally occurring β-lactone L-659,699, isolated from *Fusarium* sp., *Scopulriopsis* sp., and *Cephalosporin* sp. is a potent inhibitor of cholesterol biosynthesis. The key step in its synthesis involves a highly diastereoselective aldol condensation of chiral crotonate imide (**237**) with aldehyde **238** (Scheme 61).[71] The chiral center at C-7 was introduced via (*R*)-citronellal, which was used for the preparation of **238** (seven steps, overall yield of 9%).

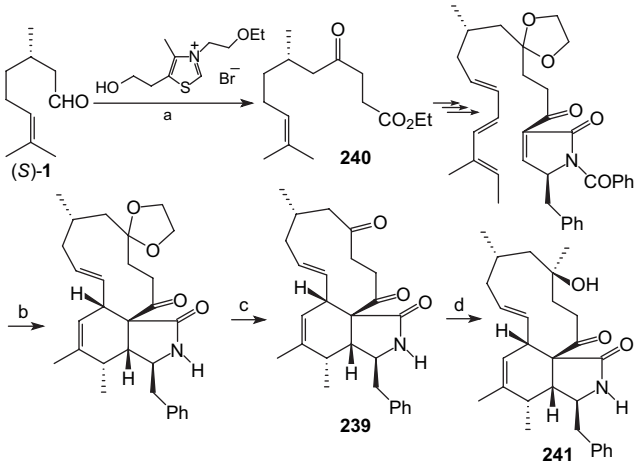


Scheme 60. Reagents and conditions: (a) 2 equiv CBr_4, 4 equiv PPh_3, CH_2Cl_2, 0 °C, 30 min, then **1**, 25 °C, 2 h; (b) (1) 2 equiv ^{n}BuLi, THF, −80 °C, 1 h; (2) 2 equiv TMS-Cl, −80 °C to rt, 18 h, 76% (two steps); (c) (1) O_3, CH_2Cl_2, −80 °C, 15 min; (2) Me_2S, AcOH, −80 °C to rt, 18 h; (d) 2 equiv CBr_4, 4 equiv PPh_3, CH_2Cl_2, 0 °C, 30 min, then **234**, 25 °C, 2 h; (e) (1) 2 equiv ^{n}BuLi, THF, −80 °C, 1 h; (2) H_2O, −80 °C to rt, 2 h, 74% (three steps); (f) ^{n}BuLi, **235**, THF, −80 °C, 1 h, then **236**, −80 to −30 °C, 4 h, 93%; (g) (1) NH_4F, Bu_4NHSO_4, CH_2Cl_2, rt, 48 h, 96%; (2) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 25 °C, 2 h, 95%; (h) 10% $CpCo(CO)_2$, toluene, reflux, *hν*, 4 h, 74%; (i) 8 equiv $[Ag(Py)_2]MnO_4$, CH_2Cl_2, 25 °C, 8 h, 62%; (j) *hν*, air, $CHCl_3$, 25 °C, 18 h, 67%.



Scheme 61. Reagents and conditions: (a) (1) CH_3MgI, 80%; (2) CrO_3–Py, CH_2Cl_2, 93%; (3) $HOCH_2CH_2OH$, *p*-TsOH, 38%; (b) O_3, Me_2S; (c) (1) $(EtO)_2POCH_2CO_2Et$, NaH, 47%; (2) H_2, Pd/C; (d) Bu_2BOTf, Et_3N, 66%.

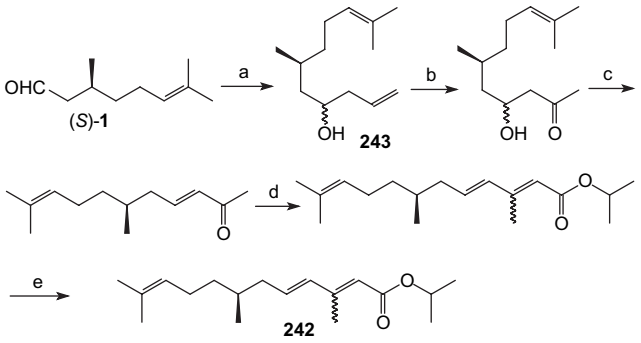
The key intermediate in the preparation of (16*S*)-16-methyl-10-phenyl[11]cytochalasa-6(7),13^t-diene-1,18,21-trione (**239**) is the γ-keto ester **240** that was obtained from the thiazolium salt catalyzed conjugate addition of (*S*)-citronellal to ethyl acrylate (Scheme 62).[72] Cytochalasa-1,18,21-trione (**239**) reacts with methyl magnesium chloride to afford the precursor of naturally occurring cytochalasin H (**241**).



Scheme 62. Reagents and conditions: (a) ethyl acrylate, dioxane, 58%; (b) (1) toluene, 80 °C, 16 h, 58%; (2) MeOH, aq NaOH, 84%; (c) aq HCl, THF, 20 h, rt, 80%; (d) MeMgCl, THF, 84%.

2.3. Synthesis of alycyclic compounds

S-(+)-Methoprene (**242**), an optically active juvenile hormone analog, was synthesized in six steps from (*S*)-citronellal (**1**, Scheme 63).[73] The key intermediate (6*S*)-6,10-dimethyl-1,9-undecadien-4*R*/*S*-ol (**243**) was obtained from the reaction of (*S*)-**1** with allyl magnesium chloride.

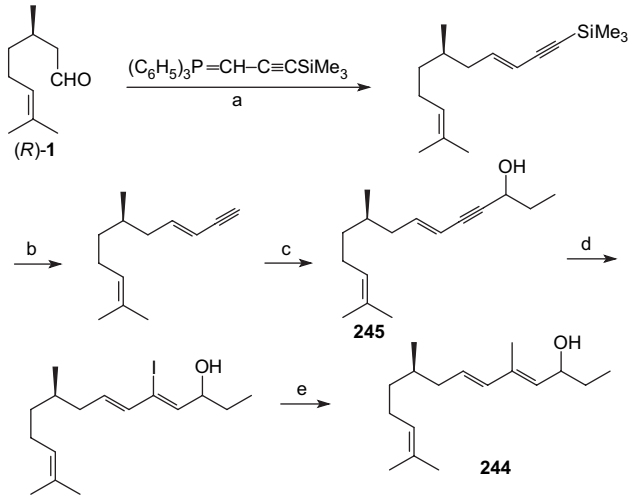


Scheme 63. Reagents and conditions: (a) $CH_2{=}CHCH_2MgCl$, Et_2O, 20 °C, 15 h, 79%; (b) O_2, $PdCl_2$, CuCl, DMF, H_2O; (c) TsOH, Na_2SO_4, benzene, reflux, 1 h, 60%; (d) isopropoxyethynylmagnesium bromide, Et_2O, −10 °C, Ar, 3 h, then 20 °C, 1 h, 80%; (e) (1) $Hg(OAc)_2$, MeOH, 5 °C, 1 h, then 20 °C, 24 h; (2) $NaBH_4$, 0 °C, aq NaOH, 70%.

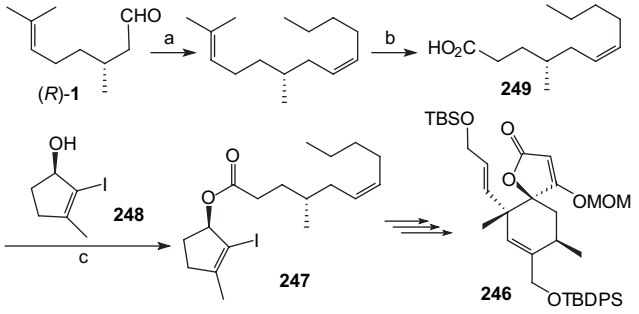
The (4*E*,6*E*)-5,9,13-trimethyl-4,6,12-tetradecatrien-3-ol (**244**) has juvenile hormone activity against the yellow mealworm, *Tenebrio molitor* (Scheme 64).[74] (*R*)-Citronellal was used as starting material for the synthesis of the key chiral propargylic alcohol derivative **245**.

Spirotetronate (**246**) was prepared to assign the stereochemistry of the quartromicins. The key compound **247** was obtained by coupling of (*R*)-2-iodo-3-methyl-2-cyclopentenol (**248**) with the acid **249** in the presence of DCC and DMAP (Scheme 65).[75] In a similar way, the epimer of **246** was synthesized starting from (*S*)-citronellal.

Stellettadine A (**250**, Scheme 66), a bisguanidinium alkaloid isolated from a marine sponge *Stelleta* sp., is an inducer of larval metamorphosis in ascidians. Mori and co-workers have described the convergent synthesis of both



Scheme 64. Reagents and conditions: (a) THF, ^{n}BuLi; (b) $(C_4H_9)_4NF\cdot 3H_2O$, DMF, 60%; (c) (1) ^{n}BuLi; (2) CH_3CH_2CHO, 66%; (d) (1) $LiAlH_4$, MeONa; (2) I_2, 74%; (e) $(CH_3)_2CuLi$.



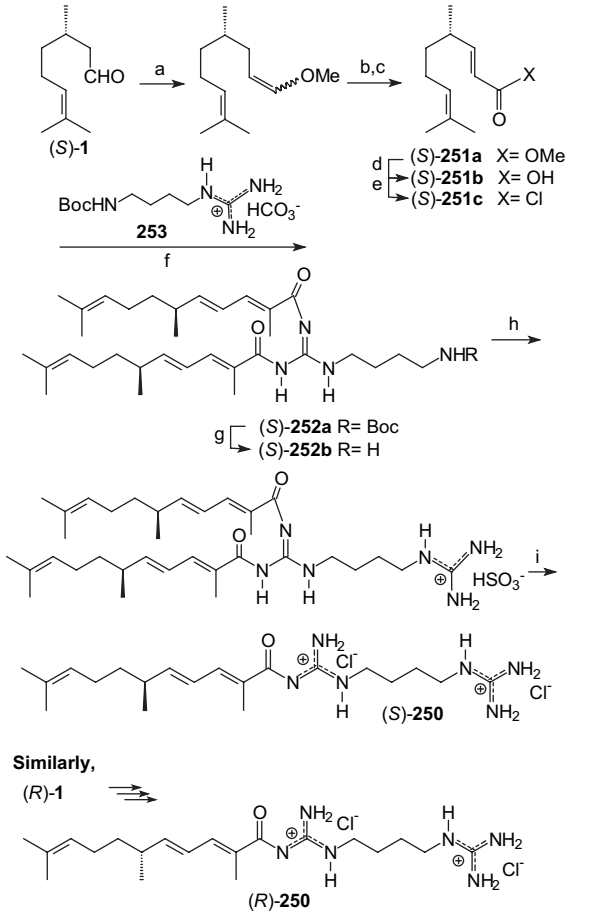
Scheme 65. Reagents and conditions: (a) $Ph_3PC_5H_{11}Br$, KHMDS, THF, 88%; (b) (1) Sharpless A.D.; (2) $NaIO_4$, THF/H_2O; (3) Jones oxidation, 80%; (c) (1) **248**, DCC, DMAP, CH_2Cl_2; (2) $^{n}Bu_3SnH$, AIBN, 64%.

enantiomers, starting from (*R*)- and (*S*)-citronellal (Scheme 66).[76] The key intermediate **251c** was obtained from (*S*)-citronellal after four steps (36% overall yield) and transformed to **252a** by reaction with **253**. The naturally occurring (*S*)-stellettadine dihydrochloride (**250**) was obtained after two more steps. The overall yield after nine steps was 13% based on (*S*)-**1**. For the synthesis of (*R*)-**250**, (*R*)-**1** was used in an analogous reaction, allowing the absolute configuration of naturally occurring **250** established as *R*.

3. Cyclization of citronellal to isopulegol

(−)-Isopulegol (**254**, Fig. 15) is a very important intermediate in the industrial production (Takasago process) of (−)-menthol (**255**, Fig. 15), which is widely employed in pharmaceuticals, agrochemicals, cosmetics, toothpastes, chewing gum, and toilet goods.[1a,4,6a,77] As only (−)-isopulegol (**254**) affords the correct configuration in **255**, its synthesis requires a high stereoselectivity.

The isopulegol preparation involves an ene type cyclization of (*R*)-citronellal (**1**), which occurrs with 100% atom economy and results in four possible stereoisomers: isopulegol (**254**), *neoiso*isopulegol (**256**), *neo*isopulegol (**257**), and



Scheme 66. Reagents and conditions: (a) $Ph_3P(Cl)CH_2OMe$, PhLi, Et_2O, 15 min, rt; (b) $Pd(OAc)_2$, $Cu(OAc)_2$, aq $NaHCO_3$, MeCN, rt, overnight, 48%, (two steps); (c) $Ph_3P{=}CMeCO_2Me$, C_6H_6, reflux, 1 h, 86%; (d) aq NaOH, MeOH, THF, rt, overnight, 87%; (e) $(COCl)_2$, 2-methylbut-2-ene, CH_2Cl_2, rt, 4 h, quant.; (f) **253**, TMSCl, CH_2Cl_2, $^{i}Pr_2NEt$, rt, then 40 °C, 5 h, 62%; (g) *p*-TsOH, 2-methylbut-2-ene, MeOH, rt, overnight, 84%; (h) $NH_2C(NH)SO_3H$, MeOH, Et_3N, rt, 1 h; (i) KOH, MeOH, 10 °C, 4 h, then HCl, 67% (two steps).

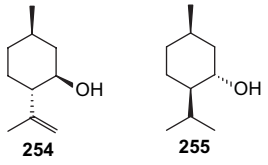
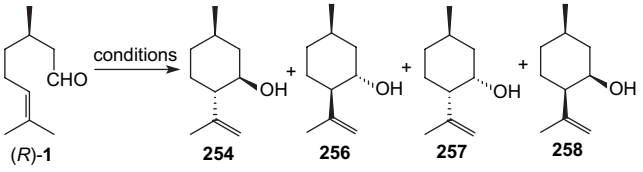


Figure 15. (−)-Isopulegol (**254**) and (−)-menthol (**255**).

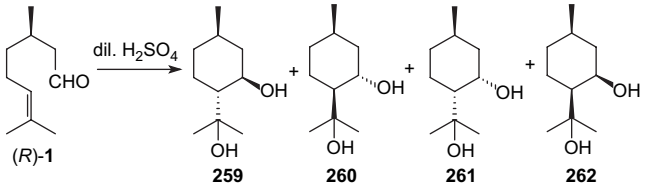
*iso*isopulegol (**258**).[78] Although (−)-isopulegol is economically more important, their isomers are also useful intermediates in total asymmetric synthesis[79] (Scheme 67).



Scheme 67. Isomers of isopulegol from ene-cyclization of (*R*)-citronellal (**1**).

Neat citronellal is converted to isopulegol by heating between 130 and 200 °C[27,80–86] or under the action of

ultraviolet light.[87] The thermal cyclization is accelerated by active carbon,[81] silica gel,[82,88] diatomaceous earth doped with SiO_2, metal oxides,[83] boric acid,[84] Ni sulfate in a H_2 stream,[85] or Cu–Cr and Cu–Cr–Mn catalysts.[86] The first described method for the acid catalyzed ene-cyclization of (*R*)-citronellal to (−)-isopulegol employed aqueous sulfuric acid.[89–93] However, this protocol is not efficient for the isopulegol synthesis, because a large amount of co-products, especially *cis*- and *trans*-*p*-menthane-3,8-diols (**259**–**262**) are formed by a concurrent Prins-type cyclization (Scheme 68). On the other hand, these glycols, which can be used as insect repellents[92] are also economically important.



Scheme 68. Isomers of *p*-menthane-3,8-diols from Prins-type cyclization of (*R*)-citronellal (**1**).

Due to their repellent effects, the stereoselective syntheses of menthane-3,8-diols still attracts the attention of both industrial[94] and academic chemists.[95] A variant of the Prins-type cyclization conditions was used to obtain up to 80% yield of the *p*-menthane-3,8-diol after stirring citronellal and H_2SO_4 at 55 °C for 10 h.[94] Aiming to improve the yields of isopulegol, a bromination/elimination sequence was employed, but the yields of isopulegols were poor (30% of a 3:1 mixture).[96] The use of superacids (FSO_3H/SO_2) was also described, but isopulegol was detected only as intermediate.[97] When citronellal was subjected to a fluorocyclization using HF–Et_3N complexes, 8-fluoro-isopulegols were the main products, while isopulegol was obtained as minor component of the crude reaction mixture.[98] Isopulegol, among the 6,7-epoxy derivate of citronellal, can also be prepared using peracids to promote the acid-catalyzed intramolecular cyclization of citronellal.[99]

Greater selectivity toward (−)-isopulegol was achieved using Lewis-acid catalysts. The first successful Lewis-acid catalyzed procedure was described by Nakatani and Kawashima nearly 30 years ago;[26] they employed $ZnBr_2$ as a catalyst and benzene as a solvent. The reaction was performed at 5–10 °C for 10 min and the cyclization product was obtained in 70% yield and 94% selectivity. The use of aqueous $ZnBr_2$ solution for the cyclization of citronellal (Takasago process) improved the yield of isopulegol to 92%.[100] More recently, Takasago Co. has patented the use of tris(2,6-diarylphenoxy)aluminum as a better cyclization catalyst.[101] The selectivity of the ene-cyclization reaction is a function of several factors like the Lewis-acid solvent employed and reaction temperature. Besides $ZnBr_2$,[26,102–104] several homogeneous and heterogeneous catalysts have been used. When the ene-cyclization is performed in the presence of homogeneous $(Ph_3P)_3RhCl$[105] and $SbCl_5$,[26] $TiCl_4$,[26] $NbCl_5$,[106] $TaCl_5$,[106] $PhCH_2(Et)_3N^+[Mo(CO)_4ClBr_2]^-$,[107] $Mo(CO)_4Br_2$,[107] Zn/TMS-Br,[108] Zn/TMS-I[108] or concd HCl,[109] *neo*isopulegol is preferentially obtained, while isopulegol is the main product when other Lewis acids are employed. The Lewis acids used in the selective preparation of isopulegol are $ZnCl_2$,[26,110] ZnI_2,[26] $AlCl_3$,[26] BF_3,[26] $FeCl_3$,[26] $SnCl_4$,[26,111] $TiCl_4$,[26] $SnCl_3(OCH_3)$,[26] $SnCl_3(OC_2H_5)$,[26] $Ti(OR)_4$,[26] $SbCl_3$,[26] Zn/TMS-Cl,[108] $Sc(OTf)_3$,[112] SmI_2,[113] $InCl_3$,[106] $Bi(OTf)_3$,[114] and Me_2AlCl.[115]

Due to the easy separation and reuse of these materials, the use of heterogeneous catalysts is a more attractive alternative for the industrial production of fine chemicals. Because no salt residuals and a drastically reduced amount of VOCs are generated, it is also a greener process. Aiming to improve the stereoselectivity to (−)-isopulegol (**254**, Scheme 67), several heterogeneous catalysts, like zeolites,[116–125] Al_2O_3,[126] SiO_2–Al_2O_3,[126] TiO_2–ZrO_2,[126] $FeSO_4$,[126] $NiSO_4$,[126] $Ti(SO_4)_2$,[126] $Zr(SO_4)_2$,[126] SiO_2 under high pressure,[127] hydrous zirconia,[128] sulfated zirconia, carbon molecular sieves (S-ZrO_2/CMS),[129–131] metal cation-exchanged montmorillonite,[132,133] Al/Fe-pillared clays (Al/Fe-PILC),[134] and silica-supported catalysts have been studied with excellent result.[135–142] A high selectivity to isopulegol was achieved with the use of the organic resin 5,5′-(9,10-anthracenediyl)diresorcionol.[143] In this 'host–guest' type solid-state reaction, the organic solid forms a hydrogen-bonded adduct with citronellal, which is converted to isopulegol with a selectivity of ca. 98%, via an intra-adduct ene-cyclization.[143]

Heterogeneous catalysis under solvent-free conditions can be performed under microwave irradiation.[133,144–146] While no increase in the reaction rate was observed when montmorillonite was heated by microwaves,[133] the reaction rate of the cyclization of citronellal adsorbed on Y zeolites[144] and graphite[146] was dramatically enhanced in comparison to reactions under thermal conditions. Recently, Jacob et al.[145] described a simple, green, and efficient method for the ene-cyclization of (*R*)-citronellal to isopulegol in the presence of $ZnCl_2$ supported on SiO_2 under microwave (MW) radiation. Isopulegol was obtained with a selectivity of 76% after irradiation for 1.5 min in an unmodified household MW oven in 100% yield. The same protocol was applied for the direct preparation of isopulegol from the essential oil of citronellal (*C. nardus*, 40–51% of (*R*)-citronellal) in excellent yields.[145]

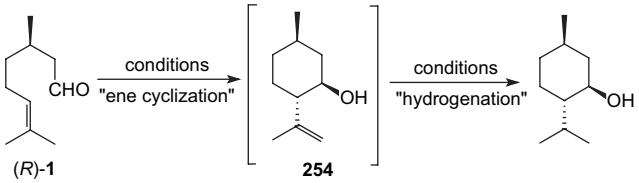
A chiral zinc reagent, prepared in situ from dimethylzinc and optically pure (*R*)-(+)-1,1′-bi-2-naphthol (molar ratio, 1:1) was employed in the selective cyclization of both enantiomers of citronellal.[147] The authors observed exclusively the formation of (−)-isopulegol (**254**) starting from (*R*)-citronellal whereas (+)-isopulegol was the only product obtained from (*S*)-citronellal. Table 1 presents a number of selected examples in converting citronellal to isopulegol.

By using bifunctional copper catalysts,[142] Ru-$ZnBr_2$/SiO_2,[141] and Ir-β-zeolites,[122] it is possible to obtain (−)-menthol directly from (*R*)-citronellal. This is done through an acidic ene-cyclization and subsequent hydrogenation occurring in a single step. The one-pot conversion of citronellal to menthol can also be selectively catalyzed by either a bifunctional Ni/Zr-β zeolite catalyst or a dual catalyst system of Zr-β and Ni/MCM-41, giving high diastereoselectivity toward menthol (Scheme 69).[148] These are very efficient protocols, because they eliminate the tedious and expensive separation and purification of the intermediate (−)-isopulegol (**254**).

Table 1. Selectivity on the synthesis of isopulegol

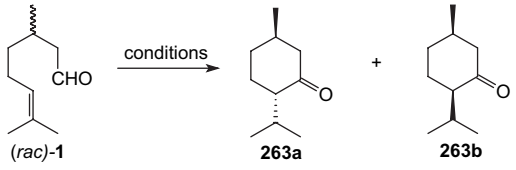
Conditions	Yield (%)	Ratio **254/256/257/258**	Ref.
180 °C/Ar/30 h	90	60:5:20:15	27
Cu–Cr–Mn/200 °C/7 h	80	71:0:21:8	86
$ZnBr_2$/PhH/5 °C/15 min	70	94:0:6:0	26
$SbCl_5$/PhH/5 °C/15 min	22	43:0:57:0	26
$NbCl_5/CH_2Cl_2$/−40 °C/6 h	98	45.5:0:54.5:0	106
Zn/TMS-Br/THF/rt/1 h	50	24:2:55:2	108
$Bi(OTf)_3\cdot H_2O/CH_2Cl_2$/rt/5 min	46	78:0:22:0	114
Sn-β-zeolite/MeCN/80 °C/1 h	91	90:0:10:0	119
S-ZrO_2/CMS/$PhCH_3$/95 °C/0.5 h	91	65:35 (other compounds)	129
Al/Fe-PILC/CH_2Cl_2/25 °C/1.5 h	98	80:0:20:0	134
Organic solid/cyclohexane/70 °C/150 h	[a]	98:0:2:0	143
$ZnCl_2/SiO_2$/MW (488 W)/1.5 min	100	76:24:0:0	145

[a] The products were not isolated.



Scheme 69. Direct preparation of (−)-menthol from (*R*)-citronellal (**1**).

The cyclization of citronellal under free-radical conditions in the presence of peroxides gives a mixture of menthone (**263a**) and isomenthone (**263b**, Scheme 70).[149,150] The yields, however, are modest (15–24%) and the selectivity is very low (**263a/263b** ratio =58:42 to 67:33). An improvement upon the radical citronellal cyclization was achieved (up to 75% yield) when di-*tert*-butyl hyponitritite (TBHN, 7.5 mol%), $^{i}Pr_3SiSH$ (10 mol%), and $CaCO_3$ (8 mol %) in dioxane were used to promote the radical-chain reaction.[151] When Al/Fe-pillared clays (Al/Fe-PILC) are used as heterogeneous catalyst, a mixture of menthone and isomenthone could be prepared in similar yields and a better selectivity (**263a/263b** ratio=69:31).[134]

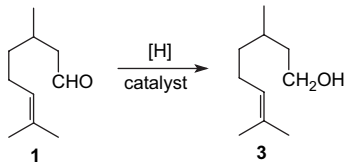


Scheme 70. Menthone (**263a**) and isomenthone (**263b**) from citronellal (**1**).

4. Hydrogenation to citronellol and oxidation to citrollenic acid

Although the most used method for the preparation of citronellol (**3**) is the selective hydrogenation of citral,[121,136,139] citronellal can also be used as precursor to citronellol.[152,153] The use of citronellal as precursor is especially useful when a highly pure enantiomer is required, and both heterogeneous[152–157] and homogeneous[158–168] catalysts are used in this conversion (Scheme 71).

Like citronellal, citronellol is a versatile compound in the cosmetic and perfumery industry and an important reactant in the total synthesis of chiral compounds.[1a,18,24,43,169] The



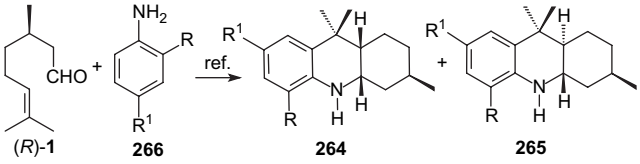
Scheme 71. Citronellol from citronellal.

reduction systems used for the selective hydrogenation of citronellal to citronellol are the Ru/TiO_2, Ru/SiO_2,[140,152] polymer-stabilized noble metal (Pt or Ru) colloids,[153a] and a Pt/C two phase system using toluene and aqueous alkaline solution.[153b]

When citronellal is subjected to oxidation with silver oxide[170] or silver nitrate[160] citrollenic acid is obtained in nearly quantitative yield. Citrollenic acid is rarely found in nature[171] and was used to assign the enantiomeric composition of natural and non-natural citronellal.[170] It is a useful chiral source in the total synthesis of pheromones[172] and non-natural compounds.[173]

5. Synthesis of octahydroacridines

Octahydroacridines (OHAs, **264** and **265**) are a class of pharmacologically interesting compounds and an efficient synthesis of them starts from citronellal (**1**) and *N*-arylamines (**266**, Scheme 72, Table 2). This Lewis-acid catalyzed imine-Diels–Alder reaction is the most atom-economic way to OHAs, with high yields and, in some cases, 100% stereoselectivity.

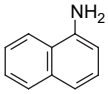


Scheme 72. Octahydroacridines from citronellal and *N*-arylamines.

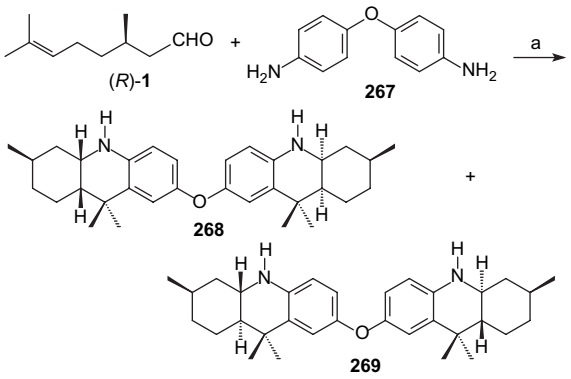
The transformation described in Scheme 72 may be catalyzed by $SnCl_4$,[174] $Cr(CO)_3$,[175] molecular sieves,[176] $BiCl_3$[177] or $TiCl_3$.[178] The use of solid-supported aniline in the presence of $Yb(OTf)_3$ was also described.[179] However, the use of trifluoroethanol[178] or ionic liquid[180] as solvent eliminates the necessity of a Lewis acid. When 4,4′-oxydianiline (**267**) was used as an aromatic precursor, the cis-bisadduct **268** and trans-bisadduct **269** were obtained in 87% yield after 1.5 h at room temperature (Scheme 73).[180]

Recently, Jacob et al.[181]described a very simple and eco-friendly procedure for the preparation of 1,2,3,4,4a,9,9a, 10-octahydroacridines (**264** and **265**) by hetero-Diels–Alder reaction of (*R*)-citronellal (**1**) and amines **266** in the presence of a supported catalyst under solvent-free conditions and MW irradiation. They found that the reaction was clean, fast, and highly selective, with results comparable to the best obtained by conventional methods (Table 2). This green protocol was applied to the reaction between *o*-toluidine and the essential oil of citronellal (containing 40–51% of (*R*)-citronellal) and the desired product was obtained in 79% yield,

Table 2. Synthesis of octahydroacridines starting from citronellal and anilines

Entry	R	R^1	Yield (%)	Ratio **264/265**	Ref.
1	H	H	84	31:67	174
			98	0:100	177
			82[a]	49:51	178
			69[b]	20:80	178
			95	50:50	180
			78	50:50	181
2	CH_3	H	84	42:56	174
			50[c]	3:97	175
			34[d]	24:76	175
			96	3:97	177
			67[a]	30:70	178
			85[b]	45:55	178
			92	25:75	180
			83	33:67	181
3	CH_3	OH	84	0:100	176
4	H	CO_2Me	84	0:100	176
5	H	CO_2H	54	0:100	176
6	H	$C_{10}H_{21}$	84	0:100	176
7	H	CH_3	97	6:94	177
			72[a]	39:61	178
			89[b]	48:52	178
			95	33:67	180
			75	64:36	181
8	H	Cl	97	5:95	177
			68[a]	33:67	178
			95[b]	45:55	178
			93	33:67	180
			85	50:50	181
9	H	F	96	5:95	177
			90	33:67	180
10	H	Br	70[a]	38:62	178
			94[b]	44:56	178
11	H	OCH_3	93	7:93	177
			66[a]	42:58	178
			95[b]	49:51	178
			89	45:55	180
12	H	OC_2H_5	92	8:92	177
			87	40:60	180
13	Br	CH_3	92	5:95	177
			86	40:60	180
14	CO_2H	H	92	75:25	181
			95	5:95	177
15			68[a]	16:84	178
			86[b]	42:58	178
			94	20:80	180
			87	50:50	181

[a] The reaction was carried out with 10 mol % of $TiCl_3$.
[b] The reaction was carried out in TFE.
[c] The reaction was carried out at −78 °C in toluene.
[d] The reaction was carried out at −78 °C in CH_2Cl_2.

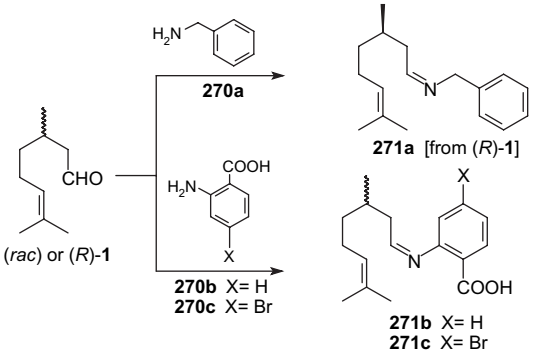


Scheme 73. Reagents and conditions: (a) [BMIM]BF_4, rt, 1.5 h, 87%.

together with unreacted geraniol, citronellol, geranyl acetate, and other minor constituents of the starting oil.[181]

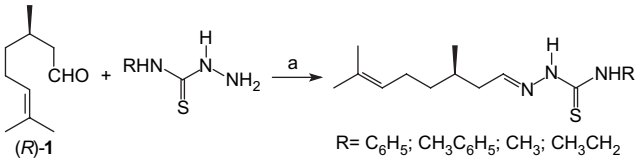
6. Synthesis of chiral imines (Schiff bases) and hydrazones

The reaction between citronellal and an amine can be stopped at the imine stage. The Schiff base obtained can be subjected to different transformations (Scheme 74). When (*R*)-citronellal (**1**) was reacted with benzylamine (**270a**), the Schiff base **271a** was obtained in quantitative yield. As a part of a study on the biomimetic cyclizations of chiral imines, **271a** was reduced to the respective cyclohexylamine and the isomeric ratios were evaluated.[182] In a similar way, *rac*-citronellal reacted with anthranilic acid (**270b**) or 5-bromoanthranilic acid (**270c**) in EtOH, to afford the respective imines **271b** and **271c**. These ligands were used in kinetic studies in the thermal decomposition of metal complexes (M=Co, Ni, Cu, and Zn).[183] When the methyl ester of phenylglycine was employed as amine, the respective instable imine was obtained selectively.[184]



Scheme 74. Chiral imines from citronellal.

The condensation of (*R*)-**1** with thiosemicarbazide under ultrasonic agitation in the presence of ethanol gives the corresponding thiosemicarbazones in quantitative yield (Scheme 75).[185]



Scheme 75. Reagents and conditions: (a) EtOH, ultrasonic agitation, 40 °C, 60 min, 85–91%.

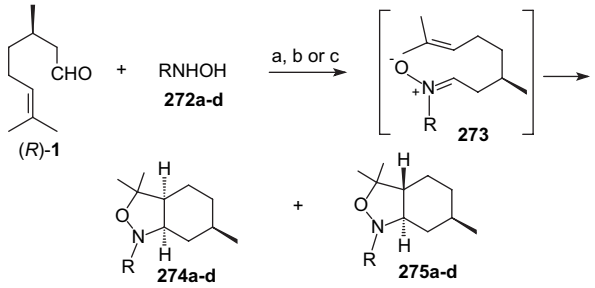
In a similar way, chiral hydrazones were diastereoselectively synthesized by reaction of (2*S*,4*S*,5*R*)-3,4-dimethyl-2-hydrazido-5-phenyl-1,3,2-oxazaphospholidin-2-oxide with (*R*)-**1** in refluxing ethanol.[186] 4-Nitrobenzoylhydrazone, a chiral hydrazone derived from (*S*)-**1**, undergoes an intramolecular [3+2] cycloaddition in the presence of a chiral zirconium complex catalyst to afford the *trans*-pyrazolidine derivative with high selectivity.[187]

The acid catalyzed cyclization (*p*-TsOH) of citronellal with γ-butyro lactam gives stereoselectively the *N*-alkenyl γ-butyro lactam in 49% yield.[188] The synthesis of chiral

α-(N^2-tosylhydrazino)nitriles, the one-carbon homologation of citronellal, was performed via its tosylhydrazone, which involves the addition of Et_2AlCN to the hydrazone.[189] The rhodium acetate-catalyzed hydroacylation between citronellal and diisopropyl azodicarboxylate affords, after 48 h at 25 °C, the corresponding hydrazino imide in 74% yield.[190]

7. Synthesis of hexahydro-2,1-benzisoxazolines

(*R*)-Citronellal (**1**) was employed in the synthesis of chiral bicyclic isoxazolidines (CBIs) by means of its condensation with *N*-organyl hydroxylamines **272**. The reaction occurs via an intramolecular 1,3-dipolar cycloaddition of unstable nitrone derivatives **273** (Scheme 76, Table 3).[191–193]



Scheme 76. Reagents and conditions: (a) NaOMe, MeOH/toluene, reflux, 2–3 h; (b) EtOH, rt, 24 h, then HCl until pH 2; (c) $LiClO_4$, CH_3CN, rt, 6.5–7.5 h.

Table 3. Synthesis of chiral bicyclic isoxazolidines (CBI) starting from (*R*)-citronellal (**1**)

Entry	R	Yield (%)	Ratio **274/275**	Ref.
1	CH_3	65	13:87[a]	191,192
		65	3:97[b]	191,192a
		67	11:89	192b
2	C_2H_4	71	17:83	191
3	$(Me)_2CH$	74	[c]	191
4	C_6H_5	31	0:100	191
		92	0:100	193
5	$C_6H_4CH_2$	85	0:100	193
6	H	76	33:67	193

[a] The reaction was carried out at 138 °C.
[b] The reaction was carried out at 25 °C.
[c] The **274/275** ratio was not determined.

Citronellal was used as starting material in a new general method for the synthesis of *N*-unsubstituted isoxazolidine derivatives. By reaction of citronellal with 5-hydroxypentanal oxime in the presence of Bu_2SnO in refluxing toluene, a mixture of the respective trans- and cis fused isoxazolidines was obtained in 76% yield (trans/cis ratio=2:1).[194]

8. Synthesis of dihydro-oxazines

The oxazine subunit is present in the structure of several alkaloids, for example, nitraramine (**276**), demethylxestospongin (**277**) or haematopodin (**278**, Fig. 16).

Asinger condensation is a highly versatile synthetic method for the synthesis of many heterocycles including 2,5-dihydro-2*H*-1,3-oxazines. A chiral Asinger condensation was

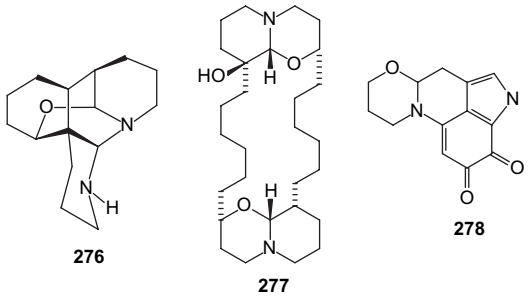
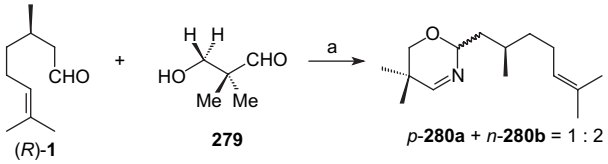


Figure 16. Structures of nitraramine, demethylxestospongin and haematopodin.

developed starting from 3-hydroxy-2,2-dimethylpropionaldehyde (**279**) and (*R*)-citronellal (**1**) in the presence of ammonia (Scheme 77).[195] The *p*- and *n*-products **280a** and **280b** were obtained in a remarkable 1:2 ratio, although the inducing stereogenic center is several bonds apart from the newly formed stereocenter. However, the relative configuration of the two diastereomers was not determined.



Scheme 77. Reagents and conditions: (a) NH_3, $CHCl_3$, 0 °C, then rt, 18 h, >50%.

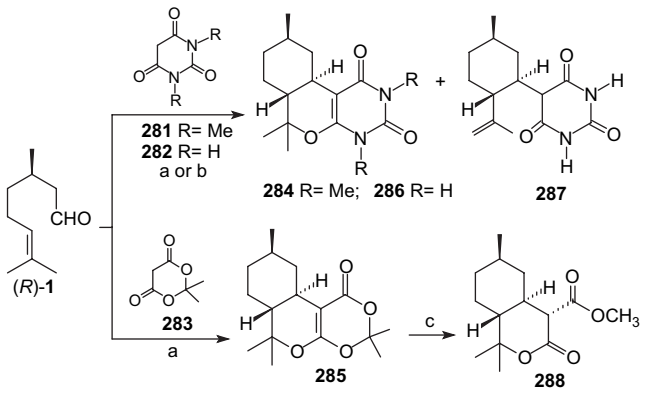
A highly diastereoselective organocatalyzed (L-pyrrolidinyltetrazole) asymmetric synthesis of chiral dihydro-1,2-oxazines starting from both (*R*)- and (*S*)-**1** was described.[196] This multicomponent reaction sequence produces dihydro-1,2-oxazine in 61% (83% de, from (*R*)-**1**) and 67% yield (99% de, from (*S*)-**1**).

A modified version of the multicomponent Asinger reaction was employed for the reaction between (*R*)-citronellal (**1**), α-chloro-α-methyl-propionaldehyde, NH_3, and NaSH.[197] This atom-economic protocol affords, in one step, chiral 3-thiazolines in good yield.

9. Synthesis of polycyclic compounds by domino Knoevenagel hetero-Diels–Alder reactions

Both enantiomers of citronellal have been used as key materials in several domino Knoevenagel hetero-Diels–Alder reactions, for chiral polycyclic compounds with high stereoselectivity and atom economy (Scheme 78).[198] Reaction of (*R*)- or (*S*)-citronellal **1** with *N*,*N*-dimethylbarbituric acid (**281**), barbituric acid (**282**), and Meldrum's acid (**283**) provides the respective enantiomeric tricyclic dihydropyrans through a 100% stereoconrolled intramolecular hetero-Diels–Alder (IHDA) cycloaddition (Scheme 78).[199,200]

In the presence of ethylenediammonium acetate at 30 °C, **281** and (*R*)-citronellal (**1**) gave, within 5 min, exclusively the enantio- and diastereomeric pure tricyclic **284** in 97% yield, and small amounts of the self-condensation product



Scheme 78. Reagents and conditions: (a) ethylenediammonium acetate, 30 °C, 5 min, 97% for **284** and 95% for **285**; (b) THF, Py, water, reflux, 61% of **286** and 29% of **287**, considering that **1** was recovered;[199] (c) (1) concd HCl, methanol, reflux, 8 h; (2) CF_3CO_2H, CH_2Cl_2, rt, 48 h, 79%.[200]

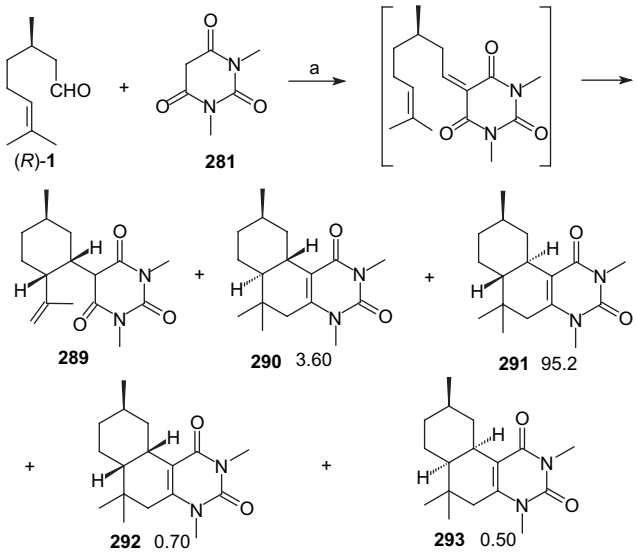
of **1**. Under the same conditions, **283** gave 95% of **285**. Barbituric acid (**282**) reacts with (*R*)-**1** to afford 34% of tricyclic **286** and 16% of **287**. As **1** was recovered, with respect to converted **1**, the yields were 61% of **286** and 29% of **287**.

The enantiomers of all products could be accessed through the use of (*S*)-citronellal (**1**) instead of (*R*)-**1**. Moreover, no diastereomers of any product were detected, so it is assumed that initially alkylidene derivatives are formed by a Knoevenagel condensation followed by a fast concerted cycloaddition totally stereocontrolled by the chiral center of the citronellal. The by-product **287** was formed by an intramolecular ene reaction.

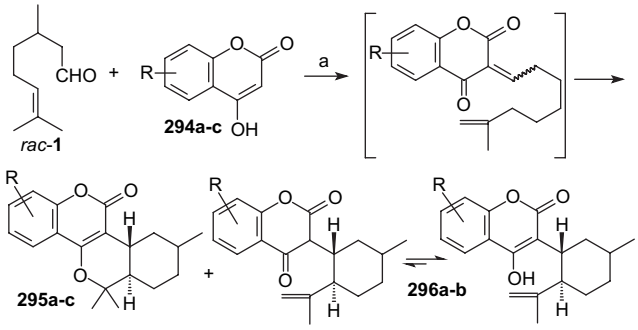
The adduct **285** can be easily deprotected to the racemic or the enantiomeric forms of the α-methoxycarbonyl lactone **288**, based on the starting stereochemistry of citronellal employed.[200] The adducts **284** and **285** have also been synthesized in a glass microchip under pressure driven flow, using the reagents and conditions described in Scheme 78.[201]

In order to perform a detailed study of the induced diastereoselectivity observed in the intramolecular hetero-Diels–Alder (IHDA) reaction of 1-oxa-1,3-butadienes described above (Scheme 78), citronellal was used to obtain experimental data for the comparison with theoretical calculations.[202,203] The Knoevenagel condensation of (*R*)-**1** with *N*,*N*-dimethyl barbituric acid (**281**) affords, in addition to the alkylidene-α,α′-dioxo **289**, the four possible diastereomers **290**–**293**, with **291** as main product (Scheme 79). The authors explained the high trans selectivity by the existence of a non-symmetric transition state, while the diastereofacial differentiation observed was explained by dominant 'conformational effects'.

Natural and synthetic coumarin derivatives are reported to have important biological activities such as anticoagulant, insecticidal, antihelminthic, hypnotic, antifungal, and HIV protease inhibition. Unsymmetrical 1,3-diones (**294**) were reacted with citronellal (**1**, Scheme 80, Table 4, entries 1–3) to give the intramolecular hetero-Diels–Alder adduct **295** and the intramolecular domino Knoevenagel ene adduct **296**. The highest yields and selectivity were obtained under MW irradiation.[204]



Scheme 79. Reagents and conditions: (a) CH_2Cl_2, rt, 24 h, ethylenediammonium acetate (cat.), 61% (**290**+**291**+**292**+**293**) and 29% yield (**289**).



Scheme 80. Reagents and conditions: (a) ethanol, reflux (4–7 h, 53–69%) or MW irradiation (12 s–3 min, 75–81%).

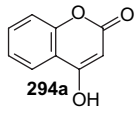
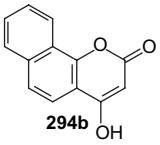
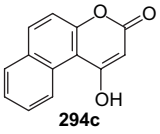
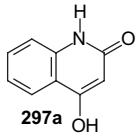
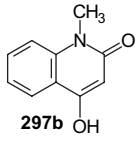
The skeleton of pyranoquinoline constitutes a fundamental part of numerous natural products and has distinct properties of general interest. A simple approach to pyranoquinoline derivatives from aliphatic aldehydes was developed using citronellal (**1**) as the carbonyl compound (Scheme 81, Table 4, entries 4 and 5).[205] The IHDA reaction of racemic citronellal with 4-hydroxy quinolinones (**297a**,**b**) furnished a mixture of **298a**,**b** and **299a**,**b**. The highest chemoselectivity and chemical yields were obtained in the presence of Et_3N and under MW irradiation [**298**/**299** ratio=83:17 and yield=68% (from **297a**) and 80% (from **297b**)]. The ene products **299** showed tautomeric mixtures of the lactam enol and keto-lactam forms in a ratio of 80:20.

When 1λ^6,2,6-thiadiazine-3,5-diones were employed instead **294**, the thio-adduct of the domino Knoevenagel hetero-Diels–Alder reaction, analog to **295**, was obtained.[206]

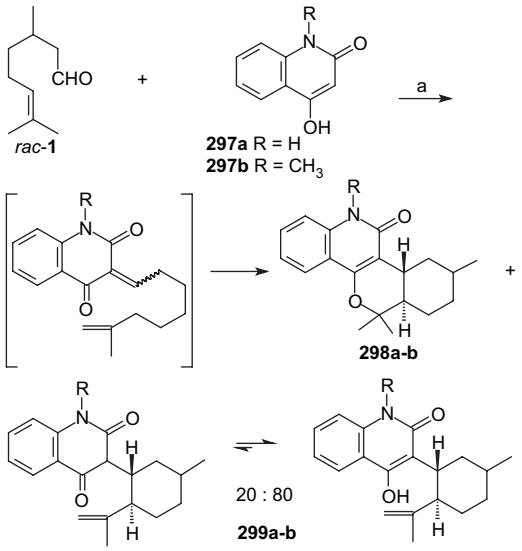
10. Synthesis of hexahydrocanabinols

As previously described in Section 2.2 of this review, non-natural and natural hexahydrocannabinols (HHCs) have interesting pharmacologic properties.[32–34] A simple method toward both diastereomers of hexahydrocannabinol (HHC, **300a**), a non-natural psychotropically active compound

Table 4. Reaction of 1,3-diones with citronellal[a]

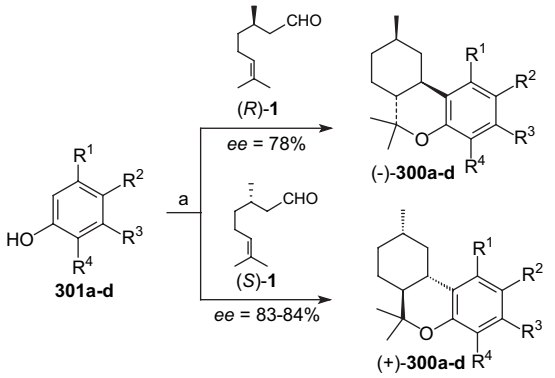
Entry	1,3-Dione	Time	Yield (%)	Ratio **295/296**	Ref.
1	 **294a**	12 s	81	88:12	204
2	 **294b**	3 min	75	84:16	204
3	 **294c**	2.5 min	78	84:16	204
4	 **297a**	3 min	68	84:16	205
5	 **297b**	4.5 min	80	83:17	205

[a] Reaction performed under MW irradiation.



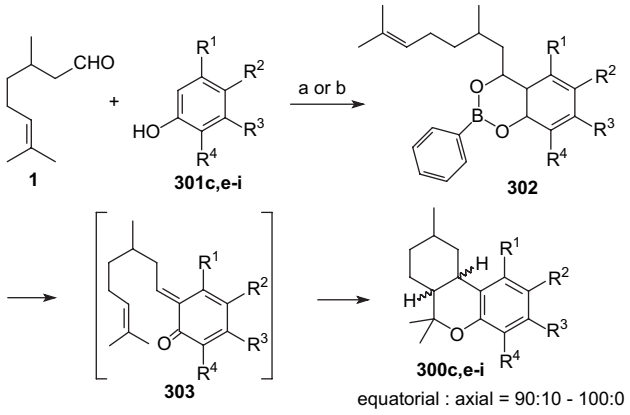
Scheme 81. Reagents and conditions: (a) base (EDDA, triethylamine or piperidine), ethanol, reflux (4.5–10 h, 41–55%) or MW irradiation (2–5 min, 54–80%).

closely related to natural cannabinoids, and related compounds **300b–d** has been developed. The one-step synthesis involves the diethylaluminum chloride-assisted coupling of suitable phenols **301** with (*R*)- or (*S*)-citronellal (**1**) in toluene for 21 h (Scheme 82, entries 1–4, Table 5).[207] The yields ranged from 41 to 78% and the enantiomeric excess was in the range of 76–84%. The desired products were produced without formation of their respective diastereomers. Since the configuration at C-3 in citronellal (**1**) is maintained, a number of HHC derivatives can be synthesized in optically pure form by this procedure.



Scheme 82. Reagents and conditions: (a) Et_2AlCl, toluene, 21 h, 41–78%.

Starting from the bisethoxyethyl ether form of olivetol (**301a**, R^1=OH, R^2=R^4=H, R^3=C_5H_{11}), (−)-hexahydrocannabinol (**300a**) was enantioselectively synthesized in 53% yield (Scheme 83, entry 1, line 2, Table 5). The desired compound **300a** was obtained under mild conditions through the *o*-quinone methide mediated intramolecular hetero-Diels–Alder reaction of the coupling product of (*R*)-**1** with the protected phenol **301a**.[208,209]

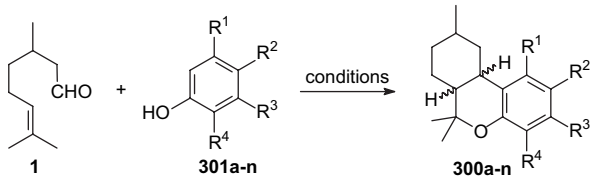


Scheme 83. Reagents and conditions: (a) $C_6H_5B(OH)_2$, acetic acid (excess), toluene, reflux, 43–90%;[210] (b) (1) $PhBCl_2$, Et_3N, DMAP, CH_2Cl_2, 0 °C, 15 min; (2) benzene, 215 °C, 18 h.[211]

Alternatively, a number of hexahydrocannabinoids (HHC, **300**) were prepared using phenylboric acid as a catalyst.[210] This general procedure involves heating activated phenols (**301**) with citronellal (**1**) to reflux in the presence of phenylboric acid and excess of acetic acid. The HHCs were formed in 43–90% yield (Table 5, entries 3, 5–9) and the epimeric equatorial:axial ratios were between 90:10 and 100:0.

Benzodioxaborins (**302**) were shown to be the intermediates and are proposed to undergo conversion into quinomethide (**303**) followed by a rapid intramolecular cycloaddition of the double bond to this functionality under the employed acid conditions (Scheme 83). It appears that this reaction may be additionally driven by the restoration of aromaticity. The overall efficiency of *o*-quinone methide formation and cycloaddition was influenced by substituent effects.

Table 5. Synthesis of hexahydrocannabinols (HHC) and related compounds

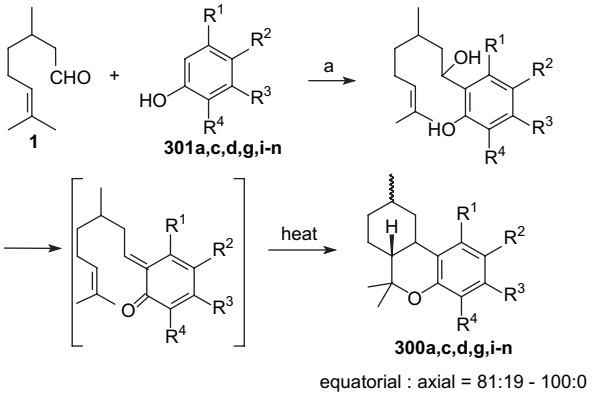


Entry		R^1	R^2	R^3	R^4	Yield (%)	Ref.
1	a	OH	H	C_5H_{11}	H	57[a]	207
						53[b]	208
						69[c]	207
						59	214
2	b	OH	H	CH_3	H	41[a]	207
						43[c]	207
						48	211
3	c	OMe	H	OCH_3	H	76[a]	207
						78[c]	207
						86	210
						69	214
4	d	H	H	H	H	69[a]	207
						73[c]	207
						19	214
						42	215
5	e		$-C_6H_4-$	H	H	52	210
6	f	H	H		$-C_6H_4-$	52	210
7	g	H	H	OCH_3	H	71	210
						33	214
8	h	H		$-OCH_2O-$	H	90	210
						60	214
9	i	H	H	OH	H	43	210
						47	214
10	j	OH	COMe	H	H	73	214
11	k		$-C_4H_4-$	H	H	86	214
12	l	H	H		$-C_4H_4-$	88	214
13	m	H	OCH_3	H	H	19	214
14	n	OH	H	OH	H	41	214

[a] (*R*)-Citronellal (**1**) was used as starting material.
[b] The bisethoxyethyl ether of olivetol (**301a**) was employed in the condensation step. Compound (−)-**300a** was obtained after deprotection with PPTS in MeOH/$CHCl_3$.
[c] (*S*)-Citronellal **1** was used as starting material.

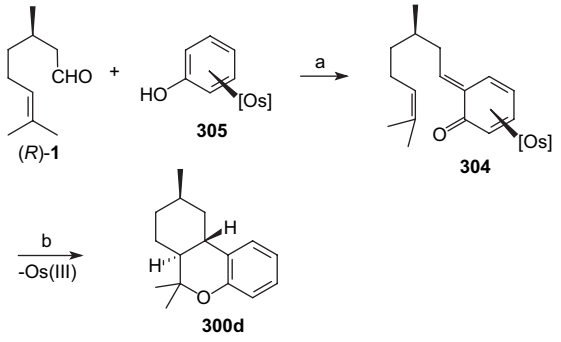
Benzodioxaborins (**302**) were also intermediates involved in the synthesis of several HHCs when $PhBCl_2/Et_3N$ was employed as cyclization promoter instead of phenylboric acid.[211] However, drastic conditions (215 °C, 18 h) are necessary to convert the benzodioxaborins into the desired HHCs (48% yield, two steps). If *N*-methylanilines are used instead of phenols, benzoxaazaborine is formed as an intermediate. Its subsequent opening under basic conditions gives *o*-hydroxyalkyl anilines, which were converted to the 5-aza analogs of HHC in reasonable yields (51–73%) after heating (80–180 °C, 0.25–32 h).[212] In a similar way, when 2-methoxy-5-(methylamino)pyridine was submitted to *o*-hydroxyalkylation with citronellal in the presence of $PhBCl_2$, octahydrobenzo[*b*][1,5]naphthyridine was obtained in 40% yield.[213]

A base-catalyzed variant of the reaction between citronellal and phenols is also described.[214] This protocol involves the heating of phenols (**301**) with citronellal (**1**) in the presence of quinoline for 1.5–91 h (Scheme 84). The advantage to this procedure is that no activated phenol is required. Although the epimeric ratios are less favorable when basic conditions are employed, a number of hexahydrocannabinoids (HHC) were synthesized with yields between 19 and 88% and equatorial:axial ratios between 81:19 and 100:0 (Table 5).[214] The critical difference between the mechanisms of acid- and base-catalyzed annulations is that phenoxide, the reactive species under basic conditions, is a much stronger nucleophile than un-ionized phenol. On the other hand, the absence of an acid activator when basic media is used requires vigorous conditions. As a result of higher temperatures, the epimeric ratios were even less favorable.



Scheme 84. Reagents and conditions: (a) quinoline, heat, 1.5–91 h, 19–88%.

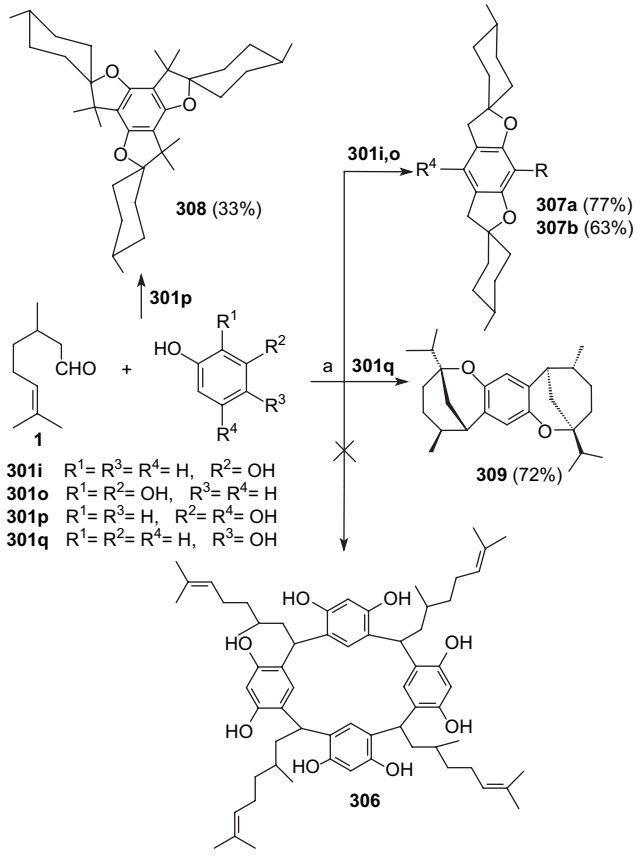
Recently, the *o*-quinone methide (*o*-QM, **304**) generated by reaction between the η^2-osmium coordinated phenol **305** and (*R*)-citronellal (**1**) was used in the synthesis of HHC **300d**.[215] The key step in this synthesis is an intramolecular Diels–Alder and demetalation reaction of the *o*-QM **304** in the presence of ceric ammonium nitrate (CAN, Scheme 85).



Scheme 85. Reagents and conditions: (a) pyridine, CH_3CN, 20 °C, 5 h, 80.3%; (b) CAN, CH_3CN, 20 °C, 18 h, 52.5%.

11. Synthesis of benzodifuranes by condensation of citronellal with electron-rich phenols

Aiming toward the synthesis of chiral resorcinarenes (**306**), an important class of electron-rich cyclophanes, citronellal (**1**) was submitted to an acid catalyzed condensation with several electron-rich phenols **301i,o–q** (Scheme 86).[216,217]



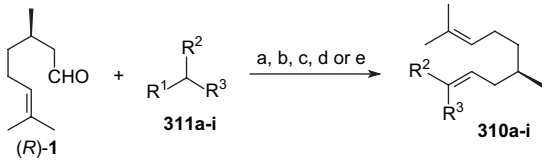
Scheme 86. Reagents and conditions: (a) EtOH, concd HCl, 0 °C→reflux, 12 h.

Instead of the desired product, the non-chiral benzodifuran [2+1] adducts **307a**,**b** were formed in 63–77% yield from resorcinol (**301i**) and pyrogallol (**301o**), respectively. Phloroglucinol (**301p**) and hydroquinone (**301q**) showed a quite different behavior under the same reaction conditions, affording, respectively, the [3+1] adduct **308** (33% yield) and the dioxocane [2+1] adduct **309** (72% yield, Scheme 86). The authors have investigated the reaction mechanism and found that the first step of the reaction is the cyclization of citronellal to isopulegol. This observation was confirmed because the use of isopulegol in these reactions instead citronellal gives the same products in comparable yields.

12. Preparation of chiral 1,7-dienes

12.1. Via Knoevenagel reaction

(*R*)-Citronellal (**1**) was employed by Tietze and co-workers for the preparation of several chiral 1,7-dienes (**310**) by means of Knoevenagel-type reactions (Scheme 87).[174,218–224] The acid catalyzed intramolecular ene reaction of 1,7-dienes **310** is a very useful method to access trans-substituted cyclohexanes. The dienes were synthesized through condensation of citronellal (**1**) with 1,3-dicarbonyls or analog compounds **311** in the presence of piperidinium acetate at rt,[218–221] KF/Al_2O_3,[223] ^{n}BuLi/THF[224] or by using basic Cs-beta zeolite.[225] Yields of **310** ranged between 82 and 90% (Scheme 87, Table 6).



Scheme 87. Reagents and conditions: (a) CH_2Cl_2, piperidine/AcOH (0.1 equiv), 0 °C, then rt, 1 h, 82–90%;[218,219] (b) AcOH (solvent), piperidine (0.1 equiv), anhydrous Na_2SO_4 or 3 Å molecular sieves;[220,221] (c) KF/Al_2O_3, rt, 5h,[223] (d) ^{n}BuLi, THF, −40 °C, 1 h, then rt, 2 h;[224] (e) Cs(beta) zeolite, rt, 72 h.[225]

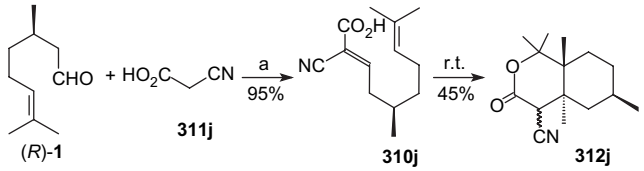
However, when citronellal was reacted with cyanoacetic acid (**311j**, R^1=H, R^2=CO_2H, R^3=CN), the respective 1,7-diene **310j** was obtained in 95% yield, which cyclized at

Table 6. Chiral 1,7-dienes (**310**) from (*R*)-citronellal (**1**) via Knoevenagel reactions

Entry	R^1	R^2	R^3	**310**	Yield (%)	Ref.
1	H	CO_2CH_3	CO_2CH_3	**a**	82	218–220
					87[a,b]	221
						222
2	H	CO_2Et	CO_2Et	**b**	84	218,220
3	H	CN	CN	**c**	84	218,220
					38	225
4	H	CO_2CH_3	CN	**d**	90	218,220
5	H	$COCH_3$	$COCH_3$	**e**	87	218,220
6	H	CO_2CH_3	$COCH_3$	**f**	66[c]	220
7	H	CO_2Bzl	CO_2Bzl	**g**	66	220
8	H	CN	SeC_6H_5	**h**	42[d]	223
9	TMS	SCH_3	SCH_3	**i**	90	224

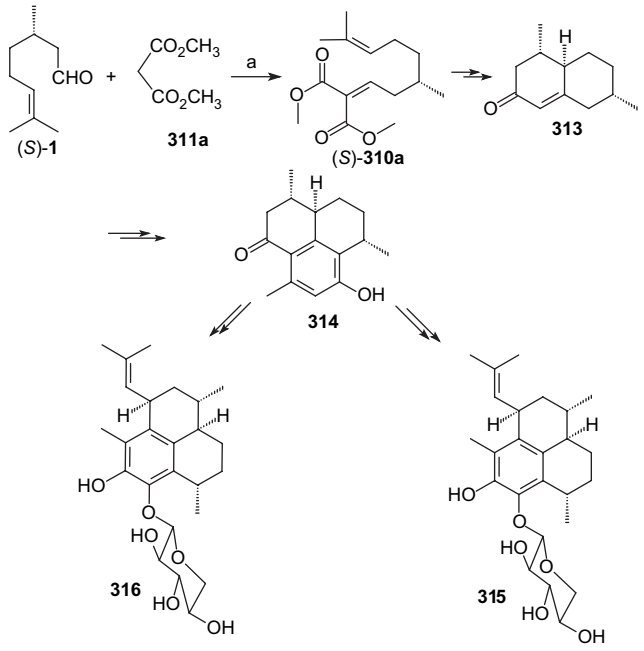
[a] (*S*)-Citronellal (**1**) was employed as starting material.
[b] The crude diene was employed in the following steps of the synthesis.
[c] A mixture of *Z* and *E* isomers of **310f** was obtained (*Z*/*E* ratio=65:35).
[d] A mixture of *Z* and *E* isomers of **310h** was obtained (*Z*/*E* ratio=60:40).

room temperature to give the cyclohexane **312j** in 45% yield (Scheme 88).



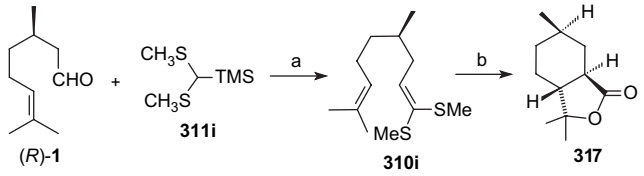
Scheme 88. Reagents and conditions: (a) (1) aq NaOH, 0 °C, 15 min; (2) concd HCl.

The 1,7-diene (*S*)-**310a**, obtained by the Knoevenagel reaction of (*S*)-citronellal (**1**) with dimethyl malonate (**311a**), was employed in the preparation of **313** and **314**. These are key compounds for the total synthesis of pseudopterosin A (**315**) and pseudopterosin B (**316**), potent anti-inflammatory terpenoids (Scheme 89).[222]



Scheme 89. Reagents and conditions: (a) CH_2Cl_2, piperidine/AcOH (10 mol%), rt, 12 h, 95%.

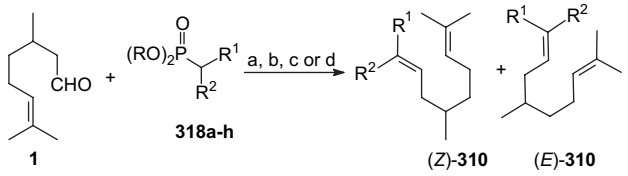
The unsaturated ketene dithioacetal **310i** obtained from (*R*)-**1** and submitted to an oxidative cyclization in the presence of CAN afforded the chiral bicyclic γ-butirolactone **317** in 45% yield (two steps from (*R*)-**1**, Scheme 90).



Scheme 90. Reagents and conditions: (a) ^{n}BuLi, THF; (b) CAN (6 equiv) 20:1 CH_3CN/H_2O, 12 h, 25 °C, 45% (two steps).

12.2. Via Wittig-type reactions

Chiral 1,7-dienes were also prepared by Wittig-type reactions,[226–249] reacting citronellal with dialkyl phosphonates.[226–230] Using this type of reaction, several functionalized (carbonyl, organochalcogenium, acylsilane) dienes were prepared with elongation of the carbon chain and high *E*-stereoselectivity (Scheme 91, Table 7). A solvent-free Horner–Emmons reaction using DBU/SiO_2 was also described. By using this clean procedure, ethyl (*E*)-5,9-dimethyl,2,8-decadienoate and ethyl (*E*)-5,9-dimethyl-2-fluoro-2,8-decadienoate were obtained in good yields.[231] The use of polymer-supported phosphonates in Horner–Wadsworth–Emmons (HWE) reactions was also described.[230] When the Merrifield-supported mixed fluorinated phosphonates were employed, however, preferentially *Z*-alkenes were obtained.[230b]



Scheme 91. Reagents and conditions: (a) DMF, $NaNH_2$, −10 °C→rt, 12 h;[226] (b) THF/HMPA, LDA, 0 °C;[227,246] (c) NaH, THF or Et_2O, rt, 1–4 h;[247–249] (d) ^{t}BuOK, THF, −78 °C, 30 min, then −25 °C, 10 min.[229]

The preparation of chiral phosponates starting from citronellal was also described. The, α-hydroxy-[232] and α-aminophosphonates[233] derived from citronellal were synthesized in 92 and 94% yield, respectively. Citronellal was also used in Wittig reactions with non-stabilized ylides for the preparation of *E*-alkenes.[234,235] These were employed as chiral precursors in the synthesis of trialkylamonium compounds possessing inhibitory plant growth activity. Reaction of **1** with 2,2,2-triphenyl-5-vinyl-1,2λ^5-oxaphospholane produced chiral 3-hydroxy 1,5,11-trienes in good yields.[236] A catalytic amount of a new ruthenium-(trimethylsilyl)diazomethane complex in the presence of PPh_3 was used for the methylenation of (*R*)-citronellal, giving 4,8-dimethyl-1,7-nonadiene in 84% yield after 7 h at 25 °C.[237]

Chiral *Z*-1-iodo-[238,239] and 1-bromo-1,7-dienes,[240] α-alkylidene-β-ethoxycarbonyl cyclopentanones, γ-butyrolactones,[241] and isoxazoles[242] were also obtained starting from citronellal via Wittig-type reactions. For the selective preparation of *E*-1-iodo-1,7-dienes, Takai reaction was

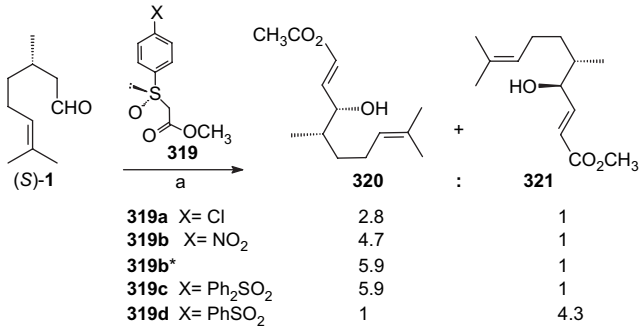
Table 7. 1,7-Dienes **310** from citronellal (**1**) via Wittig-type reactions

Entry	R^1	R^2	*Z*/*E* ratio	Yield (%)	Ref.
1	H	$COCH_3$	0:100	84	226
2	CH_3	$COCH_3$	5.5:94.5	83	226
3	C_2H_5	$COCH_3$	19.3:80.7	82	226
4	H	COC_2H_5	0:100	47	226
5	H	$CO_2C_2H_5$	6.5:93.5	75	226
			0:100	92	230a
			63:37	46	230b
			0:100	47	246
			2:98	54	231
6	CH_3	$CO_2C_2H_5$	20.1:79.1	58	226
7	C_2H_5	$CO_2C_2H_5$	43.9:56.1	67	226
			40:60	71	246
8	C_4H_9Te	C_4H_9Te	—	90	227
9	H	COTBMS	2:98	97	228
10	H	CN	81:19	81	229
			30:70	85	230a
11	H	CON(Me)OMe	0:100	94	249
12	H	$CH{=}CHCO_2Me$	5:95	88	241
13	F	$CO_2C_2H_5$	30:70	77	231

employed as an alternative procedure starting from (*S*)-citronellal and $CrCl_3$/Zn in the presence of NaI.[243] Alternatively to the elimination of vinyl halides, terminal alkynes derived from citronellal could be prepared directly in good yields (72–96%) via an in situ preparation of dimethyldiazomethylphosphonate.[244] An efficient approach to 1,3-polymethyl functions, which are present in structures of several antibiotic macrolides and insect pheromones, was developed starting from both enantiomers of citronellal using the chiral phosphonate (1′*R*,2′*R*)-2′-hydroxycyclohexyl diethylphosphono-acetate.[245]

12.3. Via hydroxylative Knoevenagel condensation

The enantioselective variation of the hydroxylative Knoevenagel condensation is a valuable chain extension method, because it affords polyfunctionalized compounds for structural investigations. Aiming to test the efficiency of new chiral α-sulfinyl esters in the stereoinduction of γ-hydroxy-α,β-unsaturated enoates, the reaction of several chiral sulfinyl esters (**319**) with (*S*)-citronellal (**1**) was performed (Scheme 92).[250]



Scheme 92. Reagents and conditions: (a) piperidine (2 equiv), CH_3CN, 10 °C, 60 h, 62–80%; *In this case, 4 equiv of piperidine was employed.

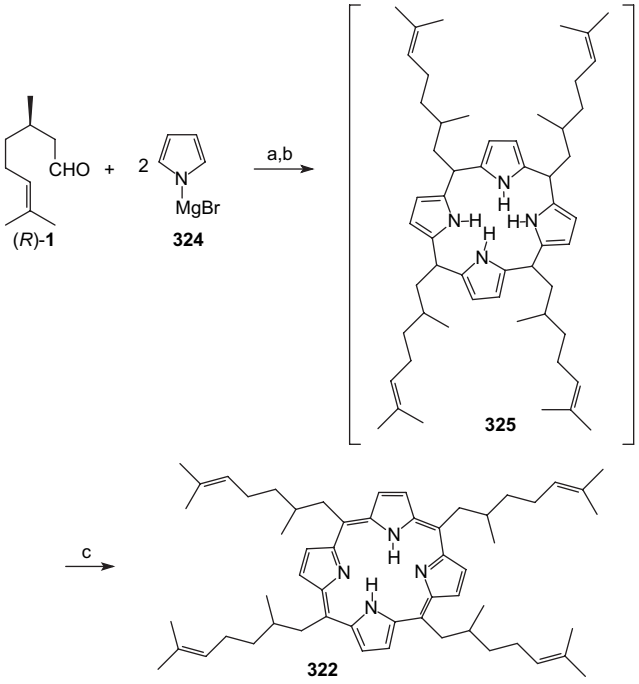
This sulfoxide piperidine aldehyde condensation (SPAC) was also employed in the synthesis of chiral (*E*)-γ-hydroxy- and (*E*)-γ-keto-α,β-unsaturated sulfoxides[251] and (*E*)-γ-hydroxyenones,[252] (*E*)-γ-hydroxy-α,β-unsaturated phenylsulfones,[253] 3-hydroxy-1-alkenylphosphonates,[254] and (*E*)-γ-hydroxyacrylonitriles[255] starting from (*R*)- and (*rac*)-**1**.

A very closely related SPAC adduct, (*E*)-γ-hydroxy-α,β-unsaturated aldehyde,[256] was obtained in 79% yield through the use of (3,3-diisopropoxypropyl)-triphenylarsonium ylide and citronellal. The arsonium ylide acts as a synthetic equivalent of the β-formyl vinyl anion. When the unsaturated (5,5-diethoxy-2-(*E*)-pentenyl)-triphenylarsonium ylide was employed, the corresponding 6-hydroxy-2,4-(*E*)-dienal was obtained in 58% yield.[257]

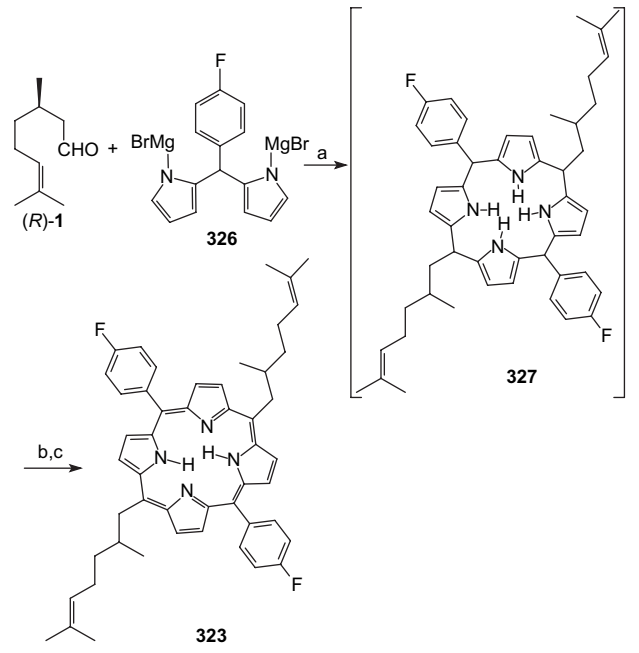
An alternative route to chiral allylic alcohol involves the direct addition of vinylmetals (Mg, Li, Al) to citronellal.[258] The vinyl alcohols were obtained in 57–84% yield, with vinylalane showing the best result.

13. Synthesis of porphyrins

Superstructured porphyrins with different types of functionalities in the same molecule are interesting, because they may have useful properties for photodynamic therapy, molecular recognition, and structure–activity studies. A simple approach to new macrocyclic chiral porphyrins (**322** and **323**) was developed (Schemes 93 and 94, respectively) through reaction of (*R*)-citronellal (**1**) to pyrrole derived Grignard reagents.[259]



Scheme 93. Reagents and conditions: (a) CH_2Cl_2, 4 h; (b) H_2O, H^+; (c) air, 48 h, 7.8% (three steps).



Scheme 94. Reagents and conditions: (a) CH_2Cl_2; (b) DDQ oxidation; (c) H_2O, H^+, 4.7% (three steps).

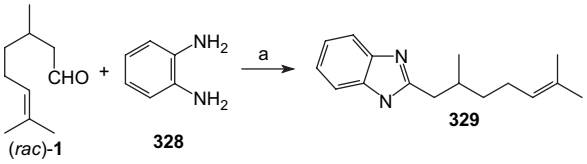
To achieve **322**, (*R*)-**1** was reacted with pyrrolemagnesium bromide (**324**) for 4 h. Quenching the magnesium bromide salt with aqueous-acid-catalyzed media afforded the

porphyrinogen **325** (not isolated). After 48 h of air oxidation, **322** was obtained in 7.8% yield (Scheme 93).

It was pointed out that magnesium bromide was an ideal promoter to enhance the eletrophilic power of aldehyde carbonyl, the nucleophilicity of the pyrrole C-2 carbon and, last but not least, to minimize the attack at the nitrogen by ensuring the C-2 regioselectivity. It is important to note that all stereogenic centers of the final products came from (*R*)-citronellal (**1**). It was also suggested that the mechanism of these transformations is analogous to that proposed for the arylation and hetero-arylation of protected carbohydrates. When 4′-fluorophenyldipirrylmethanebis-magnesium bromide (**326**) was used as nucleophile in CH_2Cl_2, the porphyrinogen **327** was obtained (not isolated). After oxidation with 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) followed by aqueous-acid treatment, **323** was obtained in 4.7% yield (Scheme 94).

14. Synthesis of imidazol derivatives

When citronellal (**1**) was reacted with *o*-phenylenediamine (**328**) in the presence of $Yb(OTf)_3$ as Lewis acid, 2-(2,6-dimethylhept-5-enyl)-1*H*-benzimidazole (**329**) was obtained in 81% yield after stirring for 30 min at room temperature (Scheme 95).[260] Using 3-dimethylhydrazono-1,1,1-trifluoro-2-propanone as a nitrogenated compound in the presence of $AcOH/AcONH_4$ affords the corresponding chiral 4-trifluoromethylimidazole in 51% yield.[261]

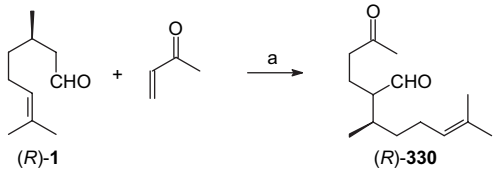


Scheme 95. Reagents and conditions: (a) $Yb(OTf)_3$ 0.05 mol %, CH_2Cl_2, rt, 30 min, 81%.

A two-step synthesis of (*S*)-1-citronellyl imidazoles from (*S*)-citronellal via 4-tosyloxazolines was described.[262] This procedure involves the transformation of the 4-tosyloxazoline derived from citronellal to the respective imidazole by treatment with NH_3 or $MeNH_2$. With the aim to determine the enantiomeric excess of citronellal samples, they were reacted with *N*,*N*′-dimethyl-1,2-diphenyl ethylene diamine (DMPEEDA).[263] The diastereomeric imidazolidine derivatives were easily separated on a silica gel column and converted into enantiomerically pure citronellal.

15. 1,4-Addition to vinyl ketones: preparation of chiral octenal

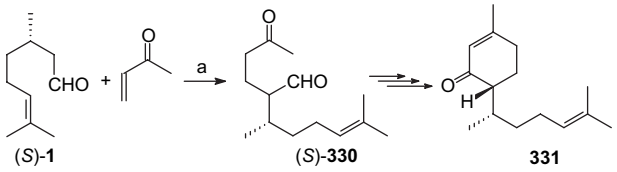
Racemic and pure (*R*)-citronellal (**1**) was employed in a new procedure for the 1,4-addition of naked aldehydes to electron-deficient olefins, like methyl vinyl ketone (MVK). The reaction was catalyzed by diethylamino(trimethyl)-silane (DEATMS) and affords chiral, highly functionalized (3*R*)-3,7-dimethyl-2-(3-oxobutyl)-6-octenal (*R*)-**330** in 96% yield (Scheme 96).[264,265] The octenal (*R*)-**330** is useful in the preparation of substituted 2-cyclohexen-1-one derivatives, versatile starting materials for the syntheses of natural products, such as terpenoids.



Scheme 96. Reagents and conditions: (a) Et_2N–TMS (10 mol %), CH_3CN, reflux, 46 h, N_2, 96%.

A similar reaction uses heterogeneous catalysts and ionic liquid.[266] This greener approach allowed for the 1,4-addition to other Michael acceptors like acrylonitrile and 4-penten-3-one. Additionally, the catalyst can be reused for further syntheses.

The 1,4-conjugate addition of (*S*)-citronellal (**1**) to MVK was the key step in the synthesis of the cyclohexenone derivative **331**, isolated from *Stevia purpurea*,[267] and other natural bisabolane-type monocyclic sesquiterpenoids[268] (Scheme 97).



Scheme 97. Reagents and conditions: (a) Et_2N (0.2 equiv), toluene, 80 °C, 24 h, 87%.

16. Miscellaneous

As briefly mentioned in Section 1, there are several articles where citronellal is one of the substrates used in systematic studies involving reactions like cross-[269] and self-condensations,[270] preparation of α-methylene carbonyl compounds,[271] α-phenylseleno-[272] and α-silyloxy citronellal,[273] functionalized furans,[274] pyrroles,[274c] chiral cyclic sulfinates,[275] and 2-substituted cyclohexanone.[276]

Unmodified citronellal was used as a nucleophile in a new asymmetric Mannich reaction affording β-formyl-substituted α-amino acids in 42% (from (*S*)-**1**) and 45% yield (from (*R*)-**1**) and 100% de.[277] (*S*)-Citronellal was used in the diastereoselective hetero-Diels–Alder reaction with Danishefsky's diene to give diastereomerically enriched dihydropyranone derivates in good yields (85–99%). The stereoisomerism of the products can be modulated by appropriate choice of chiral Schiff base–Cr(III) complex catalyst.[278]

Reactions where a nucleophilic addition at the carbonyl of citronellal is involved were used to prepare chiral functionalized esters,[279] alcohols,[280] nitriles,[281] acyl cyanides,[282] ketones,[283] and tetracyclic chiral quinones.[284]

Besides all of the aforementioned uses, citronellal plays an important role in systematic studies, for example, when

modifications at the carbonyl unit or at the isolated double bond are involved. Here, citronellal is the compound of choice because of high interest in the preparation of functionalized compounds, and/or to study the influence of the chiral moiety in the stereoselectivity of new methodologies. Thus, protection of the carbonyl group on citronellal using the acetal,[285] 1,3-dithianes,[286] 1,3-oxathiolanes,[287] selenoacetals,[288] thioacetals,[289] 3-methylbenzothiazolines,[290] imidazoles,[291] silyl ethers,[292] and α-alkoxyorganostannane[293] has been described. Sulfonium ylides were employed in the transformation of the carbonyl moiety of citronellal into the respective epoxides (Corey–Chaykovsky epoxidation)[294] and unsaturated oxaspiropentanes, which are intermediates in the biosynthesis of steroids.[295]

Several chiral homoallylic alcohols have been synthesized from citronellal by a Barbier-type allylation induced by Cu(II)–Mg,[156] $SnCl_2 \cdot 2H_2O$–Mg,[296] aqueous $SnCl_2$/KI,[297] or bidirectional asymmetric allylboration.[298] Allylstannation with dibutylallyltin chloride,[299] allyltitanation with Cp_2TiCl_2[300] or with allylic acetate/$CoBr_2$[301] or with tetraallylstanane/ionic liquid[302] of citronellal were also described to afford the corresponding homoallylic alcohols. The addition of allyl magnesium bromide to (*R*)-citronellal, followed by quenching with acryloyl chloride, gives the corresponding chiral acrylate ester (74% yield). The polyunsaturated ester was submitted to a ring closing metathesis (RCM), catalyzed by Grubbs's catalyst, to afford the α,β-unsaturated ketone derivate in 86% yield.[303]

Several functionalized α,β-epoxides were selectively obtained starting from citronellal and the lithium enolate of α-chloroamides[304] and esters.[305] These epoxides were used for the synthesis of (*E*)-α,β-unsaturated amides[304] and esters,[305] α-hydroxyamides[304a] and 2,3-dideuterioesters[306] using SmI_2. When citronellal was reacted with the lithium enolate of methyl dichloroacetate, the respective α,α-dichloro-β-hydroxy ester was obtained in 93% yield, which was employed for the preparation of chiral (*Z*)-α-chloro-α,β-unsaturated esters.[307] In a similar way, citronellal was converted to α-halo-β-hydroxy esters, by reaction with the lithium enolate of α-chloro esters.[308] These were then used for the synthesis of (*Z*)-α-halo-α,β-unsaturated esters[308a] and 2,3-dideuterioesters[308b] in good yields.

17. Conclusions

In recent years, the increasing interest generated by the chemical and pharmaceutical industry to develop more selective processes and also the use of raw materials from renewable sources has stimulated the search for new natural starting materials. This can replace current reagents and processes that have low atomic efficiency. Citronellal is an attractive compound in organic synthesis for several reasons: it is easily available from natural sources (e.g., from citronella and eucalyptus oil) or synthetically prepared (Takasago process); it is cheap and both enantiomers are available with high degrees of purity.

As outlined in this review, citronellal is a key compound in numerous organic syntheses for the insertion and/or induction of chirality in more complex naturally or non-naturally occurring molecules. When citronellal is used in one of its pure forms (*R* or *S*), it is possible to prepare chiral molecules with high enantioselectivity, while avoiding expensive and tedious separation and purification steps.

Citronellal, as well as several related natural compounds, can be considered as a Swiss Army Knife for the organic chemist, because they are excellent commodities in the flavors and fragrances industries. It is a versatile reagent (it possesses a chiral center, an isolated double bond, and an aldehyde function) that is obtainable from renewable sources at competitive prices, biodegradable, and can be used in numerous processes with high intrinsic atomic efficiency and enantioselectivity.

These synthetic aspects match with several green chemistry principles and make citronellal an excellent tool for the implementation of cleaner and environmentally benign processes. This has a major positive effect on different segments of the chemical and pharmaceutical industries. We hope that this review can motivate synthetic organic chemists in their search for new processes that use citronellal or other natural multi-functionalized compounds as raw materials.

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Biographical sketch

Eder J. Lenardão was born in 1968 in Sabáudia-PR, Brazil. He received his BS from State University of Londrina and MS degree from Federal University of Santa Maria-RS under the guidance of Professor Claudio C. Silveira. In 1997, he earned a PhD degree in organic chemistry at University of São Paulo, under the guidance of Professor Miguel J. Dabdoub and in 2003 he worked with Professor Antonio L. Braga at UFSM as a postdoctoral fellow. His research interest lies in the area of organic and green chemistry.

F. de Azambuja was born in 1986 in Ijuí-RS, Brazil. He joined in the Chemistry under graduation course in 2004 at State University of Campinas (Brazil), graduating in 2007. As Undergraduate Student Researcher under the direction of G. Perin, he worked in the synthesis of organochalcogen compounds using new cleaner approaches. At the moment, his research interests are focused in Heck arylation and its applications.

G. V. Botteselle was born in 1984 in São Luiz Gonzaga-RS, Brazil. He started his under graduation course in 2002, at Unijuí (Brazil), graduating in 2007. In 2002, he started to work as Undergraduate Student Researcher under the direction of Professor R. G. Jacob in research focused in organic synthesis with essential oils and using the principles of green chemistry. Actually, his research interests are focused in the identification of chemical composition of essential oils.

G. Perin was born in 1969 in Maximiliano de Almeida-RS, Brazil. He received his under graduate education (1994), MSc (1996), and PhD thesis (2000) at Federal University of Santa Maria (Brazil) under the direction of Professor C. C. Silveira. In 2004, he obtained a position at the Federal University of Pelotas-RS (southern Brazil) as Professor of Organic Chemistry. His research interests are focused in the synthesis of organochalcogen compounds using new cleaner approaches.

Raquel G. Jacob was born in 1964 in Rio de Janeiro-RJ, Brazil. She received his BS (1989) and MS degrees (1994) from Federal University of Rio de Janeiro (Brazil) under the guidance of Professor Claudio C. Neto. In 1998, she earned a PhD degree in organic chemistry at University of São Paulo under the guidance of Professor Miguel J. Dabdoub and in 2005 she worked with Professor Antonio L. Braga at UFSM as a postdoctoral fellow. Her research interest lies in the area of structural modifications in essential oils and their constituents by using cleaner methods.