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The chemistry of the himachalenes and atlantones from Cedrus

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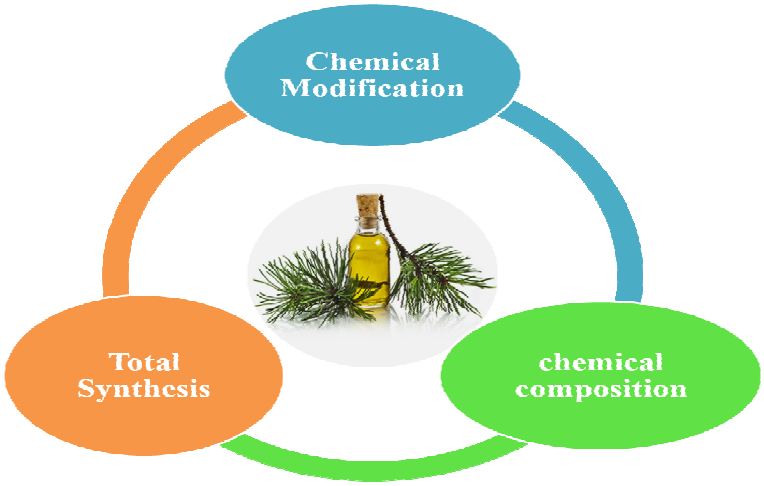
Abstract

Synthesis and functionalization of natural products are useful procedures to access and develop new and interesting molecules with biological properties. In this review we discuss the major sesquiterpenes isolated from the essential oil of cedar, which represents a family of abundant and inexpensive natural materials. Some total synthesis and chemical transformations described in the literature have been included.



Keywords: Cedar (*Cedrus*), himachalenes, atlantones, hemisynthesis, total synthesis

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1. Introduction

Plants have always been a vital source of medicines. Today the majority of the world's populations, particularly in developing countries, are treated only with traditional herbal remedies. The modern pharmaceutical industry is largely based on the diversity of secondary metabolites to find new molecules with new biological properties.[1] The study of plants represents a huge potential for discovery of new substances or new "lead compounds" if we consider that each of these plants can contain hundreds or thousands of secondary metabolites.[2] The largest pharmaceutical companies know that tropical forests and fields can become a potential sources of valuable drugs. They invest significant capital to find new substances to make drug candidates that can be commercialized. Research in this field becomes automated and pharmaceutical companies will soon have the opportunity to study millions of chemical substances per week.[3]

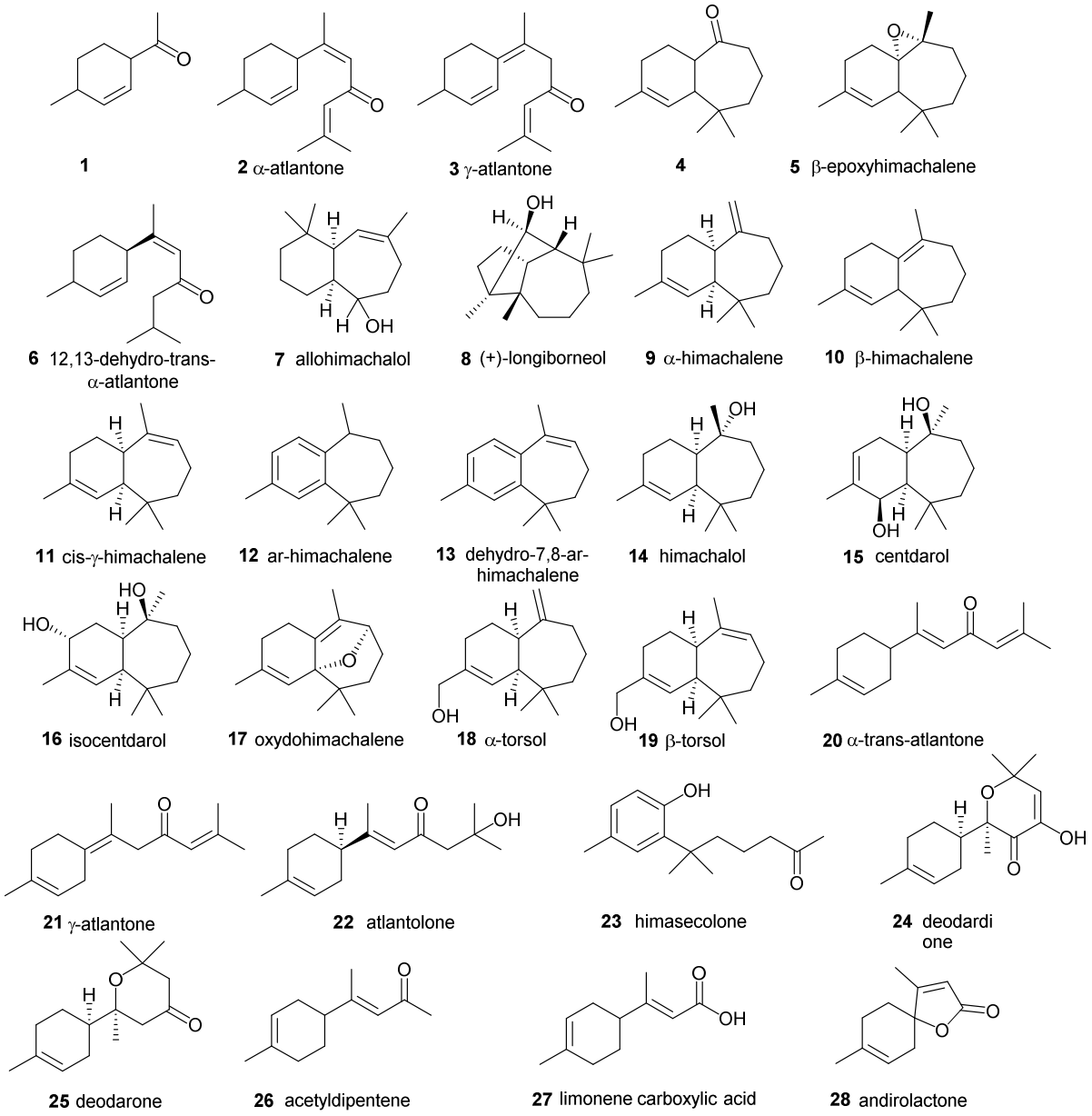
The genus Cedar belongs to the family *Pinaceae*. This kind of tree has existed since the tertiary era. In this review, the term "Cedar" refers to four species: *Cedrus brevifolia*, *Cedrus deodara*, *Cedrus libani* and *Cedrus atlantica.* The Atlas cedar (*Cedrus atlantica)* is endemic to North Africa, especially Morocco and Algeria. It is exposed to a bright and dry climate in summer. The Himalayan cedar (*Cedrus deodara*) remains the species most represented, with an estimated area of 500,000 hectares. It occurs in the regions of the Himalayas from Afghanistan to western Nepal where there is a sub-Mediterranean temperate and subtropical climate. *Cedrus libani*, the emblem of Lebanon, occupies large areas in the mountains of northern and central Lebanon.

This review covers the chemical composition of the essential oil of cedar, different routes to synthesis of major constituents of this oil and its chemical transformation.

2. Chemical Composition of the Essential Oils of Cedar

Many chemical studies have been devoted to species of Pinaceae, but very few of them dealt with *Cedrus*. The studies reported in the literature essentially treated the two species: *atlantica* and *deodara*. We report the chemical composition classifying by family of compounds of three species: a*tlantica, deodara* and *libani*.

The earliest work on the essential oils of cedar took place back in 1902, when the ketone **1** was isolated for the first time by Grimal.[4] Pfau and Plattner[5] showed the existence of two sesquiterpene ketones: α-and γ-atlantone **2** and **3**. Teisseire and Plattier[6] identified an epoxide and two sesquiterpene ketones, namely β-epoxyhimachalene **5**, 12,13-dehydro-*trans*-α-atlantone **6** and 6,6,9-trimethylbicyclo[5.4.0]undec-8-en-2-one **4**. Besides these products, Sukh Dev *et al***.**[7] isolated other sesquiterpenoid compounds, such as allohimachalol **7** and (+)-longiborneol **8** (Scheme 1).



Scheme 1. Compounds isolated from essential oil of cedar.

Ruzička *et al.*[8] discovered the existence of an optically inactive bicyclic sesquiterpene that could form a dihydrochloride by the action of gaseous hydrogen chloride in acetic acid. Rao *et al.* isolated two bicyclic optically active sesquiterpene hydrocarbons named α- and β-himachalene, **9** and **10** respectively (Scheme 1).[9] The structures of these two sesquiterpenes were identified and confirmed by Joseph and Dev.[10]

In 1961, Bredenberg and Erdtman obtained similar sesquiterpenes from the essential oils of the wood of *Cedrus atlantica* and *Cedrus libani* by fractional distillation followed by chromatography on alumina.[11] Moreover, Teisseire and Plattier[12] isolated and identified three other sesquiterpene, cis-γ-himachalene **11**, and two with the fully aromatic six-membered ring, *ar*-himachalene **12** and dehydro-7,8-*ar*-himachalene **13** (Scheme 1).

Other compounds were described, such as himachalol **14** oxydohimachalene **17**, atlantolone **22**, deodarone **25**, deodardione **24**,[13-17] centdarol **15**, isocentdarol **16**,[18,19] α-torsol **18**, β-torsol **19**, andirolactone **28**,[20] α-*trans*-atlantone **20**, γ-atlantone **21**,[21] himasecolone **23**,[22] acetyldipentene **26** and limonene carboxylic acid **27** (Scheme 1).[17] In addition, the products mentioned above, recent studies have been discovered the existence of other compounds.[23-27]

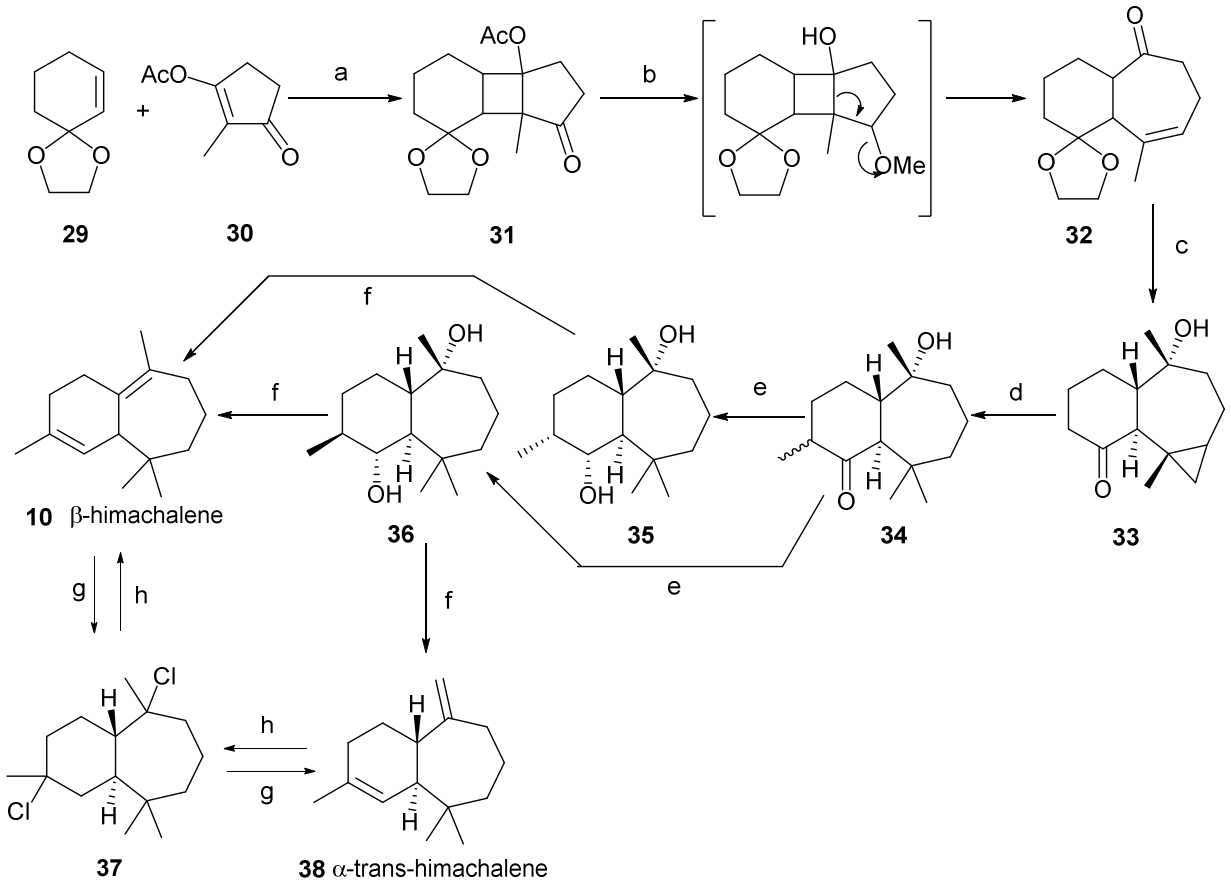
3. Total Synthesis

3.1 Synthesis of himachalenes

A significant number of methods have been developed for the synthesis of himachalenes. The first was carried out by De Mayo *et al*.[28,29] They realized a synthesis in seven steps to get the α-*trans* and β-himachalenes (Scheme 2). Indeed, β-himachalene was prepared starting from 1,4-dioxaspiro[4.5]dec-6-ene **29** and enone acetate **30** according to the reaction scheme shown. Irradiation of both compounds in cyclohexane provided a tetracyclic ketone **31**. The reduction of ketone function in the presence of sodium borohydride followed by conversion into the mesylate and hydrolysis with NaOH (0.7%) in mixture of solvent H_2O/dioxane gave a tricyclic ketone **32** in 35% yield based on **31**. The action of CH_3MgI followed by treatment with the Simmons-Smith reagent gave after hydrolysis a product **33** with a cyclopropane moiety. Then, alkylation was conducted with $CH_3I/(CH_3)_3COK$ in *t*-butyl alcohol-benzene followed by hydrogenation with (Pt/Rh) catalyst to gave **34**. Reduction of **34** with LiAlH4 gave a separable mixture of diols **35** and **36** Finally, dehydration in pyridine in presence of $POCl_3$ provided a mixture of two isomers, α-*trans*- and β-himachalene **38** and **10** respectively.

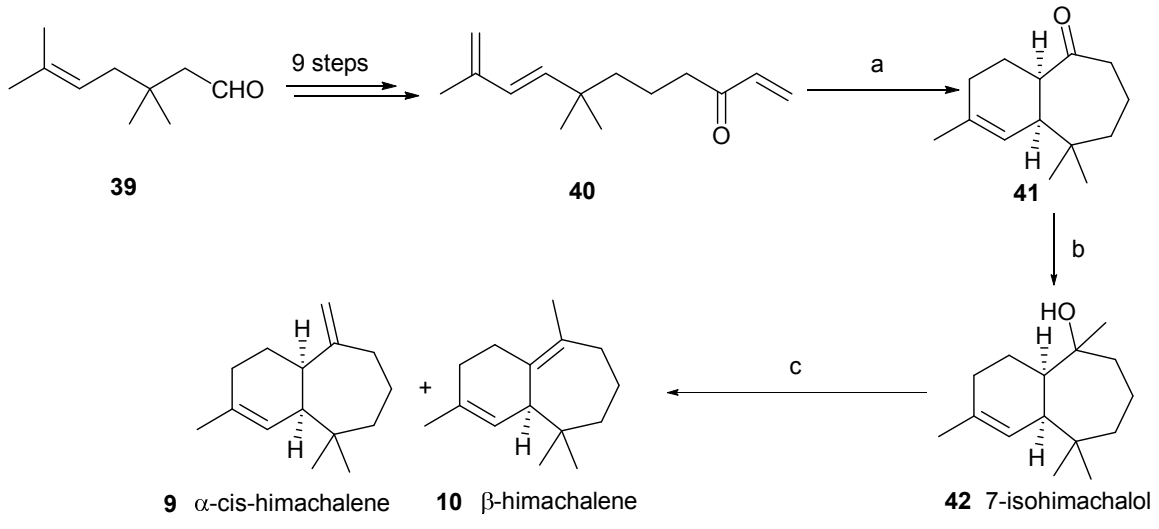
The second synthesis was conducted by Wenkert and Malmura.[30] It is based on an intramolecular Diels-Alder cycloaddition of trienone **40** (7,7,10-trimethyl-1,8,10-undecatrien-3-one) catalyzed by Lewis acid (Scheme 3). This derivative was obtained in its turn from 3,3,6-trimethyl-5-heptenal **39** in nine steps. Treatment of compound **40** with $AlCl_3$ in toluene under reflux for 2 h, then with methyllithium led to the formation of 7-isohimachalol **42**; dehydration afforded a mixture of bicyclic dienes α-*cis* and β-himachalenes.

Another trienone derivative **50** was also mentioned.[31] This derivative is successfully prepared by addition [1,2] of the enolate ester **43** with 3,3-dimethylacrolein **44** in THF at –78 ^oC. The allyl alcohol **45** so formed (72%) was dehydrated in presence of TsOH to give *trans*-dienyl ester **46** (90%). Simple reduction of the latter with $LiAlH_4$ provided the corresponding alcohol, which is oxidized in its turn by PCC at 25 ^oC to obtain dienal **47** (82%) (Scheme 4). Reaction of product **47** with complex **48** in THF at -78 ^oC followed by protection of the alcohol formed with diethyl phosphochloridate $ClPO(OEt)_2$ gave the trienyl phosphate **49** with a 85% yield. The cleavage of the silanol ether group in product **49** with potassium fluoride KF in methanol at 0 °C provided the product **50** in 85% yield. Finally, an intramolecular cycloaddition [4+2] of the product **50** in benzene at reflux gave octahydrobenzocycloheptanone **41** (90%). The same steps as previously described allow isolation of a mixture of the two isomers α-*cis*- and β-himachalenes **9** and **10** from **42**.



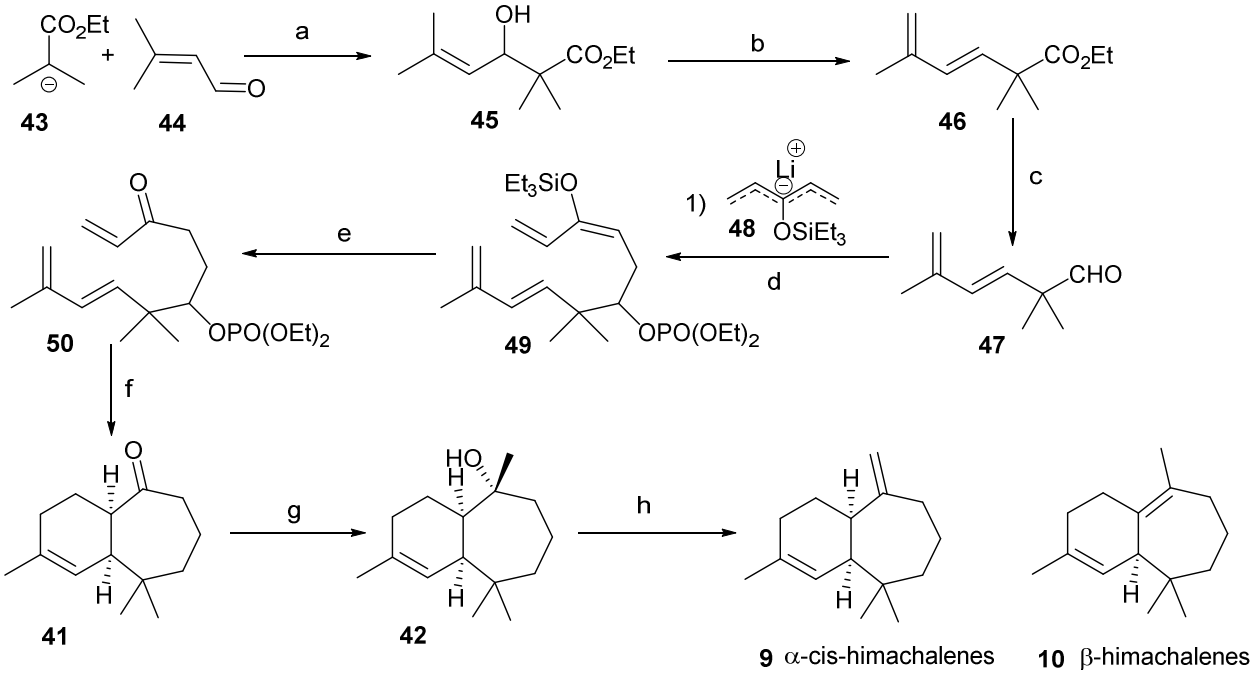
a) irradiation, cyclohexane. b) 1: $NaBH_4$. 2: MsCl, NaOH (0.7%), H_2O/dioxane. c) 1: CH_3MgI, 2: Simmons-Smith reagent. d) 1: $CH_3I/(CH_3)_3COK$, t-butyl alcohol-benzene, 2: Pt/Rh. e) $LiAlH_4$. f) $POCl_3$, pyridine. g) HCl. h) pyridine

Scheme 2. Total synthesis of α-*trans* and β-himachalenes developed by De Mayo.



a) $AlCl_3$, 110°C. b) MeLi. c) $POCl_3$/Py

Scheme 3. Synthesis of α-*cis* and β-himachalene by intramolecular Diels-Alder reaction.

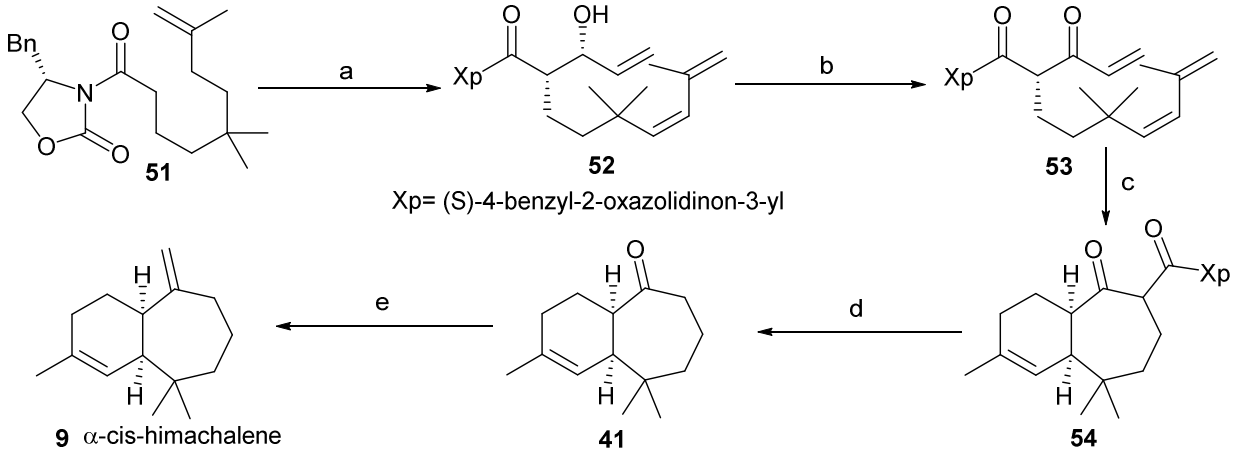


a) THF, -78 °C. b) TsOH/25°C, c) 1: $LiAlH_4$, 2: PCC, 25 °C. d) complex **48**, THF, -78 °C, 2: $ClPO(OEt)_2$. e) KF/MeOH, 0 °C. f) benzene, 80°C/18h. g) MeLi. h) 1: Li/Et_3N, 2: $SOCl_2$/Py

Scheme 4. Synthesis α-*cis*- and β-himachalene by intramolecular cyclization.

Evans *et al.*[32] used the same approach to synthesize *cis*-α-himachalene starting from a chiral dienimide **51** (Scheme 5). Reaction of this chiral compound with acrolein leads stereoselectively to allylic alcohol **52**.[33] The latter undergoes Parikh-Doering oxidation to give the trienone **53**.[34] Intramolecular [4+2] cycloaddition of the trienone **53** in presence of $ZnBr_2$ provides the product **54**, which was converted into an *S*-ethyl β-keto-thioester by action of LiSEt. Decarboxylation of the latter provides the ketone **41** and the synthesis is completed by treating with Tebbe reagent.[35]

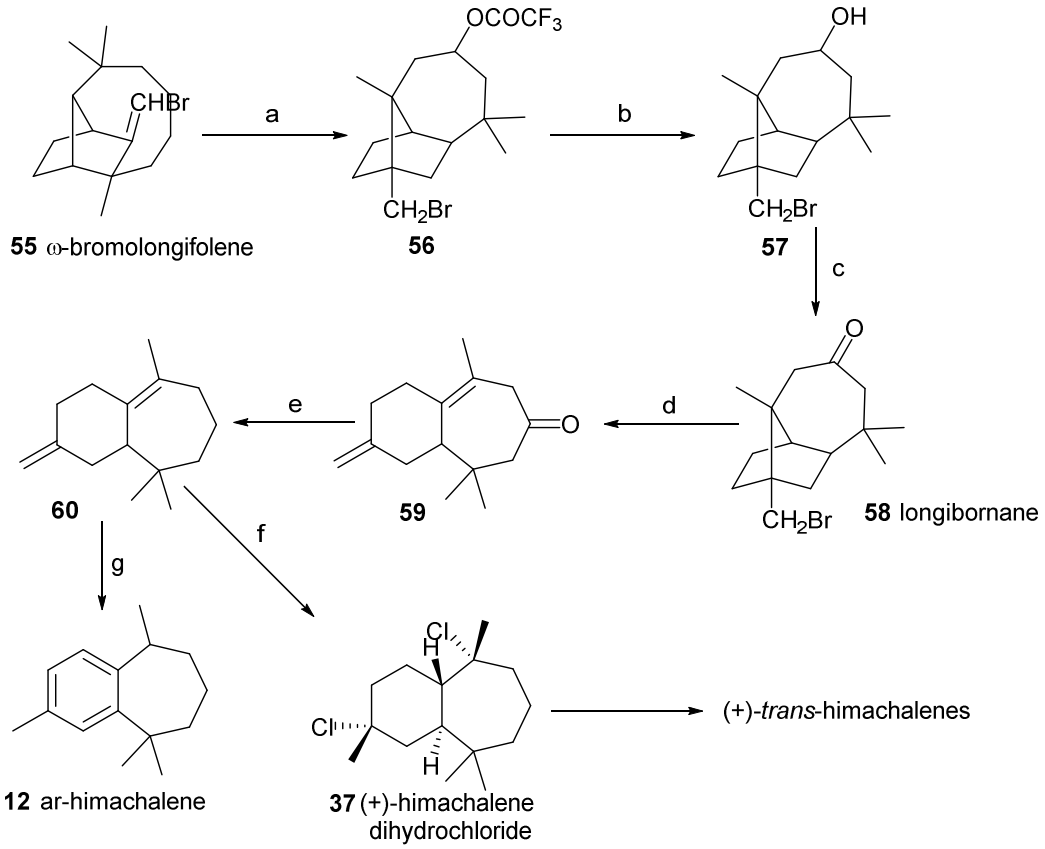
Using an intermolecular Diels-Alder reaction, Brown and Liu achieved the synthesis of α-*cis*- and β-himachalenes in eleven steps and in an effective overall yield of 21% from 4,4-dimethyl-2-cyclohexenone.[36]



a) 1:Bu_2BOTf, iPr_2NEt,isoprene 0°C. 2: Acrolein, -78°C. b) SO_3/Pyridine, DMSO/CH_2Cl_2, iPr_2NEt, -10°C. c) $ZnBr_2$ 0°C. d) 1: LiSEt. 2:$AgNO_3$ 2,6-lutidine, THF/H_2O 70°C. c) Tebbe reagent.

Scheme 5. Synthesis of *α-cis* -himachalene from *N*-acyloxazolidinone **51**.

Another synthesis in seven steps was carried out by Mehta and Kapoor starting from the tricyclic sesquiterpene longifolene.[37] This strategy allowed synthesis of (+)-himachalene dihydrochloride which is an intermediate that gave access to *trans*-himachalene derivatives and (+)-*ar*-himachalene (Scheme 6).

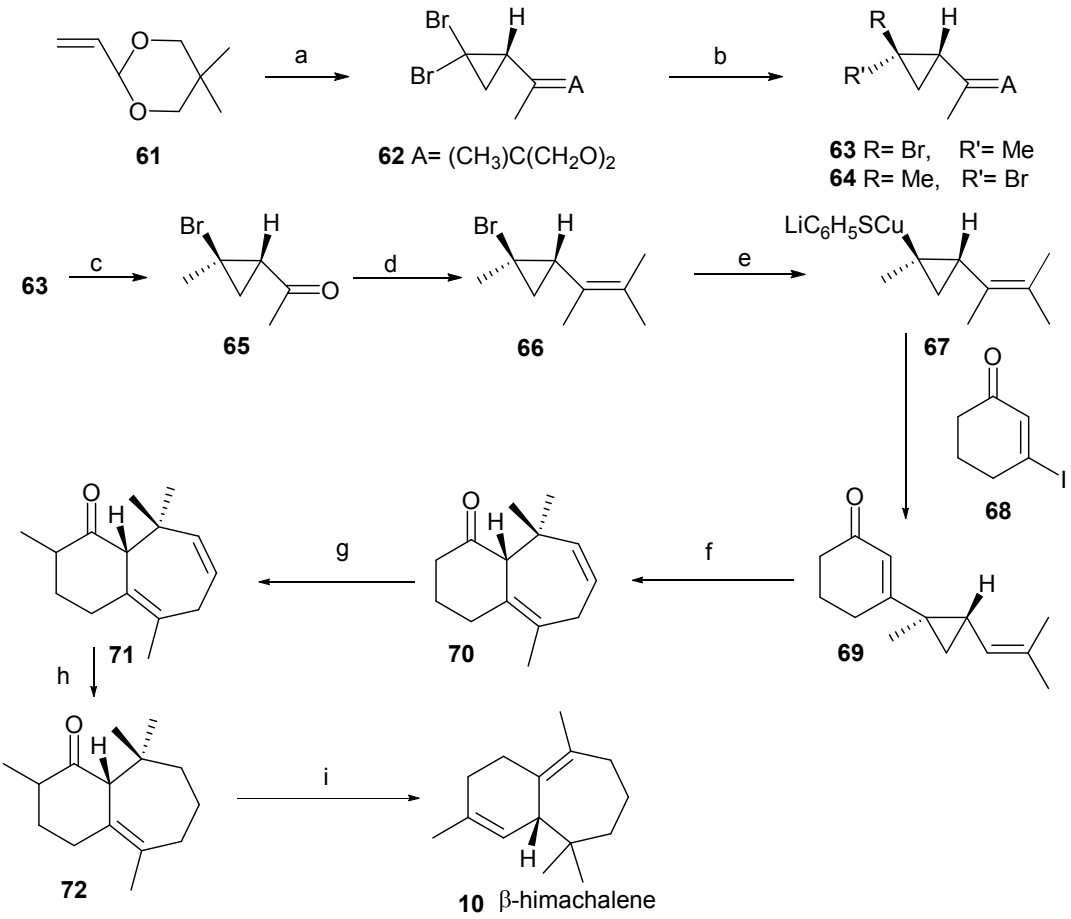


a) CF_3COOH; b) KOH/EtOH; c) Jones reagent; d) Corey method; e) Wolff-Kishner; f) HCl(gas) in acetic acid; g) Chloranil, Pd/C.

Scheme 6. Synthesis of (+)-*trans*-himachalenes.

The key step is the preparation of a bifunctional longibornane derivative **58** as the initial target. This was obtained from *ω*-bromolongifolene **55** *via* an acid-catalyzed rearrangement involving an intramolecular 1,5-hydride shift. The bicyclic ketone **59** was prepared from **58** using Corey reaction.[38] Thus, Wolff-Kishner reduction of **59** and purification ($AgNO_3$-silica gel) gave the himachalene isomer **60.** A stream of HCl gas through an acetic acid solution of **60** gave (+)-himachalene dihydrochloride **37**.[39] The latter has already been converted into β-himachalene. Thus, the *ar*-himachalene was obtained from **60** by dehydrogenation with chloranil followed by aromatization with Pd/C.

In a similar way, a study of Dev and Shastri[40] showed that α- and β-himachalene can be obtained by Wagner-Meerwein rearrangement of longipinene with a variety of acids ($BF_3.Et_20$, $HClO_4$ in aqueous dioxane, H_2NS0_20H in acetone, and H_2S0_4 in glacial acetic acid).



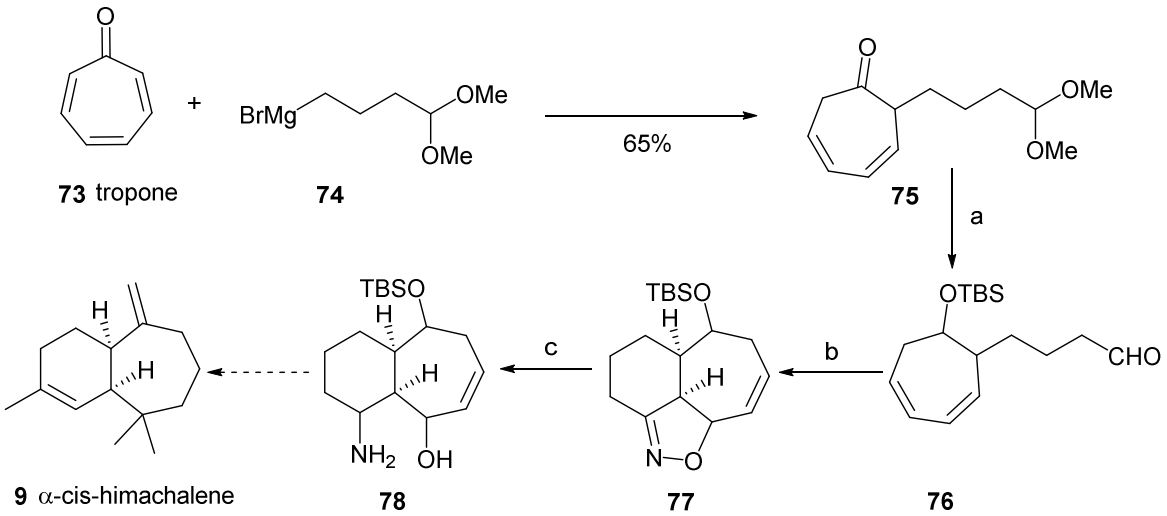
a) $CHBr_3$, NaOH. b) nBuLi, MeI. c) HCO_2H. d) $Ph_3PC(CH_3)_2$. e) 1: nBuLi, 2: PhCuLiS, f)Xylene, reflux, g)1) LDA 2) MeI, h)$(PPh_3)_3RhCl$, i) LDA.

Scheme 7. Synthesis of β-himachalene from 3-iodocyclohex-2-enone **68** and cuprate derivative **67**.

Piers and Ruediger[41] have described a total synthesis of β-himachalene **10** using cuprate **67** prepared from 5,5-dimethyl-2-vinyl-1,3-dioxane **61**. The latter reacted with bromoform and sodium hydroxide in presence of a phase-transfer catalyst to give dibromocyclopropane **62**. Treatment of the latter with *n*-butyllithium and methyl iodide gave a mixture of two epimers **63** (87-93%) and **64** (7-13%). The hydrolysis of product **63** with formic acid followed by Wittig reaction with isopropylidene triphenylphosphorane provided a brominated cyclopropane **66** which was converted into cuprate **67** by treatment with nBuLi/PhSCu. The interaction of 3-iodocyclohex-2-enone **68** with a cuprate **67** followed by thermolysis (xylene reflux) provided dienone **70** in quantitative yield. Methylation of the latter gave the compound **71**, which was converted into ketone **72** by hydrolysis in the presence of tris-triphenylphosphine rhodium chloride. The transformation of the ketone to the corresponding enol phosphate was followed by reduction to give β-himachalene **10** (Scheme 7).

α-*cis*-Himachalene has also been prepared starting from tropone **73** as described by Rigby and McGuire.[42] This strategy is based on a 1,8-addition-intramolecular cycloaddition protocol for construction of the bicyclo[5.4.0]undecane motif. The reaction of Grignard reagent **74** with tropone led to the formation of compound **75**. Then, the oxidation and protection of the corresponding alcohol provided compound **76**. The latter was then reacted with hydroxylamine hydrochloride under standard conditions. Conversion of the resultant oxime to the nitrile oxide by oxidation with sodium hypochlorite proceeded without incident and

cycloaddition ensued to give the *cis*-fused bicyclic product **77.** Reductive cleavage of the isoxazoline ring furnished amino alcohol **78** which was converted into α-himachalene **9**.[30,36,43,44]



a) 1: $NaBH_4$/MeOH, 2: TBDMSCl, imidazole, 3: TFA, aq acetone (36%). b) 1: NH_2OH HCl, TEA, 2: $NaOCl/CH_2Cl_2$ (56%). c) $LiAlH_4/Et_2O$ (95%).

Scheme 8. Synthesis of α-*cis*-himachalene from tropone.

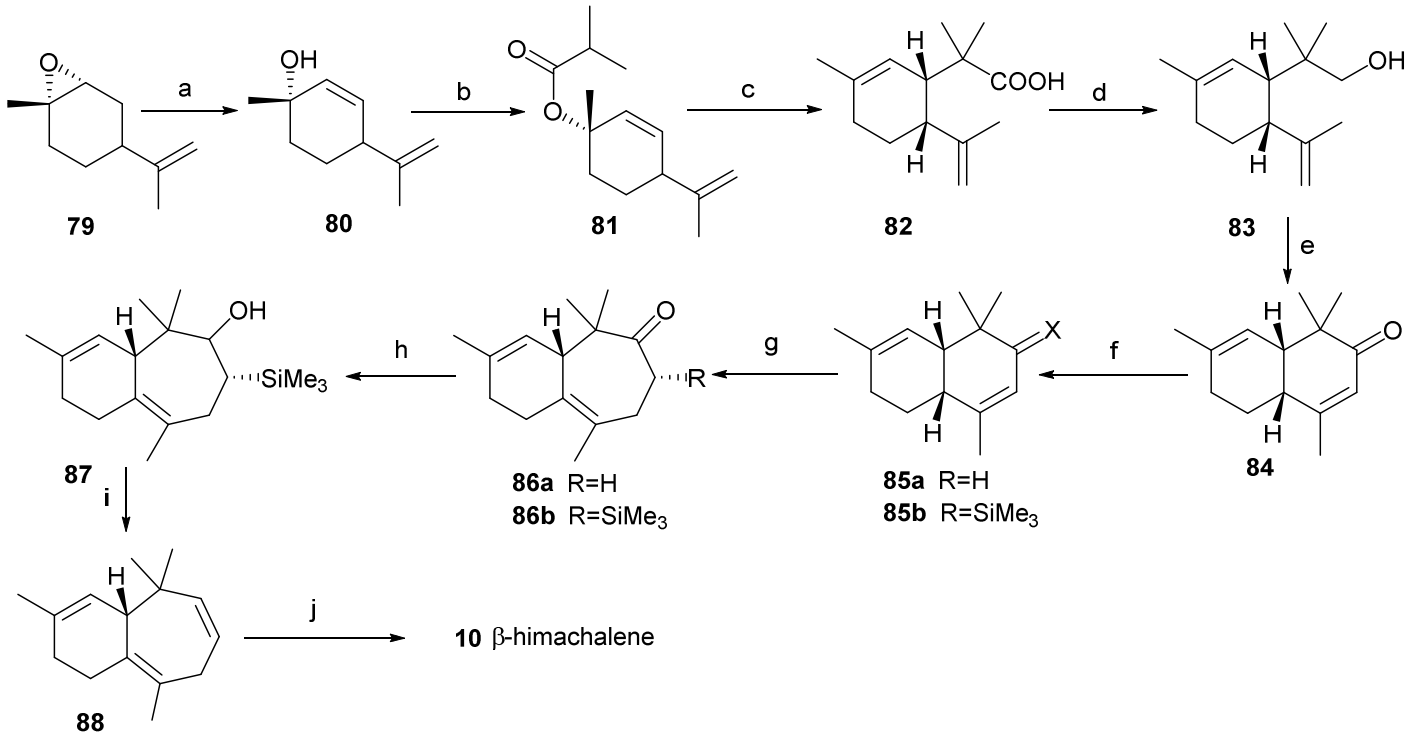
An asymmetric version of the synthesis of α-*cis* and β-himachalenes was recently reported by Ho and Chein,[45] starting from (1*S*,2*R*)-1,2-epoxy-*p*-menth-8-ene **79** in 15 or 16 steps with an overall yield of 6% (Scheme 10). The key steps include an Ireland–Claisen rearrangement, a Corey oxidative cyclization and a ring expansion.

The first step involves opening of the epoxide **79** followed by protection of the resulting alcohol **80** with isobutyric anhydride to obtain the product **81**. Acid **82** was obtained by Ireland–Claisen rearrangement of **81**. Then compound **82** was converted into **84** by a sequence of reactions involving $LiAlH_4$ reduction to **83** followed by oxidation with pyridinium chlorochromate (PCC),[46] and treatment with TsOH in benzene. Products **85a** and **85b** were obtained by treatment of **84** with ethylene glycol and trifluoroacetic acid respectively. The **85b** was transformed to the bicyclic product **86b** with expansion of the six-membered ring with Me_2SiCHN_2 and BF_3-OEt_2.[47] The study showed that the last step was regioselective, providing only one product from the migration of the methylene group. Finally, treatment of the mixture **86a/86b** with Bu_4NF in MeCN provided **86a.** (+)-β-Himachalene was obtained by a reduction of **86a**, the first time with $NaBH_4$ and then with Li in liquid ammonia.

(+)-β-Himachalene can be also obtained directly from **86b** after reduction of the ketone function followed by *syn*-elimination of *cis*-α-silylcycloheptenol derivative 87 by treatment with KH.[48] The resulting triene 88 was partially hydrogenated with $CoCl_2/NaBH_4$/EtOH (Scheme 9).

Recently, enantiospecific synthesis of (+)-*trans*-α-himachalene was performed by Srikrishna and Kumar via an intramolecular type II carbonyl-ene reaction.[49] Indeed, the (+)-*trans*-*α*-himachalene was obtained from (*R*)-carvone **89**. First step involves the preparation of compound **94**. The latter was obtained from carvone **89** in five steps. Indeed, alkylation of carvone with methyl bromoacetate followed by reduction of keto ester **90**, produce hydroxy ester **91,** which was transformed into methoxyester **92** in the presence of sodium hydride and methyl iodide. Double alkylation of ester **92** using LDA and methyl iodide gave a compound **94** in 25% yield based on carvone. Accordingly, reduction with $LiAlH_4$ followed by a mild oxidation with PCC/NaOAc

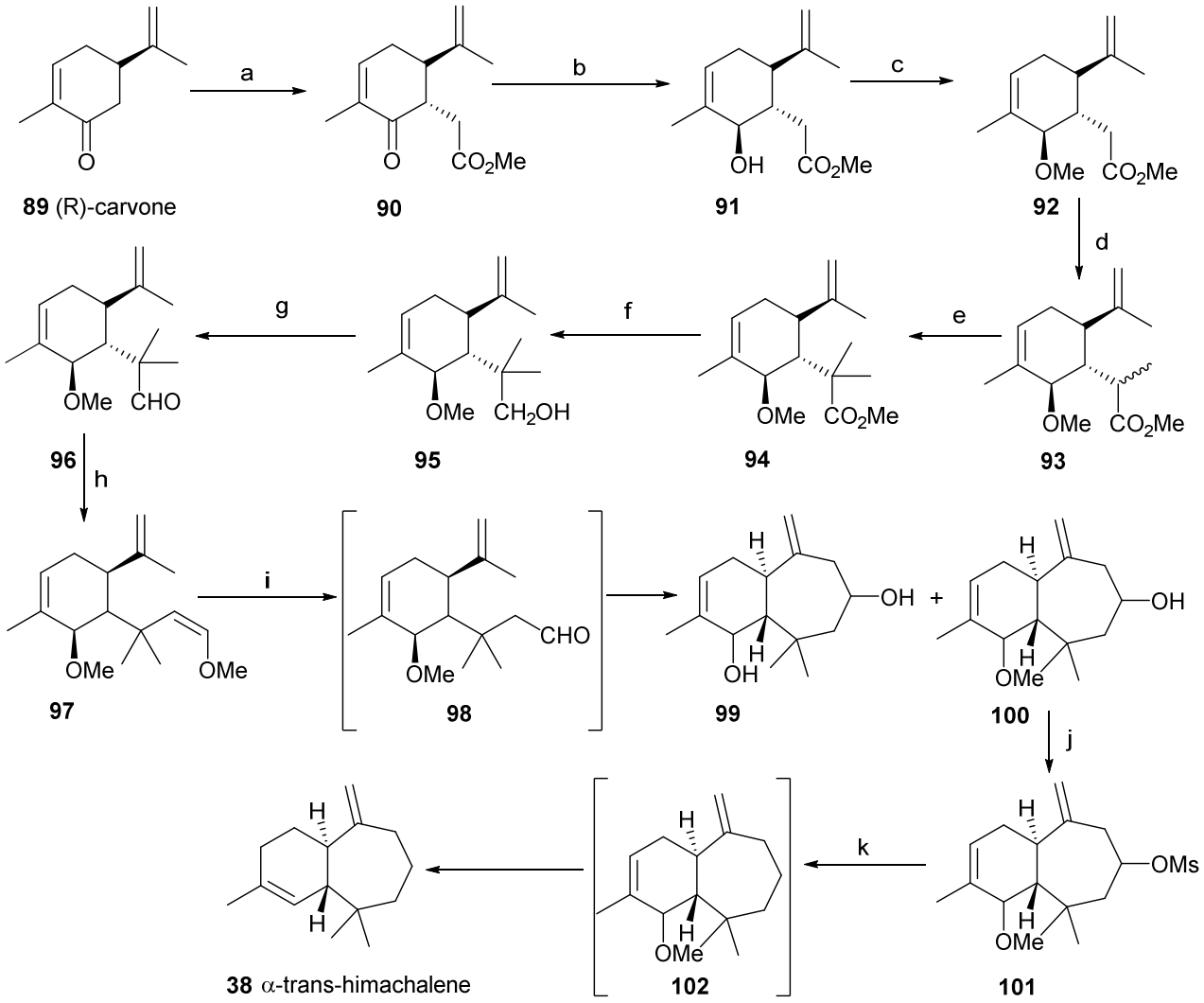
furnished aldehyde **96.** Wittig reaction with methoxymethylenetriphenylphosphorane provided enol ether **97** in a mixture of two isomers *Z* and *E* (1:1). Treatment with hydrochloric acid gave the aldehyde intermediate **98**, which undergoes spontaneous intramolecular hetero-ene reaction to give a mixture of bicyclic alcohol **100** and diol **99** with high stereoselectivity. Thereafter, the alcohol **100** was mesylated with MsCl. Thus, OMe and OMs groups are removed with lithium in liquid ammonia to obtain directly *trans*-α-himachalene **38** with 12% yield based on **98** (Scheme 10).



a) 1: Me_2NH 150°, 18h, 2: H_2O_2 150-180°, 75%. b) Isobutyric anhydride, Et_3N, DMAP; cat, CH_2Cl_2, 25°, 99%. c) LDA, THF, -78°, 1h, -40°, 30 min; Me_3SiCl, -78°; PhMe, reflux, 36h, 68%. d) $LiAlH_4$, THF, reflux, 5h, 90%. e) PCC, CH_2Cl_2, r.t, 24h; TsOH, benzene, reflux, 1.5h, 44.1%. f) Ethylene glycol, TsOH (cat), Dean-Stark, reflux, 24h, 92.1% of 87a; 2.35% CF_3COOH/H_2O, CH_2Cl_2, 10-20°, 98.8% of 87b. g) Me_2SiCHN_2, BF_3 OEt_2, CH_2Cl_2, -40°C, 2.5h, 65.3%. h) $NabH_4$, EtOH, 25°, 86.9%. i) KH, THF, 25°, 24h, 72.3%. j) $CoCl_3$ $6H_2O$, $NaBH_4$, EtOH, 25°C, 24h, 72.6%.

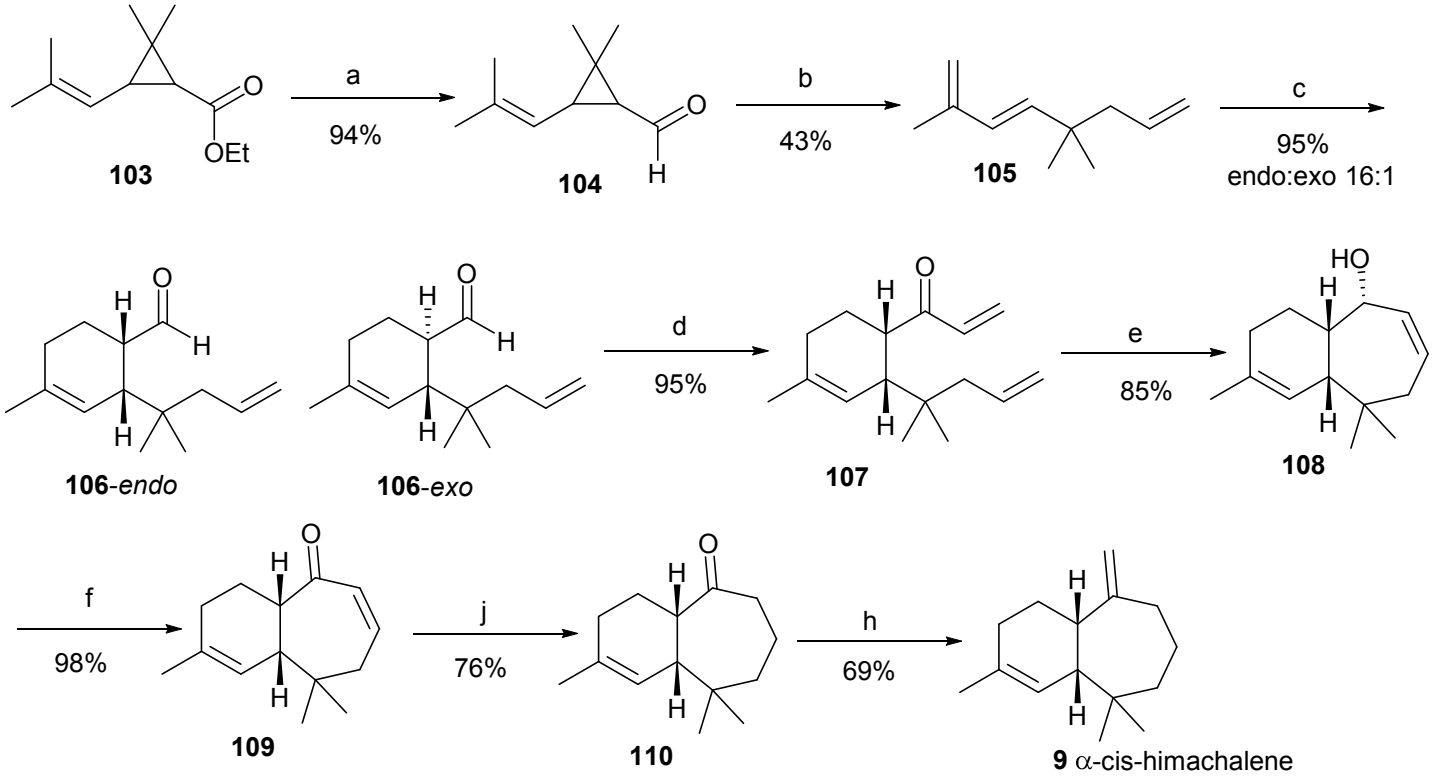
Scheme 9. Enantioselective synthesis of (+)-β-himachalene.

Finally, it should be noted that the *trans*-himachalene isomer can be obtained from its isomer *cis*-himachalene by hydrochlorination reaction with gaseous HCl followed by dehydrochloration/isomerization in pyridine or filtering on alumina.[6,29,39,50,51]



Scheme 10. Enantiospecific synthesis of (+)-*trans*-α-himachalene.

Dufour et *al*.[52] have also reported the synthesis of α-himachalene **9** starting from a commercially available mixture of ethyl chrysanthemate ester isomers **103** (Scheme 11). Reduction of **103** with $LiAlH_4$ followed by catalytic TPAP (tetrapropylammonium Perruthenate) oxidation in presence of NMO (N-methylmorpholine-N-Oxide) gave aldehyde **104** (92% two steps). Acid catalysed rearrangement with *p*-TsOH generated an aldehyde with the artemesyl carbon skeleton,[53] which underwent Wittig reaction to give triene **105** (43% 2 steps).



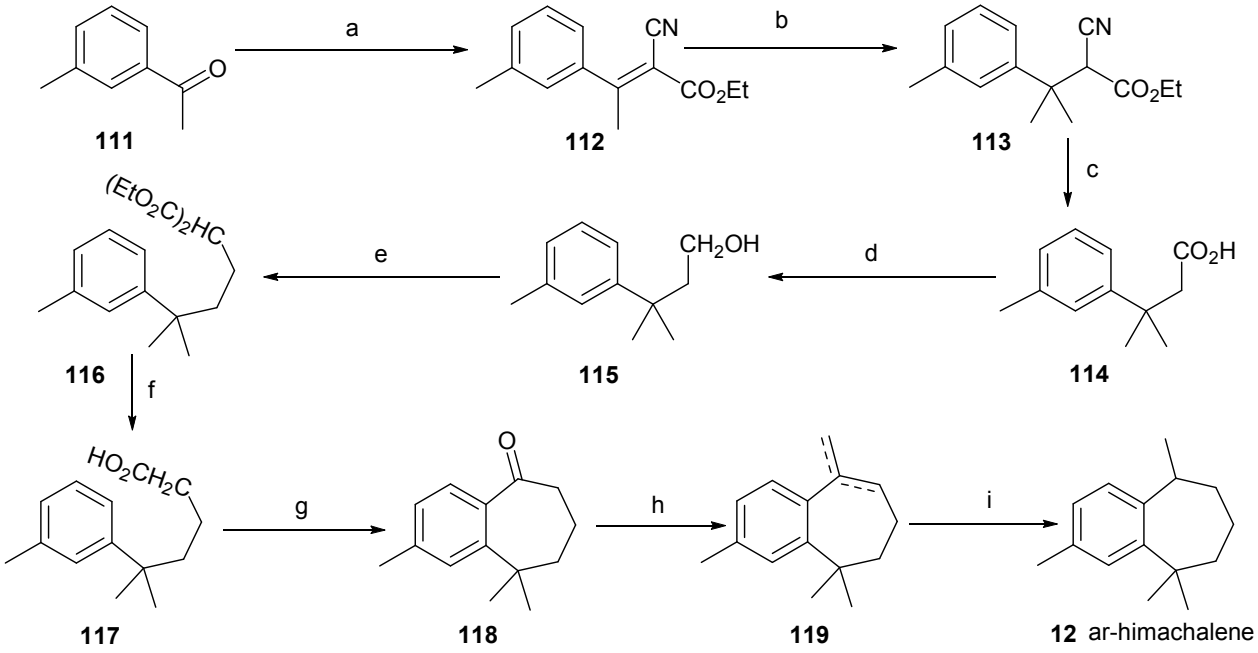
a)1: $LiAlH_4$, 2: TPAP, NMO; b) 1: *p*-TsOH, benzene, 2; $P(Ph)_3CH_2$; c) Acrolein, 20% $ZnCl_2$, CH_2Cl_2; d) $CH_2CHMgBr$; e) Grubbs' first generation catalyst, benzene; f) TPAP, NMO; j) L-Selectride; h) Tebbe reagent.

Scheme 11. Synthesis of α-himachalene from **103**.

The Dielse Alder cyclization catalyzed by differents Lewis acids ($SnCl_4.5H_2O$, $ZnCl_2$ or $ZnBr_2$), which all gave only one regioisomer and good diastereoselectivity. The best results were obtained with $ZnCl_2$ as catalyst, which gave 95% yield and an endo/exo ratio of 16/1. Then, the *endo* isomer **106** was reacted with vinylmagnesium bromide followed by ring-closing metathesis using Grubbs' catalyst to give a bicyclic compound **108**. The latter underwent an oxidation with TPAP and NMO followed by reduction of the double bond with L-Selectride to produce a compound **110** (Scheme 11). The last steps was methylenation with Tebbe reagent to obtain a disered product α-himachalene **9** (in 12% overall).

3.2 Synthesis of *ar*-himachalene

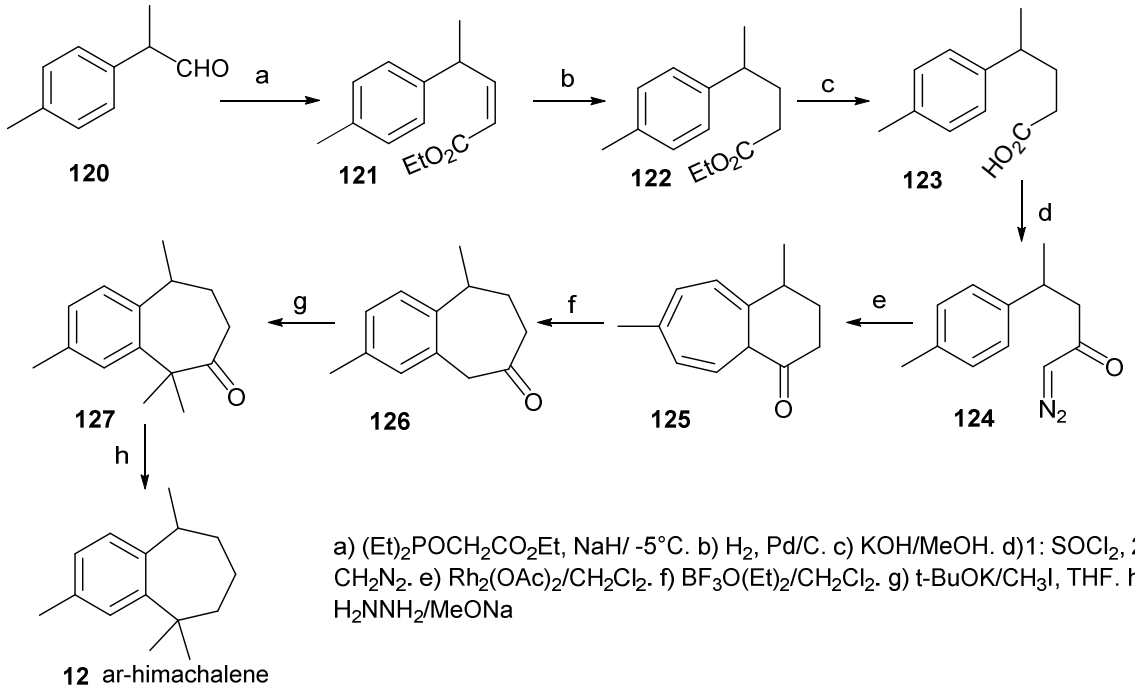
Different approaches to synthesis the *ar*-himachalene were reported in the literature such as that by Kapoor and Mehta mentioned previously.[37] The first total synthesis of *ar*-himachalene was reported by Dev's group in 1968.[54] It involved a synthesis in nine steps starting from *m*-methylacetophenone **111** according to scheme 12. Interaction of *m*-methylacetophenone with ethyl cyanoacetate furnished unsaturated ester **112,** and then the addition of MeMgI to **112** gave a saturated cyano-ester **113.** The latter was hydrolysed and decarboxylated to give **114** which was reduced to the corresponding alcohol **115**. The chain extension by two carbon atoms was achieved with malonic ester to give **117**, which readily underwent intramolecular acylation in polyphosphoric acid to obtain 5,5,7-trimethylbenzosubarone **118**. Simple hydrogenation under H_2 provided the required product **12**.



a) $CNCH_2CO_2Et$. b) MeMgI. c) MeOH,/HCl, 10% MeOH-KOH. d) MeOH, H_2SO_4, $LiAlH_4$. e)1: TsCl, Pyridine, 2: $CH_2(CO_2Et)_2$, Na. f) HCl, AcOH. g) PPA. h) MeLi. i) PtO_2, AcOH, H_2

Scheme 12. Synthesis of *ar*-himachalene from *m*-methylacetophenone **111**.

A shorter and more efficient method was described by Sonawane *et al*.[55] (Scheme 13).



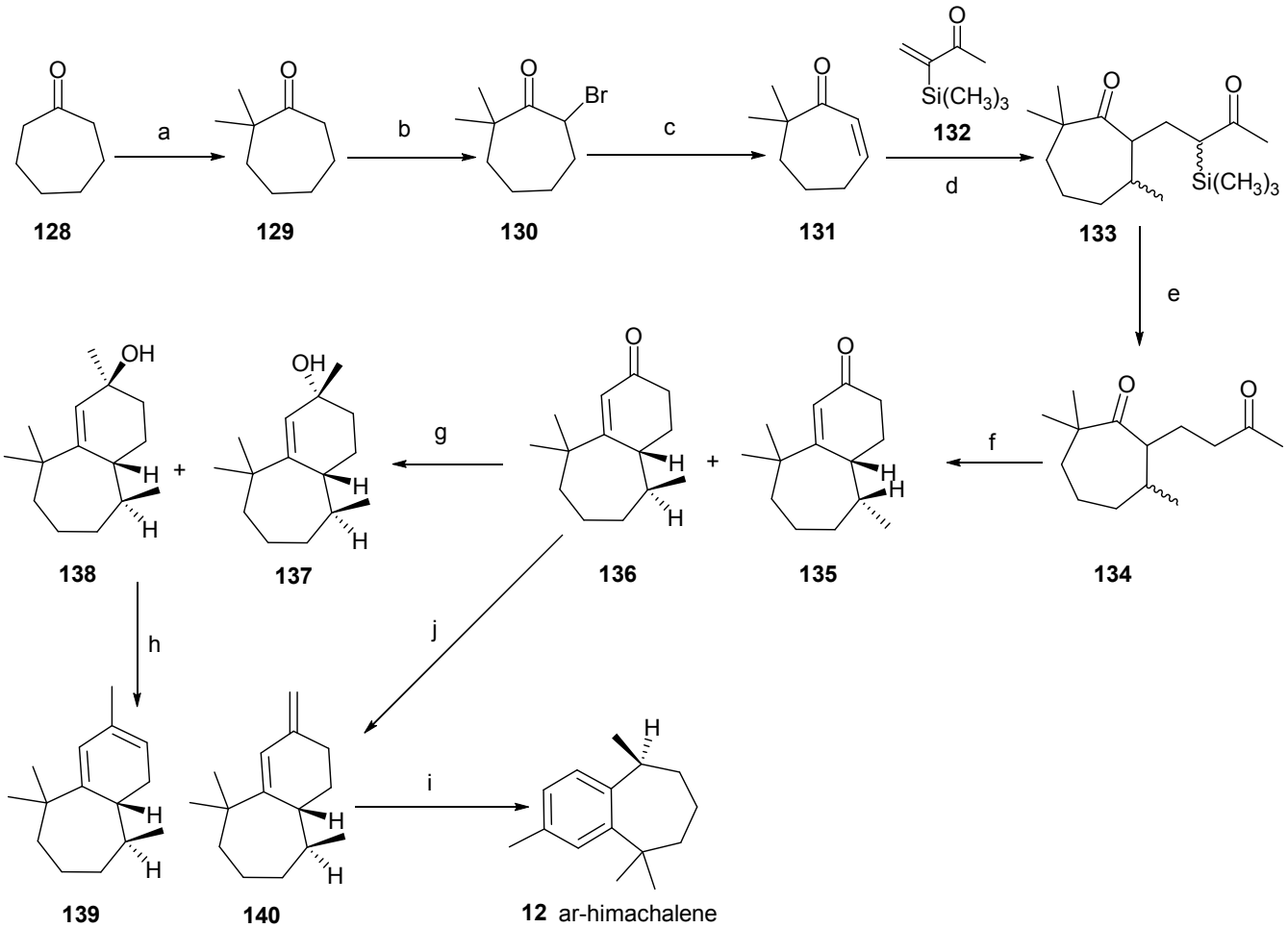
a) $(Et)_2POCH_2CO_2Et$, NaH/ -5°C. b) H_2, Pd/C. c) KOH/MeOH. d)1: $SOCl_2$, 2: CH_2N_2. e) $Rh_2(OAc)_2/CH_2Cl_2$. f) $BF_3O(Et)_2/CH_2Cl_2$. g) t-BuOK/CH_3I, THF. h) H_2NNH_2/MeONa

Scheme 13. Synthesis of *ar*-himachalene from the aldehyde **120.**

The key step of this method is based on the insertion of a carbenoid into an aromatic ring catalyzed by a rhodium complex.[56,57] The resulting product undergoes an acid-catalyzed rearrangement to give the ketone

125. The latter was demethylated and then reduced by a Wolff-Kishner reaction to achieve the *ar*-himachalene **12** (Scheme 13).

A total synthesis performed by Momany et *al.*[58] provides a series of sesquiterpenes including *ar*-himachalene. The route involved ten steps from cycloheptanone **128**. Firstly, the latter was dimethylated with MeI and *t*-BuOK in *t*-BuOH under Ireland-Marshall conditions.[59] Bromination of the resulting product **129** followed by HBr elimination using LiBr–Li_2CO_3 in DMF, provided enone **131.**[60] Interaction of the latter with Me_2CuLi followed by Michael addition in the presence of silyl ketone **132** gave silyl diketone **133**.[61] The silyl group was removed by treatment with ethanolic KOH and the resulting compound **133** was cyclized to the bicyclic products **135** and **136** in a 97/3 ratio. The predominant compound **135** reacted with MeLi to give a mixture of two diastereoisomers **137** and **138** (19:81). Both alcohols were converted into the corresponding olefin products **139** and **140** by the action of Dowex 50W-X4. Finally, aromatization with chloranil provided the desired product **12** (Scheme 14).

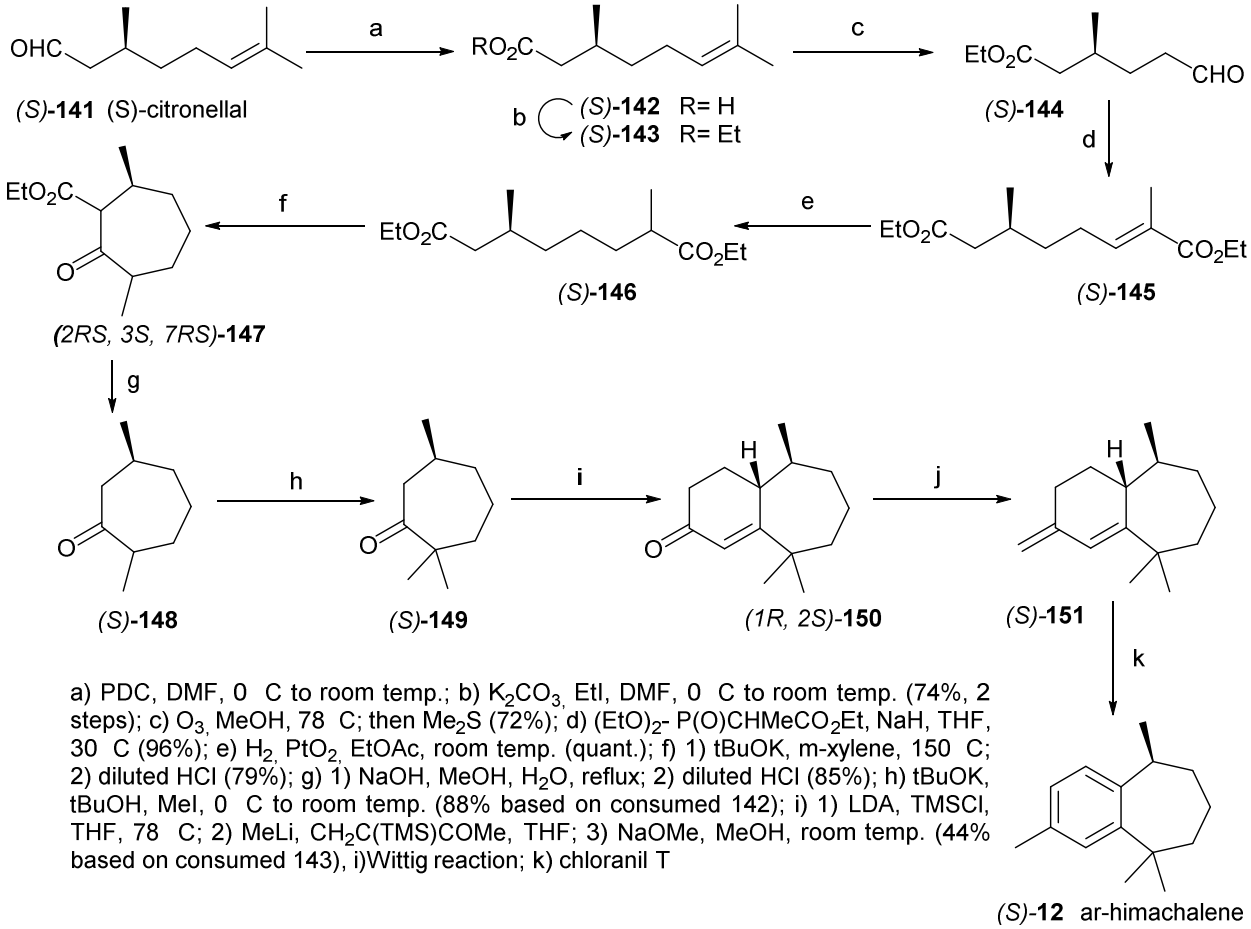


a) MeI, *t*-BuOK, *t*-BuOH, r.t. b) Br_2, Et_2O, r.t. c) LiBr, Li_2CO_3, DMF, 130°C. d) 1: Me_2CuLi, Et_2O. 2: 11, Et_2O, -78°C, e) KOH (3.5N), EtOH, r.t. f) KOH (3.5N), EtOH, reflux. g) MeLi, Et_2O, -78°C. h) Dowex 50W-X4, Et_2O, r.t. i) chloranil, benzene, 75°C. j) $Ph_3P{=}CH_2Br$, BuLi, THF, 0°C.

Scheme 14. Synthesis of *ar*-himachalene from cycloheptanone **128**.

Another method was reported by Mori *et al*.[62] This provided an enantioselective synthesis of (*R*) and (*S*) *ar*-himachalene starting from (*S*)- and (*R*)-citronellal **141** respectively. Treatment of (*S*)-citronellal (**141**) with pyridinium dichromate (PDC) provides (*S*)-citronellic acid (**142**). The latter was esterified and the resulting

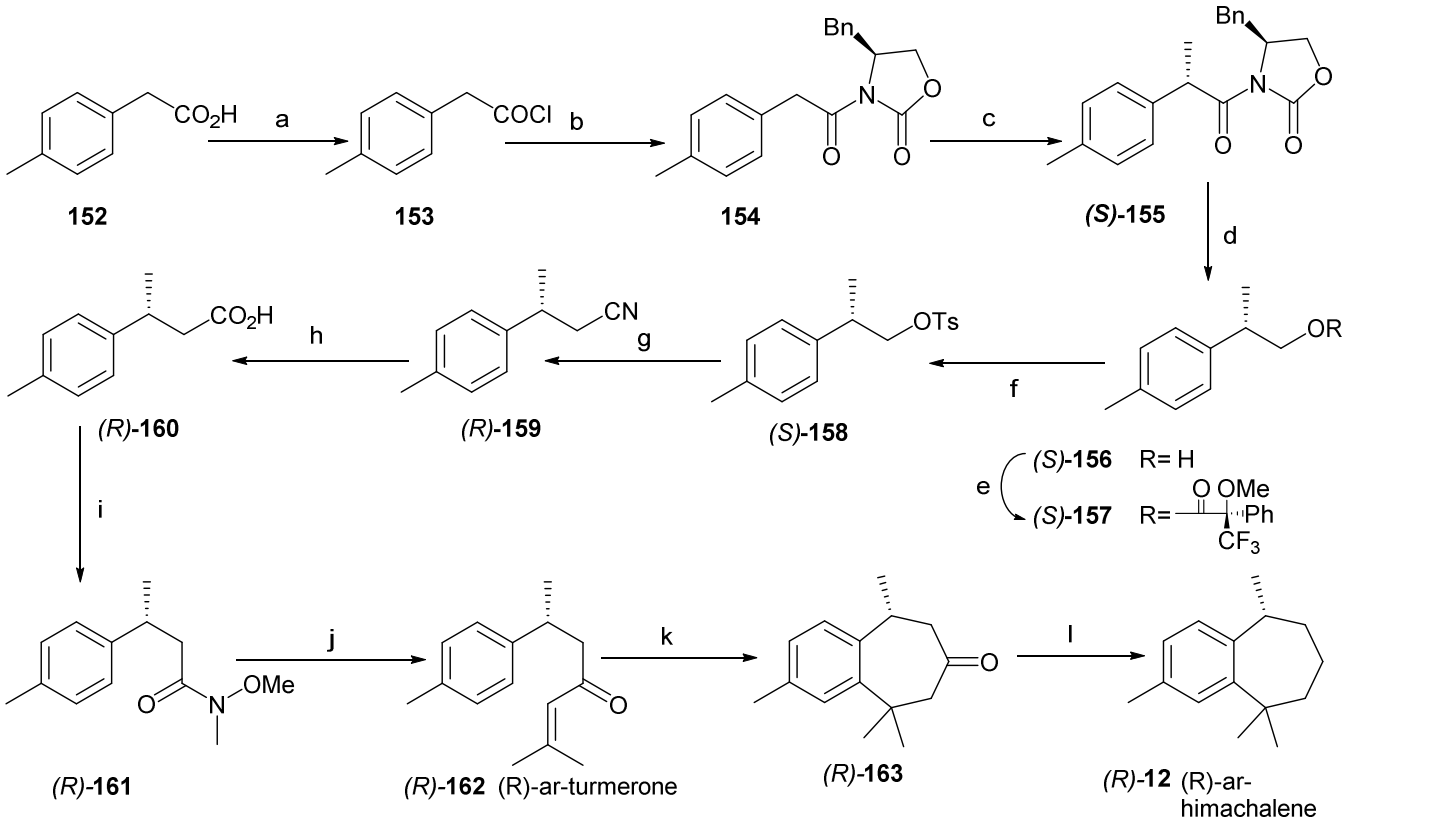
ester **143** was converted into the corresponding aldehyde **144** by ozonolysis. The mixture of *E* and *Z* diethyl ester **145** (87:13) was obtained from aldehyde **144** by Horner-Wadsworth-Emmons olefination. Catalytic hydrogenation of the double bond with Adams platinum oxide catalyst furnished diesters **146**. The β-oxo ester **147** was obtained by treatment of **146** with *t*-BuOK.[63,64] Hydrolysis and decarboxylation by heating to reflux in the presence of sodium hydroxide in aqueous methanol furnished ketone (*S*)-**148** which was methylated with potassium *tert*-butoxide and methyl iodide in *tert*-butyl alcohol to give trimethyl ketone (*S*)-**149**. The bicyclic ketone (*1R*,2*S*)-**150** was obtained by Robinson annulation of (*S*)-**151** with 3-(trimethylsilyl)-3-buten-2-one under Stork's conditions.[65,66] Finally, a Wittig reaction followed by aromatization with chloranil T provided (*S*)-*ar*-himachalene **12**. The same procedure was followed to prepare the other enantiomer (*R*) starting from (*R*)-citronellal (Scheme 15).



Scheme 15. Total synthesis of *(S) ar*-himachalene starting from *(S)*-citronellal.

One year later, Mori studied a synthesis of (*R*)-*ar*-turmerone and its conversion to (*R*)-*ar*-himachalene.[67] The first step started from (4-methylphenyl)acetic acid (**152**). Acyl chloride **153** was obtained using thionyl chloride, followed by Evans asymmetric alkylation *via (S)*-4-benzyl-3-(4-methylphenylacetyl)-2-oxazolidinone (**155**) as the key step to introduce the stereogenic center.[68] Methylation of **154** proceeded with methyl iodide and sodium hexamethyldisilazanide (NaHMDS), followed by reduction of the resulting compound with lithium aluminum hydride furnished alcohol (*S*)-**156 (**89% ee). Activation with tosyl chloride, then chain-elongation via the carbonitrile followed by hydrolysis with hot aqueous potassium hydroxide, gave acid (*R*)-**160**. The next step was conversion of acid (*R*)-**160** to Weinreb amide[69] (*R*)-**161** with *N,O*-dimethylhydroxylamine

hydrochloride, 1-ethyl-3-(3-*N,N*-dimethylaminopropyl)carbodiimide hydrochloride (EDC), (*N,N*-dimethyl-amino)pyridine (DMAP) and *N*-ethyldiisopropylamine. Treatment of the resulting amide **161** with the Grignard reagent 2-methylpropenylmagnesium bromide afforded (*R*)-*ar*-turmerone **162** (Scheme 16). Finaly, (*R*)-*ar*-turmerone was converted into *ar*-himachalene in two steps: intramolecular cyclization in the presence of $AlCl_3$ and CS_2, then the bicyclic ketone (*R)*-**163** formed was reduced with $N_2H_4 \cdot H_2O$ to give the final product (*R*)-*ar*-himachalene (**12**). It should be noted that the authors observed a solvent effect on the specific rotation values of the product (*R*)**-163**. In fact, in hexane $[\alpha]_D^{23}$= +3.8 while in chloroform $[\alpha]_D^{23}$= -2.4. A different sign of specific rotation can be explained by the fact that (*R*)-*ar*-himachalene is dextrorotatory in hexane, while levorotatory in chloroform. Indeed, this unique chiroptical behavior was the origin of the initial misassignment of the stereochemistry of the naturally occurring (*R*)**-163**. A similar results of different signs of specific rotations in different solvents were observed by Mori et *al*.[70] with (*1S*,*4S*,*5S*)-cis-verbenol.

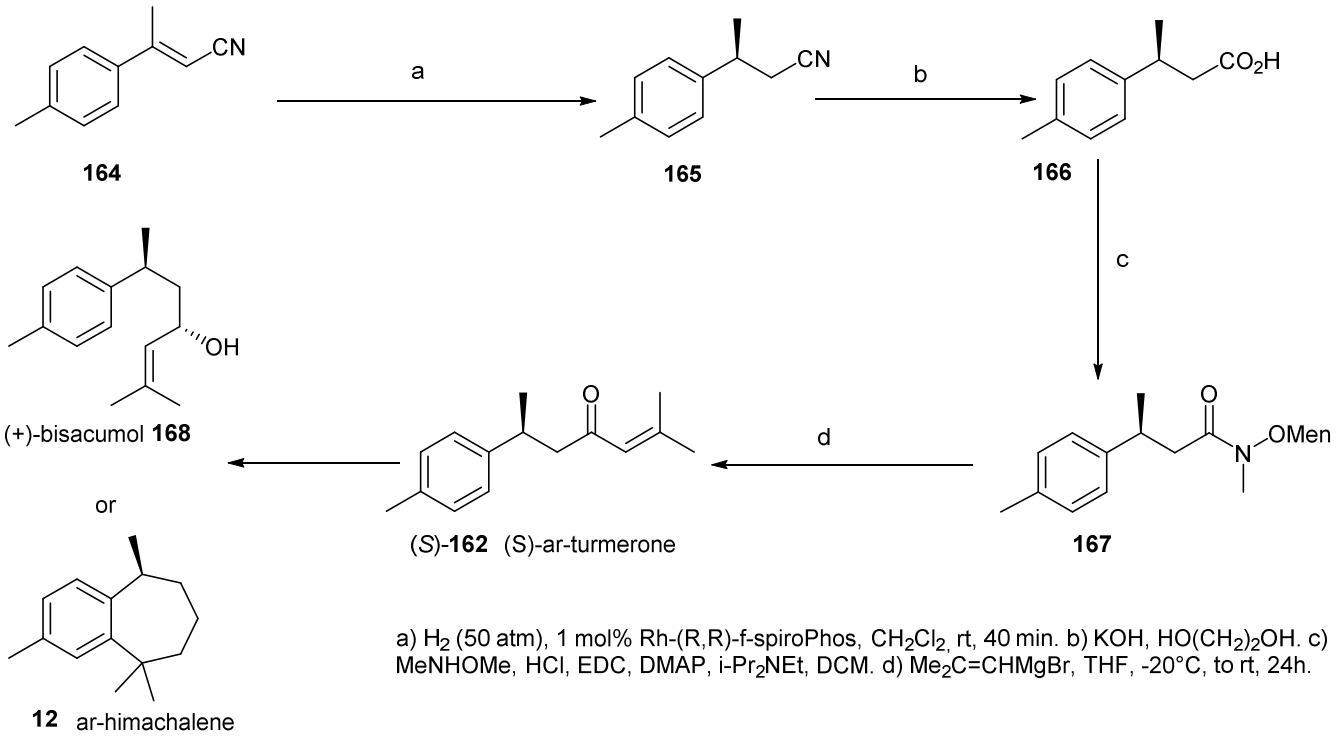


a) $SOCl_2$, C_6H_6, reflux; b) (S)-4-benzyl-2-oxazolidinone, nBuLi, THF, 78 °C, 30 min, then room temp, 79%; c) NaHMDS, MeI, THF, 78 C, 3 h, then room temp, 97%; d) $LiAlH_4$, THF, 0 °C to room temp, 69%; e) (*R*)-MTPACl, C_5H_5N, DMAP; f) TsCl, DMAP, C_5H_5N, 0-5 °C, 2 h, 95%; g) NaCN, NaI, DMSO, 110 °C, 30 min, 78%; h) KOH, $HO(CH_2)_2OH$, H_2O, 100 °C, 3 h, 91%; i) MeNHOMe.HCl, EDC, DMAP, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 0 °C, 4 d, 84%; j) $Me_2C{=}CHMgBr$, THF, 20 °C to room temp, 2 h, 88%. k) $AlCl_3$, CS_2, 40 to 20 °C, 1 h, then reflux (46 °C), 4 h, 40%; l) $N_2H_4.H_2O$, KOH, diethylene glycol, 200-210 °C, 3 h, 42%.

Scheme 16. Synthesis of (*R*)-*ar*-turmerone and its conversion into (*R*)-*ar*-himachalene.

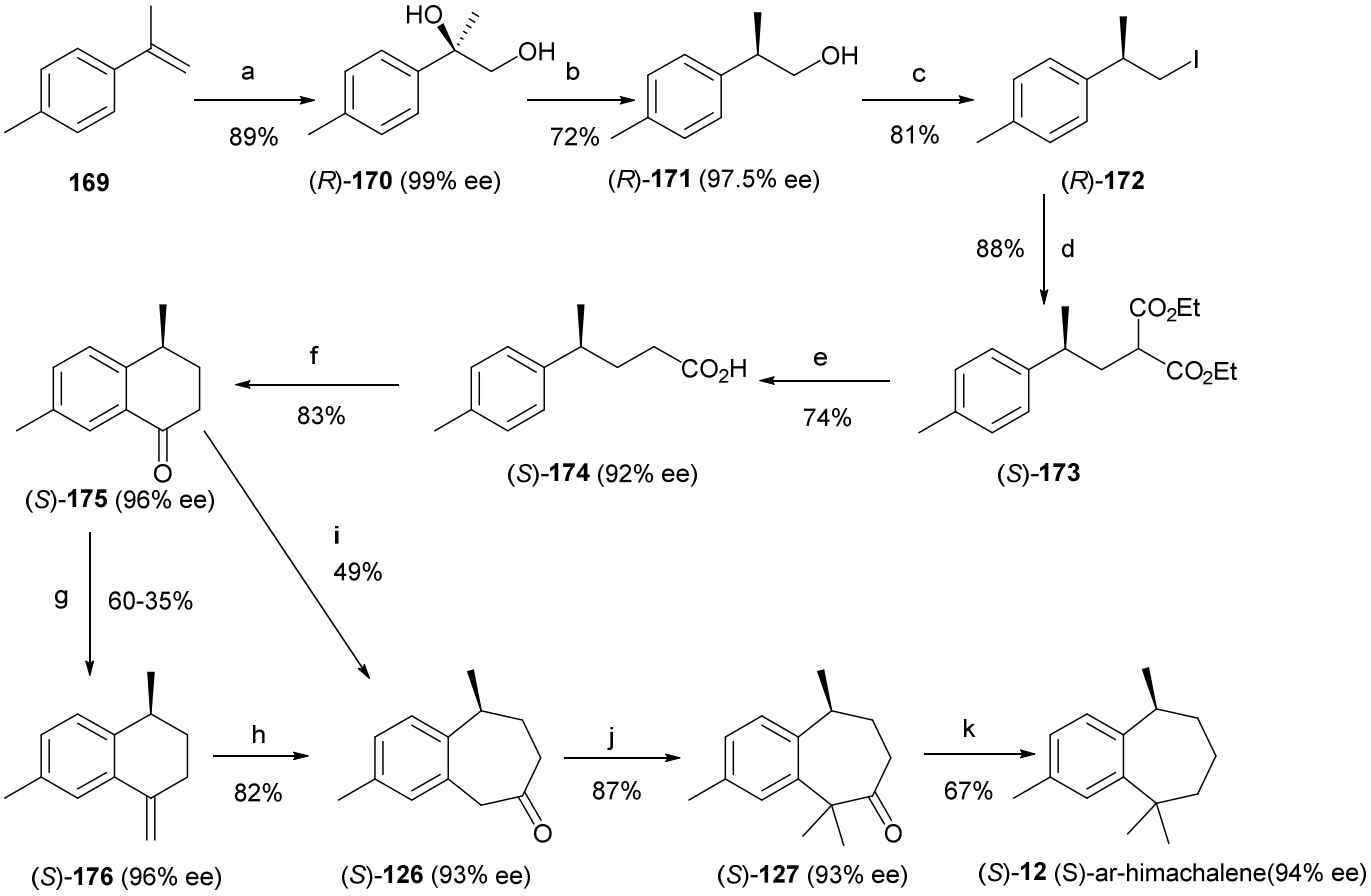
Zi *et al*.[71] have reported a new strategy for synthesis of *ar*-turmerone and its conversion into (*S*)-*ar*-himachalene and (+)-bisacumol **168**. The key reaction of this synthesis is an enantioselective hydrogenation of α,β-unsaturated nitriles catalyzed by a chiral phosphine-rhodium complex (Scheme 17). Hydrogenation of compound **164** under H_2 using the Rh-(*R,R*)-spiroPhos complex provided a product (*S*)-**165** with high yield and high enantioselectivity (99%). Then **165** was hydrolyzed to the corresponding acid **166** followed by amidation with MeNHOMe.HCl to obtain amide **167**. (*S*)-*ar*-turmerone **162** was obtained by treatment of compound **167**

with Grignard reagent Me_2C=CHMgBr. The latter was converted into (+)-bisacumol **168** by hydrogenation of the carbonyl function, or *ar*-himachalene **12** by Friedel-Crafts cyclization.



Scheme 17. Synthesis of (*S*)-*ar*-turmerone and its conversion into (*S*)-*ar*-himachalene and (+)-bisacumol.

Recently, an enantioselective synthesis of both isomers of *ar*-himachalene was carried out by Chavan *et al.*[72] starting from *α*,4-dimethylstyrene. The key reactions include Sharpless asymmetric dihydroxylation to introduce the stereogenic center and ring expansion by hypervalent iodine reagent or trimethylsilyldiazomethane ($TMSCHN_2$) (Scheme 18). Indeed, Sharpless asymmetric dihydroxylation of the dimethylstyrene **169** using AD-mix-β, furnished diol (*R*)**-170**. The latter was converted into primary alcohol (*R*)-**171** by hydrogenolysis. This step was studied with various reagents under different condition to remove the tertiary hydroxyl group and to introduce the chirality at the benzylic position. The best result was obtained with Pd/C in ethanol under pressure of H_2 (60 psi) at room temperature. The iodo derivative (*R*)-**172** was obtained by treatment of the alcohol with iodine in the presence of PPh_3 and imidazole. The latter was treated with diethyl malonate in presence of sodium hydride, with tetrabutylammonium iodide (TBAI) as a phase transfer catalyst, to obtain the diester (*S*)**-173**, which was decarboxylated to furnish acid (*S*)**-174.** Intramolecular acylation[73] of (*S*)**-174** using trifluoroacetic acid and trifluoroacetic anhydride gave (*S*)-**175**. Ketone (*S*)**-126** with seven membered ring can be prepared by two routes: directly from (*S*)-**175** with $TMSCHN_2$ and BF_3OEt_2. However, this reaction gave a low yield. To improve the yield, the authors have chosen to obtain it in two steps: Wittig reaction of ketone (*S*)-**175** followed by ring expansion of the six- to a seven-membered ring using Koser's reagent [hydroxy(tosyloxy)iodo]benzene (HTIB).[74,75] Finally, dimethylation of (*S*)**-126** with excess of methyl iodide and potassium *t*-butoxide furnished compound (*S*)**-127** which after Wolff-Kishner reduction of the carbonyl group gave the *(S)-ar*-himachalene **12.**[76]



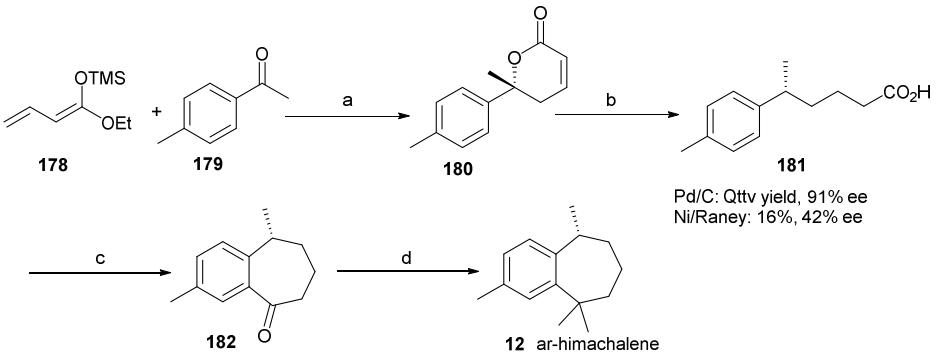
a) AD-mix-β. b) H_2, Pd/C, EtOH, 25°C, 8h. c) PPh_3, I_2, Im, $CHCl_3$, 0-25°C, 4h. d) NaH, $CH_2(CO_2Et)_2$, TBAI (10 mol%), DMF, 120 °C, 10h. e) 1: KOH, EtOH-H_2O, 2: 140 °C, 4h. f) TFA-TFAA 0-25°C, 3h. g) $Ph_3P{=}CH_3$, BuLi, THF, 5h. h) HTIB, MeOH, 0-25°C, 45min. i) $TMSCHN_2$, BF_3 $O(Et)_2$, 0°C, 45min. j) t-BuOK, MeI, THF, 0-25°C, 4h. k) N_2H_4, $2H_2O$, NaOH, diethylene glycol, 180°C, 8h,

Scheme 18. Enantioselective synthesis of *ar*-himachalene starting from *α*,4-dimethylstyrene.

Campagne et *al*.[77] have reported a straightforward strategy for the syntheses (*R*) *ar*-himachalene. Synthesis includes a catalytic and asymmetric vinylogous Mukaiyama reaction and a stereospecific hydrogenolysis of a tertiary benzylic center using Pd/C or Ni/Raney catalysts (Scheme 19). The first step was the synthesis of the lactone starting from silyldienolate **178** and methylacetophenone **179** .The reaction was carried out with a copper base catalyst associated with a various chiral ligands in the presence of 20% of TBAT (Tetrabutylammonium difluorotriphenylsilicate).The best results (93% yield and 87% ee) were observed with (*S*)-(−)-MeOBIPHEP ((S)-(−)-(6,6′-Dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine)] as a ligand.

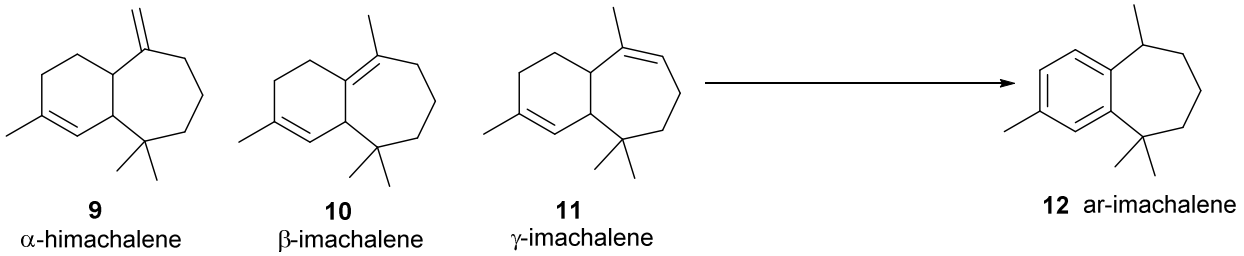
The hydrogenolysis of unsaturated lactone **180** with Pd/C or Ni/Raney under 1 atm of H_2 in ethanol at room temperature gave a corresponding acide **181**. Quantitative yield and good enantioselectivity (91 ee) were obtained with Pd/C however, Ni/Raney gave low results (16%, 42% ee). It should be noted that *ee* of acid **181** was determined by chiral HPLC after derivatization into the corresponding methyl ester with sulfuric acid in methanol. Authors showed that Ni/Raney mediated hydrogenolysis of **180** has highlighted a strong dependence of the benzylic OH group protection on the stereochemical outcome (inversion vs retention of configuration) whereas Pd/C, under different conditions, afforded 'inversion' products. With enantiomerically enriched **181**, the (R)-*ar*-himachalene can be obtained in two steps. First, in the presence of the Eaton's reagent (P_2O_5 in $MeSO_3H$), the corresponding Friedel-Crafts seven-membered acylated product **13** was

obtained in 86% yield. The ketone was transformed to the corresponding *gem*-dimethyl product using the Me_2TiCl_2 Reetz reagent[78] to give (*R*)-*ar*-himachalene **12** in 62%. This strategy yielded (*R*)-*ar*-himachalene in only four steps (35% overall yield) from *p*-methylacetophenone **179** (Scheme 18).



Scheme 19. Enantioselective synthesis of *ar*-himachalene starting from silyldienolate **178** and *p*-methylacetophenone **179**.

Several studies have shown that *ar*-himachalene can also be obtained directly from α-, β- and γ–*cis* himachalene. The reaction can be performed either on the mixture of three himachalenes or each taken separately (Scheme 18). Various dehydrogenating agents were used: selenium,[79,80] chloranil,[54] palladium,[81] Raney nickel,[82] bromine,[83] DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone).[84] The selectivity and yield of this transformation is dependent on the reagent employed and the operating conditions.[85,86]

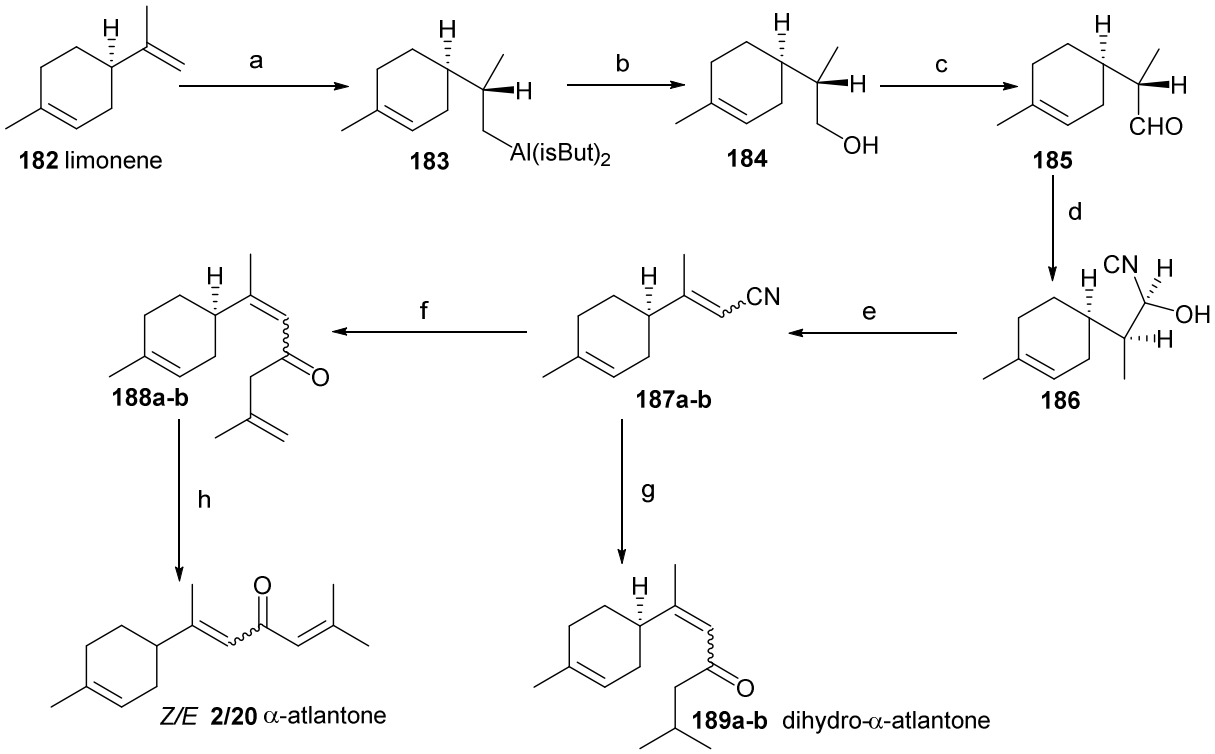


Scheme 20. Synthesis of *ar*-himachalene from α-, β- and γ-himachalenes.

3.3 Synthesis of *α*-atlantones

Atlantones represent the major ketonic fraction of the essential oil of cedar. Very few studies have been concerned with their total synthesis. The synthesis of *α*-atlantone **20** and dihydro-*α*-atlantones **189** was performed from (+)-(*4R*)-limonene **182** (Scheme 21).[86] Indeed, the exocyclic double bond C8=C9 specifically reacted with diisobutyl aluminum hydride (DIBAL) to provide the diisobutyl *p*-menthenyl aluminum **183**. The latter provided, after oxidation, a mixture of two diastereoisomers (*4R*,*8R*) and (*4R*,*8S*) *p*-menth-1-en-9-ol **184**. The mixture is dehydrogenated by Raney nickel to give two diastereoisomers (*4R,8R*) and (4*R*,8*S*) *p*-menth-1-en-9-al **185**, which transformed into cyanohydrins derivatives **186** using potassium cyanide and acetic acid. Dehydration of cyanohydrins with phosphorus oxychloride in hexamethylphosphoramide (HMPT) provided a mixture of *cis*- and *trans*-cyanolimonene **187a-b** which were intermediates to obtain atlantones and dihydroatlantones **189**. In addition, the action of allylmagnesium chloride on cyanolimonenes **187a-b** in THF

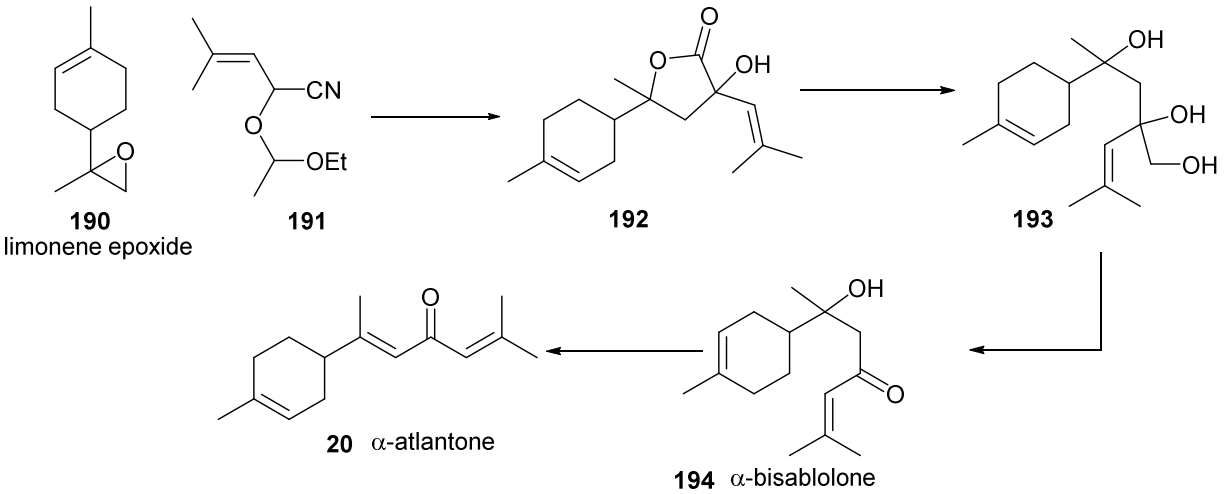
yielded the mixture of *trans*-isoatlantone **188a** and *cis*-isoatlantone **188b**, which were isomerized into *Z*- and *E*-*α*-atlantone **2** and **20** under the action of KOH/MeOH. Treatment of these cyanolimonenes by isobutyllithium gave a mixture of *trans*- and *cis*-12,13-dihydroatlantone **189a** and **189b** (Scheme 21).



a) $HAl(isBut)_2$. b) 1: $[O_3]$, 2: H_2O. c) Ni (Raney). d) HCN. e) $POCl_3$, $[CH_3)_2N_3P]$. f) MeAllylMgCl, THF. g) 1: $LiCH_2CH(Me)_2$, 2: H_2O. h) KOH/MeOH

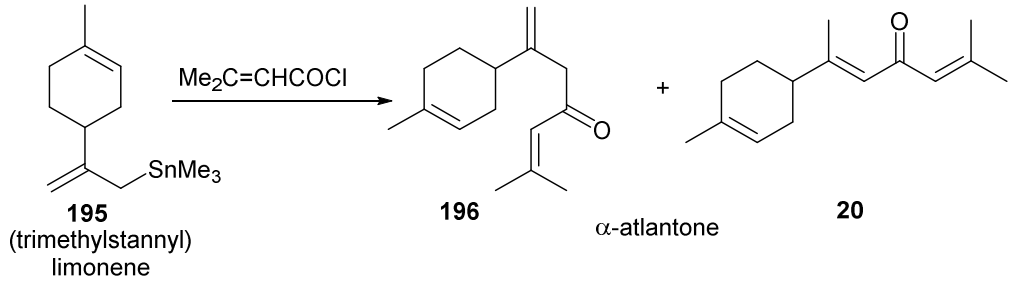
Scheme 21. Synthesis of *α*-atlantone and dihydro-*α*-atlantone from limonene.

Still from (+)-(*4R*)-limonene **182**, Malanco *et al*.[87] have reported a short synthesis of *α*-atlantone and *α*-bisablolone **194**. Epoxidation of limonene followed by monitoring their opening with protected cyanohydrins **191** gave hydroxy-lactone **192** *(*63%). The latter was then reduced with excess of lithium aluminum hydride in refluxing THF to provide triol **193** (91%). Oxidative cleavage by periodic acid furnished *α*-bisablolone **194** (55%) followed by dehydration with aqueous acetic acid (90%) at 60-70 °C for 14 h to give *trans*-*α*-atlantone **20** in 50% yield (Scheme 22).



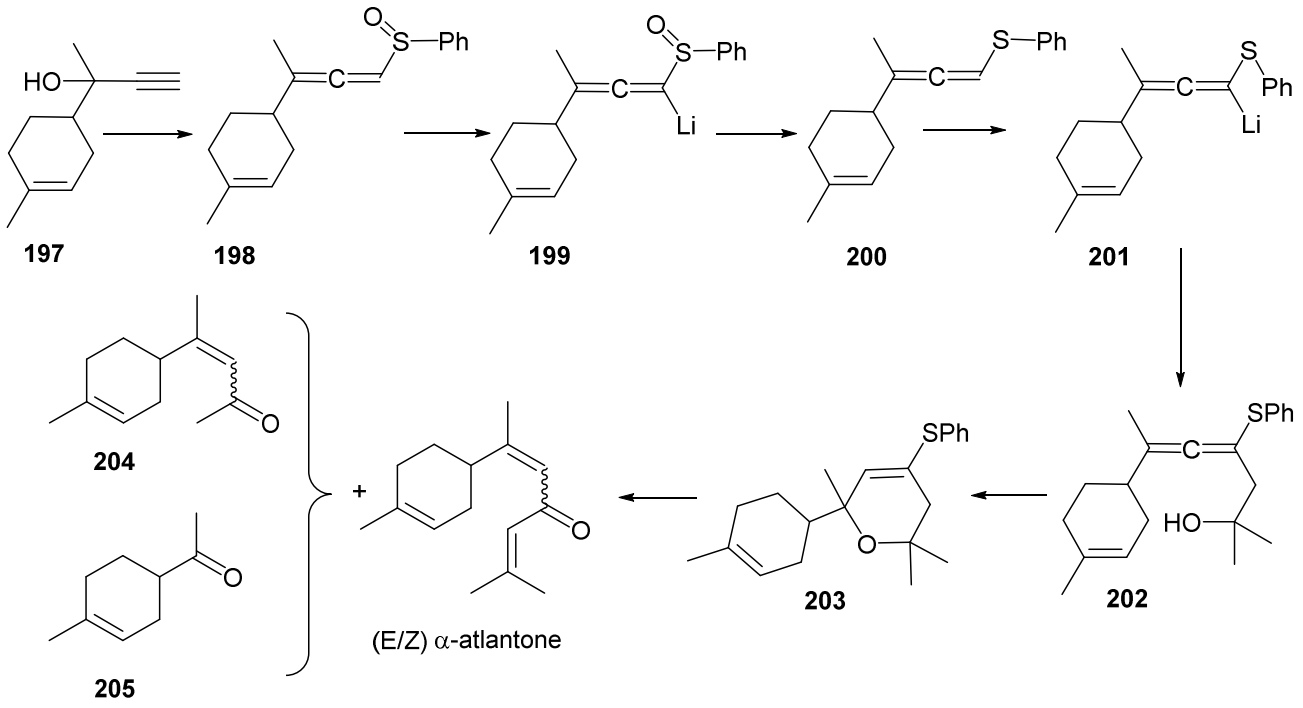
Scheme 22. Synthesis of *α*-atlantone from limonene epoxide.

Delmond *et al*.[88,89] have also reported the synthesis of (*Z*)- and (*E*)-*α*-atlantone starting from limonene. The key step of this method was to synthesize 10-(trimethylstannyl)limonene **195**, which was prepared by metallation with *n*-butyllithium-tetramethylethylenediamine complex[90,91] followed by trapping with trimethyltin chloride. Acylation of the stannane **195** with senecoyl chloride introduces the required additional isoprene unit and formed the sesquiterpene ketones **196** and **20** (Scheme 23).



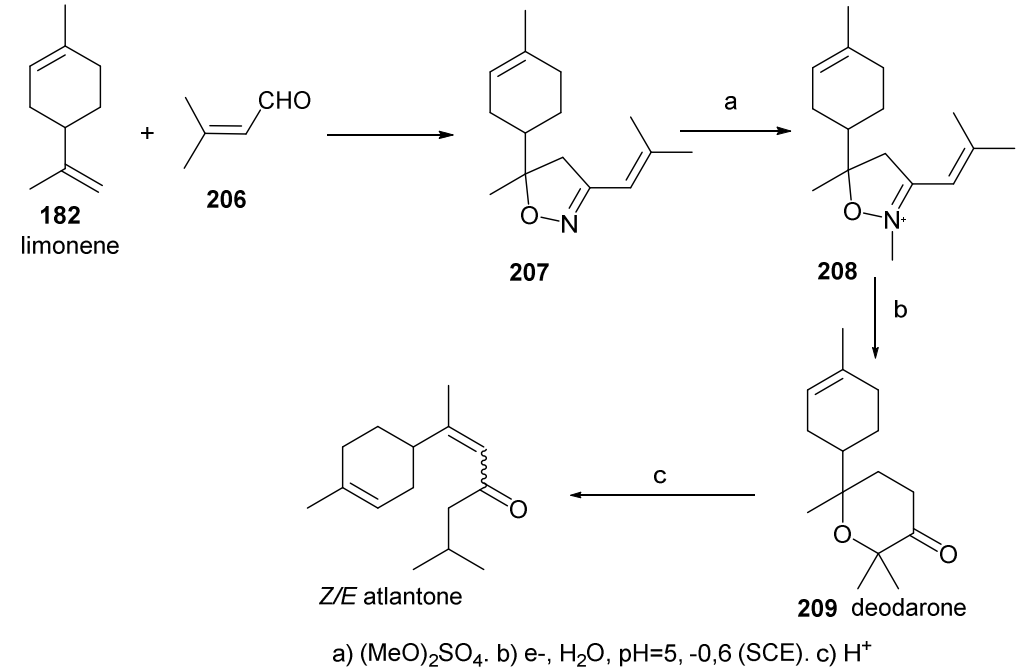
Scheme 23. Synthesis of (*Z*)- and (*E*)-*α*-atlantone from (trimethylstannyl)limonene.

Another method, developed by Cookson and Parsons,[92] involves a synthesis of allenyl sulfoxide made from propynyl alcohol **197** and benzenesulfenyl chloride.[93] Metalation of allenyl sulfoxide **198** with *n*-BuLi, followed by alkylation with a variety of electrophiles, gave compound **200** (Scheme 24**).** The oxygen atom of the sulfoxide **199** was removed using P_2S_5 and pyridine. The opening of isobutylene oxide by the lithiated allenyl sulfide **201** gave the alcohol (**202;** Ar = Ph)**.** The new allenyl sulfide **202** underwent an intramolecular cyclization by action of *p*-toluenesulfonic acid (PTSA) in THF to give compound **203**, which was converted into (*Z*)- and (*E*)-*α*-atlantone[94] **20** (*E*/*Z*=10:1) with other side products **204** and **205**.



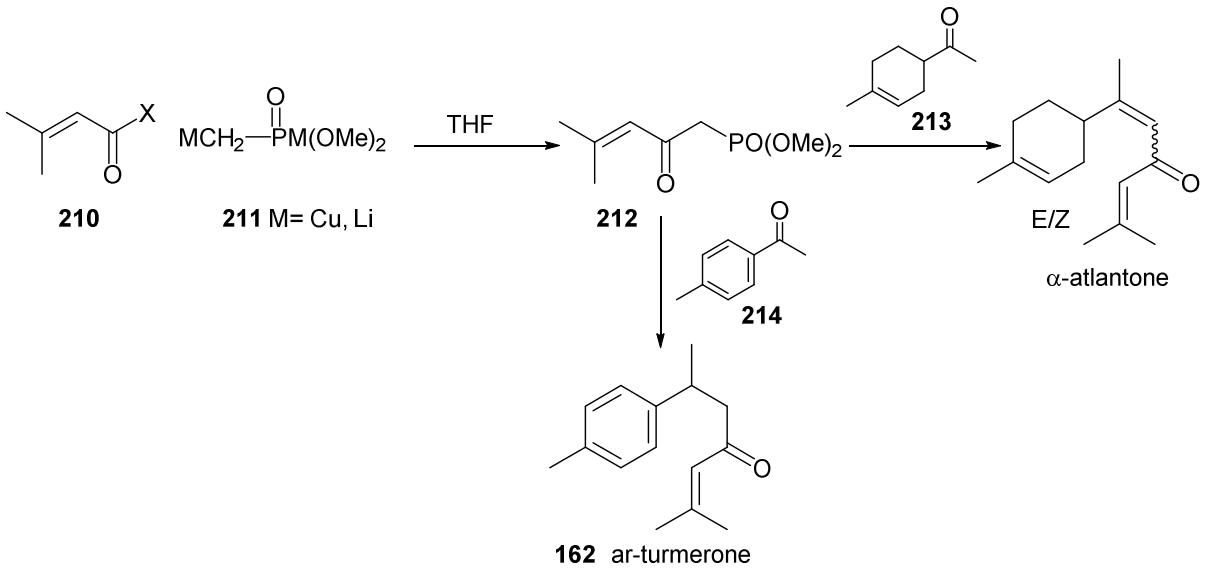
Scheme 24. Synthesis of *Z* and *E* *α*-atlantone from the acetylenic alcohol **197**.

Torssell *et al*.[95] have successfully used α,β-unsaturated nitrile oxides as a precursor in the synthesis of deodarone **209** and atlantones. Nitrile oxide prepared from senecialdehyde oxime **206** reacted with (+)-limonene **182** to furnish **207**, which was methylated with $(MeO)_2SO_4$ to give **208**. Electrolytic reduction provided access to deodarone **209** as a mixture of two diasterroisomers (1:1). In acidic medium deodarone **209** undergoes an opening of the tetrahydro-*γ*-pyrone ring to give a mixture of two isomers (*Z*)- and (*E*)-*α*-atlantone (Scheme 25).



Scheme 25. Synthesis of deodarone and atlantones.

Kakurai *et al*.[96] described a new brief synthesis of (±)-*α*-atlantone and (±)-*ar*-turmerone using dimethyl (2-oxo-4-methyl-3-pentenyl)phosphonate **212** as a precursor. The phosphonate derivative **212** was prepared from 3,3-dimethylacrylic acid derivative **210** with (dimethylphosphono)methanide **211**. Its carbanion was generated by sodium hydride in 1,2-dimethoxyethane (DME) or sodium ethoxide in ethanol and reacted with carbonyl compounds **213** or **214** to give (±)-*α*-atlantone or (±)-*ar*-turmerone **162** according to the ketone used.



Scheme 26. Synthesis of (±)-*α*-atlantone and (±)-*ar*-turmerone.

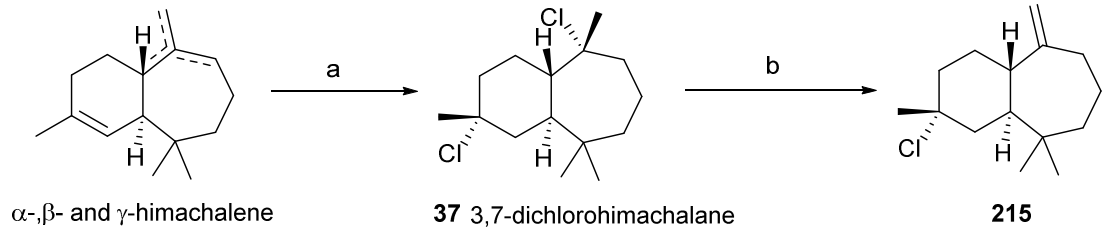
The same intermediate dimethyl (2-oxo-4-methy1-3-pentenyl)phosphonate **212** was synthesized by Blouin and Friesen from a tertiary *α*-allenic alcohol in four steps. This was used in the synthesis of (*Z*)- and (*E*)-*α*-atlantone by condensation with acetone in presence of $NaN(TMS)_2$ in THF.[97]

Recently, a new strategy for synthesizing of *ar*-atlantone and *α*-atlantone was developed by Nakajima *et al*.[98] This method is based on a sequential $TiCl_4$-promoted aldol reaction to simple ketones and base-promoted elimination to obtain β,β-substituted and α,β-unsaturated carbonyl compounds. Treatement of 4-methylpent-3-en-2-one with $TiCl_4$ and Bu_3N at -78 °C, in presence of *p*-methylacetophenone **214** or 1-(4-methylcyclohex-3-en-1-yl)ethan-1-one **213**, the reaction gave *ar*-atlantone **162** or *α*-atlantone according to the ketone used. Both products were obtained in 78% and 71% yield respectively as a mixture of two isomers *Z* and *E* with 90% for *E*.

4. Chemical Modifications of Major Compounds of the Essential Oil of Cedar

4.1 Hydrochlorination of himachalenes

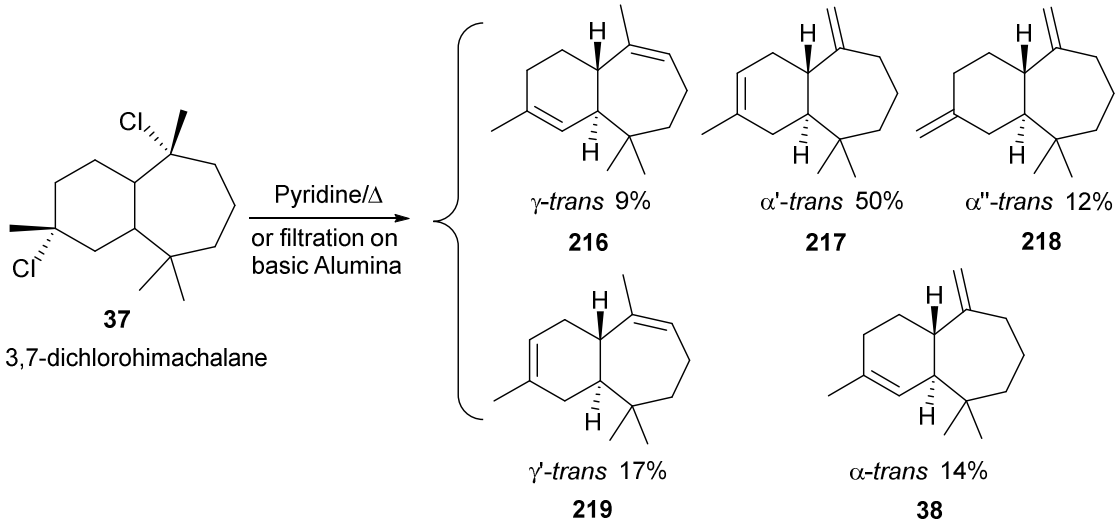
Hydrochlorination is a well studied reaction of himachalenes since it provides a pathway to synthesize *trans*-himachalenes.[39] In fact, treatment of the mixture of himachalenes with hydrochloric acid gave 3,7-dichlorohimachalane **37**; then its crystallization from methanol led to the formation of 3-chloro-7-methylene himachalane **215** by loss of an HCl molecule. The authors showed that the ring junction changes configuration during formation of the product **37**, becoming *trans* (Scheme 27).[50,51]



Scheme 27. Hydrochlorination and dehydrochlorination of himachalene.

4.2 dehydrohalogenation

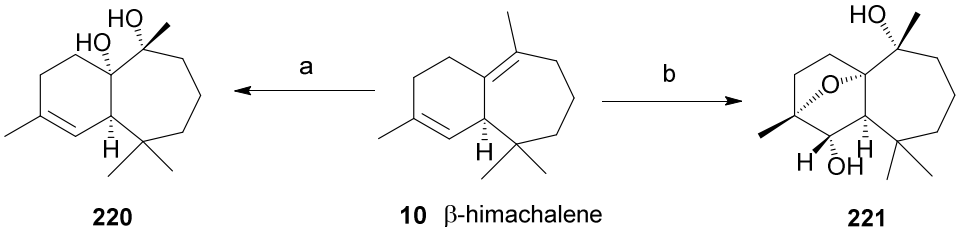
Benharref *et al.*[51] carried out the dehydrohalogenation of 3,7-dichlorohimachalane **37** by various methods. Indeed, by refluxing in pyridine or by filtration through basic alumina, they have obtained five new isomeric hydrocarbons, **216**, **217**, **218**, **219** and **38**: their results showed that the ring junction in each case was *trans*. (Scheme 28).



Scheme 28. Dehydrochlorination of compound **37**.

4.3 Oxidation of himachalenes

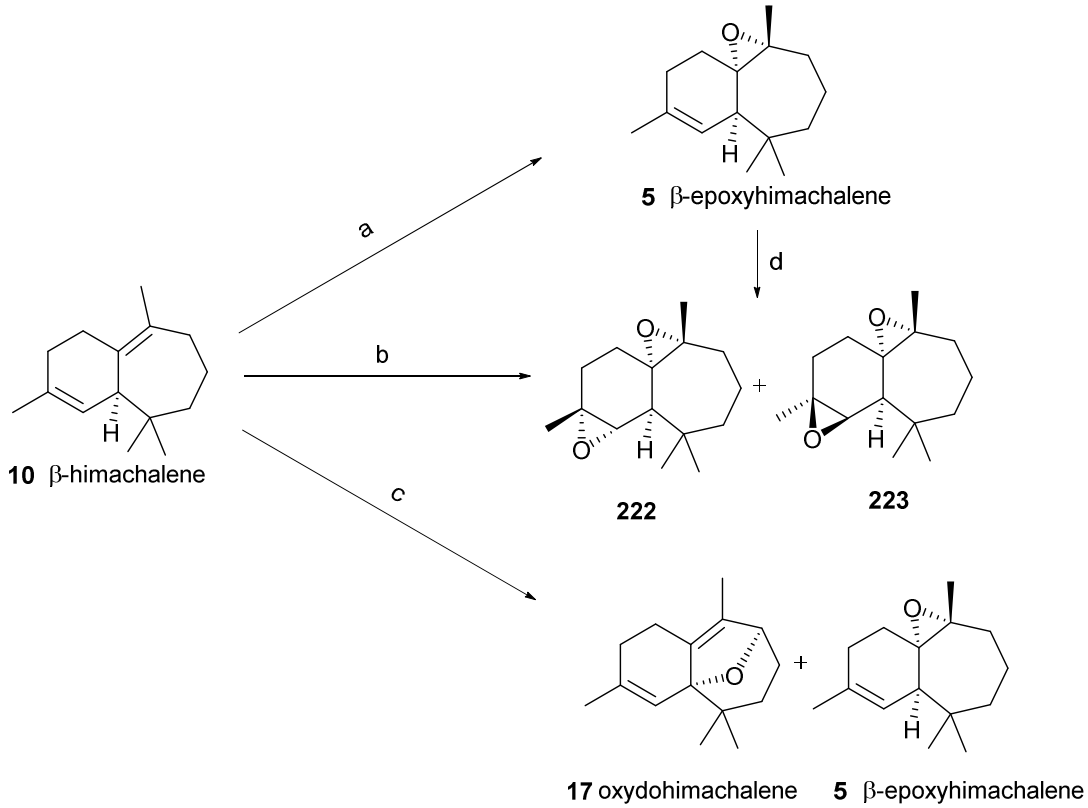
4.3.1 Oxidation with $KMnO_4$. Oxidation of β-himachalene **10** was carried out by Benharref *et al*.[99,100] using $KMnO_4$. The authors showed that the tetrasubstituted double bond reacted easily with $KMnO_4$. Indeed, treatment of β-himachalene with a stoichiometric quantity of $KMnO_4$ quantitatively produced a diol, **220**. However, with an excess of $KMnO_4$ (3 eq) in a mixture of acetone/water (9/1) the product **221** was regioselectively formed in 30% yield (Scheme 29).



a) stoichiometric quantity of $KMnO_4$, -10 °C. b) excess of $KMnO_4$ (3 eq), -10 °C

Scheme 29. Oxidation of β-himachalene with $KMnO_4$.

4.3.2 Epoxidation of himachalenes. Epoxidation of himachalenes is one of the most studied reactions since it provides new enantiomerically pure oxygenated compounds that could be used for perfumery or agrochemicals, or in pharmacology. The reactivity of two double bonds present in himachalenes with different systems has a particular interest. Thus, Dev *et al*. prepared the product 6*α*,7*α*-epoxyhimachalene **5** by action of *m*-chloroperbenzoic acid on β-himachalene (**10**) (Scheme 30).[101] The same epoxide **5** was prepared chemo- and stereo-selectively by Benharref *et al*.[102,103] The stereochemistry of the *α*-oxiran bridge in 6,7-position has been confirmed by X-ray diffraction carried out on the product **222**.[104,105] Both diepoxides **222** and **223** was obtained by treating the monoepoxide **5** with a stoichiometric amount of *m*-CPBA, as well starting from compound **10** using an excess of peracid (*m*-CPBA).



a) m-CPBA (1 eq). b) m-CPBA (2 eq). c) CuBr, t-butyl perbenzoate or H_2O_2, EtOAc or CuO_2, $Cu(NO_3)_2$, H_2O_2. d) m-CPBA (1 eq)

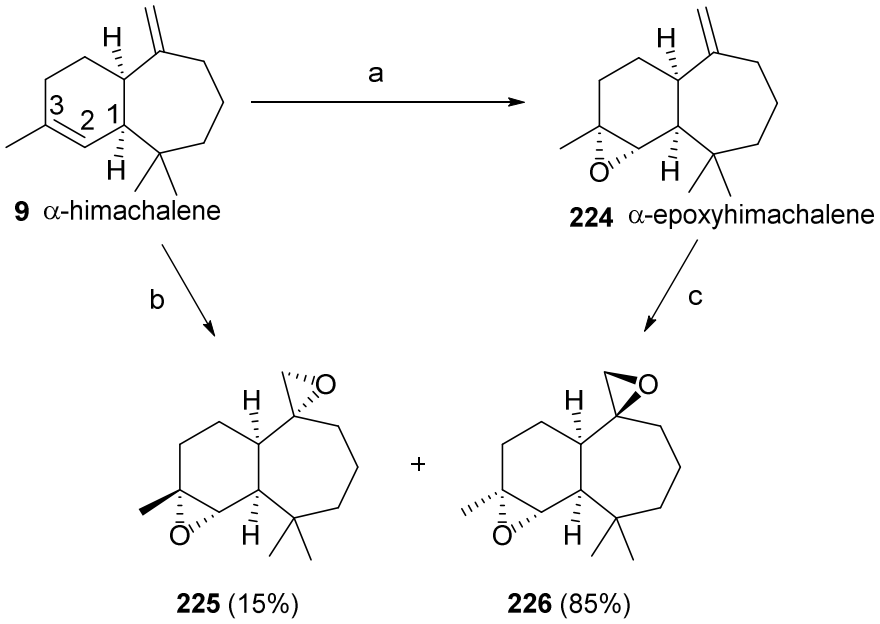
Scheme 30. Epoxidation of β-himachalene.

Metal-ion-catalyzed epoxidation of olefinic substrates has been exploited with β-himachalene (Scheme 30).[15,106] When β-himachalene isolated from *Cedrus deodara* was reacted with *t*-butyl perbenzoate in presence of cuprous bromide, the reaction led to the oxydohimachalene **17** in low yield.

However, heating β-himachalene with copper peroxide yielded besides unchanged β-himachalene (70%), oxygenated product (30%), which was shown by GC to contain 8% of oxydohimachalene **17** and 16% of the mono-epoxide **5**. The same group showed that the action of Ag_2CO_3-celite led to 5% of oxygenated product containing 21% of **17** and 19% of **5**. A similar conversion was obtained using H_2O_2 under UV light. When β-himachalene in EtOAc containing H_2O_2 (90%) was irradiated, 12% of oxygenated products were formed with 13% of oxydohimachalene **17**.[15]

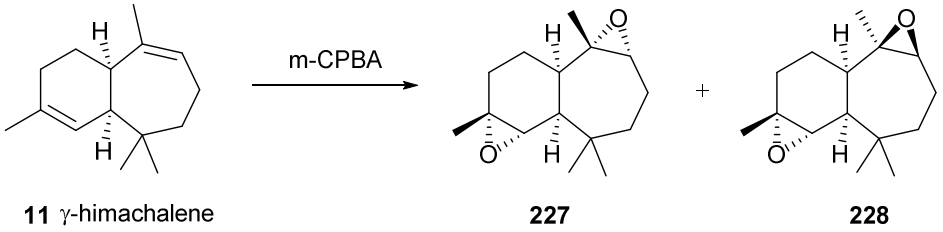
Catalytic epoxidation using organometallic catalysis was also studied. Indeed, the same reaction was carried out with 1,2,4-triazepine complexes [RuCl(TAZO)(*p*-cymene)] **C1** and [Ru(TAZS)(*p*-cymene)]$_2$ **C2** prepared from [$RuCl_2$(*p*-cymene)]$_2$ in the presence of 2-methyl-5-oxo-7-phenyl-3-thioxo-3,4,5,6-tetrahydro-2*H*-1,2,4-triazepine (HTAZO) and 2-methyl-7-phenyl-3,5-dithioxo-3,4,5,6-tetrahydro-2*H*-1,2,4-triazepine (H_2TAZS) respectively. Good stereoselectivity was observed using complexes **C1** which allowed isolation of the 6*α*,7*α*-epoxyhimachal-2-ene **5** with a chemoselectivity greater than 96% after 7h of reaction.[106]

Analogously, the epoxidation of *cis*-α-himachalene **9** led to mono- **224** or di-epoxides **225** and **226** according to the amount of peracid used (Scheme 29). The reaction also showed that the epoxidation of *cis* α-himachalene was stereoselective since only the α-side of the double bond C2=C3 was attacked. The stereochemistry of the oxirane bridge was established by X-ray crystallographic data of the major product **225**.[107,108]



Scheme 31. Epoxidation of *α*-himachalene.

In contrast, oxidation of *cis*-γ-himachalene **11** provided two diepoxides **227** and **228** regardless of the amount of the peracid used (Scheme 32). This was explained by the equivalence of the two double bonds of the structure.[108,109]

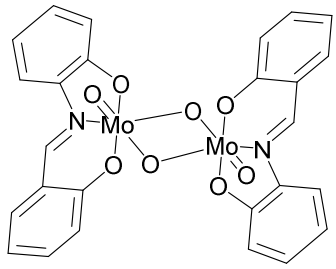


11 γ-himachalene **227** **228**

Scheme 32. Epoxidation of *γ*-himachalene.

Recent studies have shown that the epoxides **224** and **5** described previously can be obtained from a mixture of two isomeric α- and β-himachalenes. Indeed, the mixture of α- and β-himachalene on reaction with stochiometric amount of peracid gave two monoepoxides **224** and **5** in 28/72 ratio.[110]

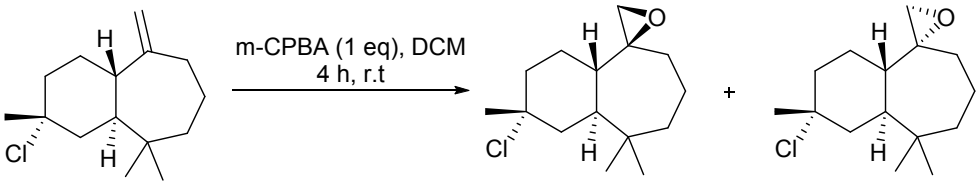
A catalytic oxidation of the himachalene mixture was carried out at 80 °C using the complex $[MoO_2(SAP)]_2$ shown in Scheme 31. Using a catalytic amount (1%) of the catalyst in the presence of TBHP as the oxygen source, both products **224** and **5** could be obtained in 80% and 90% yields after 90 min in a ratio of 33/67. and the greener conditions of the solvent-free catalyzed method claimed to be a significant improvement.[110]



Scheme 33. $[MoO_2(SAP)]_2$ complex.

Concerning the metal-catalyzed olefin epoxidation by TBHP, mostly realized with molybdenum- or vanadium-based catalysts. Poli *et al.* have proposed relevant mechanisms in organic solvents that involve the addition of TBHP to the catalyst in the activation phase. They have recently shown that the olefin epoxidation with the $[MoO_2(SAP)]$ fragment as a catalyst and TBHP as an oxidant follows a mechanism relatively similar to that operating in the presence of peracids. On this basis, the slight difference in selectivity observed between *m*-CPBA and $[MoO_2(SAP)]$/TBHP system can be attributed to the slight differences in steric interaction between the oxygen atom delivering species and the substrate in the transition state.[111]

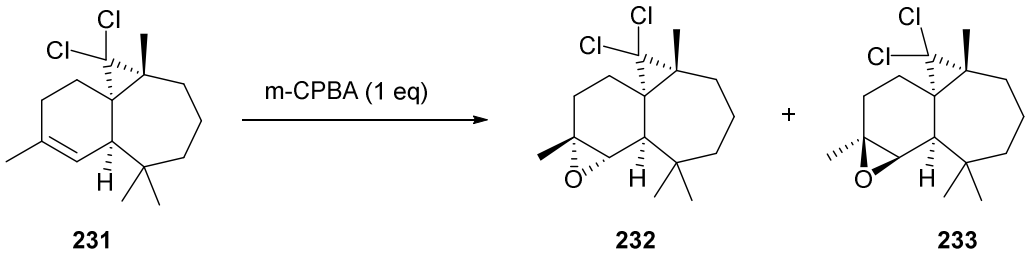
The reaction of the exocyclic double bond of 7-chlorohimachal-7,13-ene **215**, which is obtained from α-, β- and γ-himachalene by hydrochlorination, with one equivalent of *m*-chloroperbenzoic acid under the same conditions as above, provided two diastereoisomers **229** and **230** in 85/15 ratio (Scheme 34).[110]



215 7-chlorohimachal-7,13-ene **229** **230**

Scheme 34. Epoxidation of chlorohimachalene **215**.

Treatment of (*1S,3R,8R*)-2,2-dichloro-3,7,7,10–tetramethyltricyclo[6,4,0,$0^{1,3}$]dodec-9-ene **231** with a stoichiometric amount of *m*-CPBA gave two products **232** and **233** in a 70:30 ratio with 80% yield (Scheme 33).[110] Epoxidation of **231** has been also monitored under the conditions previously described for the Mo-catalyzed epoxidation of 7-chlorohimachal-7,13-ene **215**. The epoxides were isolated as a mixture of two diastereoisomers in 50:50 ratio with 80% conversion after 5 h.[110]

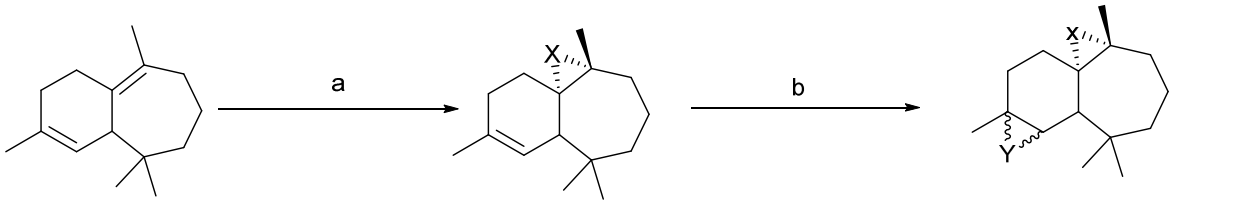


231 **232** **233**

Scheme 35. Epoxidation of compound **231**.

4.4 Gem-dihalogenocyclopropanation of β-himachalene

Several products containing a cyclopropane ring were prepared from β-himachalene. Treatment of β-himachalene **10** with a stoichiometric amount of dichlorocarbene, generated *in situ* from chloroform using NaOH as a base at 0 °C in the presence of tetrabutylammonium chloride (TBA-Cl) as a catalyst, gave the dihalogenated products **231** and **234**. Similar products were obtained using bromoform (Scheme 36**).**[112]



10 β-himachalene

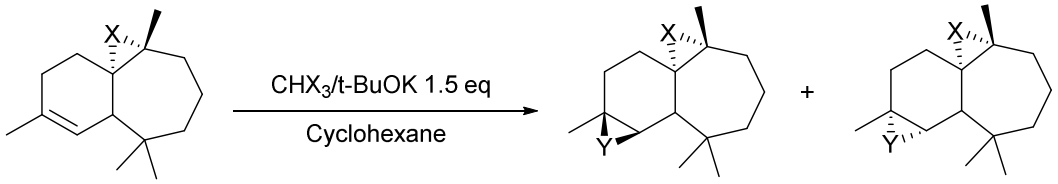
231 X= CCl_2
234 X= CBr_2

235 X= CCl_2 Y= CCl_2
236 X= CCl_2 Y= CBr_2
237 X= CBr_2 Y= CCl_2

a) CHX_3/t-BuOK 1 eq, TBA-Cl. b) CHX_3/t-BuOK 1 eq, Cyclohexane

Scheme 36. Synthesis of di-and tetra-halo-cyclopropahimachalenes.

Ourhriss *et al.*[113,114] founded that the tetrachloro-dicyclopropa-himachalenes **235** was obtained in 60% yield as two diastereoisomers in 85/15 ratio. However when they used an excess of bromoform, only the dibromated product **234** was obtained (Scheme 36). The mixed tetrahalogenated products were prepared by treatment of the dichlorocyclopropa-himachalene **231** with 1.5 equivalents of bromoform, or treatment of dibromocyclopropa-himachalene **234** under the same conditions with 1.5 equivalents of chloroform.[115,116] In order to prepare other cyclopropahimachalene derivatives they reduced the product **231** with metallic sodium in a mixture of MeOH/H_2O which gave **237** with a cyclopropane motif.[117] The gem-dihalocyclopropanation reaction of compound **238** was performed in the same condition described above and gave the products **239** and **240** with 40% and 25% yield respectively as two diastereoisomers in each case (Scheme 37).



5 X=O β-epoxyhimachalene
238 X=CH_2

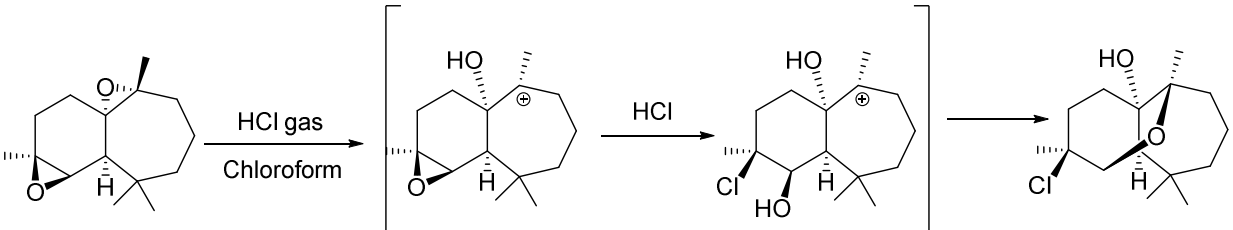
239 X=CH_2 Y= CCl_2 40%
240 X=CH_2 Y= CBr_2 25%
241 X=O Y= CCl_2 80% a/b=75/25
242 X=O Y= CBr_2 85% a/b=80/20

Scheme 37. Dihalogenocyclopropanation of **5** and **238**.

β-Epoxyhimachalene was transformed into the corresponding epoxy-dihalocyclopropa-himachalene by treatment with 1.5 equivalents of chloroform (bromoform) in hexane in the presence of *t*-BuOK at 0 °C.[118-120] The reaction led to the tetracyclic products **241** and **242** in 80% and 85% yields respectively. The products were obtained in the form of two diastereoisomers in 75/25 and 80/20 ratios respectively (Scheme 35).

4.5 Rearrangements of epoxy-himachalenes

Epoxides constitute a class of compound with high interest. They are known as important synthons in organic synthesis. These have the advantage of generating a wide variety of functions including several different polyfunctional compounds. The ring-opening of β-diepoxy-himachalene **223** was performed by bubbling HCl gas for one minute in chloroform (Scheme 38).[121] The formation of the tricyclic derivative **245** can be explained by double S_N2 type reactions. After the protonation of epoxide at position 6-7, *anti* nucleophilic attack of Cl^- at position C3 opened the 2,3-epoxide and then the oxygen at C2 in an intramolecular nucleophilic attack on the carbon C7 forms the bridging tetrahydrofuran ring.



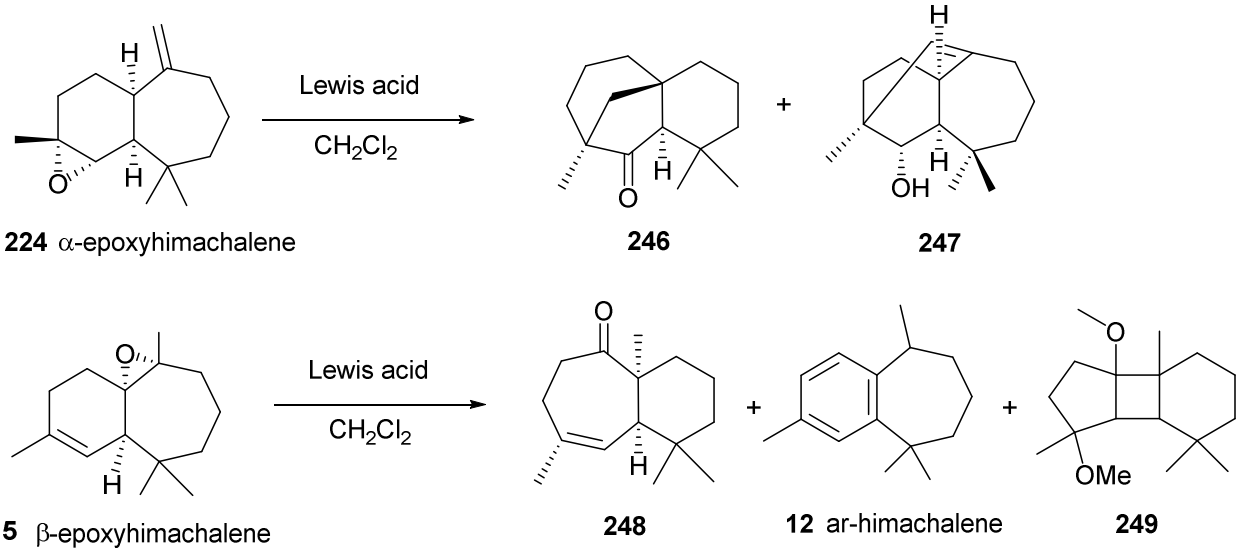
223 diepoxy-himachalene **243** **244** **245**

Scheme 38. Rearrangement of diepoxy-himachalene by HCl gas.

Rearrangement of *α*-epoxyhimachalene **224** was studied by El Haib *et al*.[122] The rearrangement of epoxide **224** in presence of a catalytic amount of Lewis acid in dichloromethane led mainly to the formation of two tricyclic products, ketone **246** and alcohol **247** (Scheme 39).

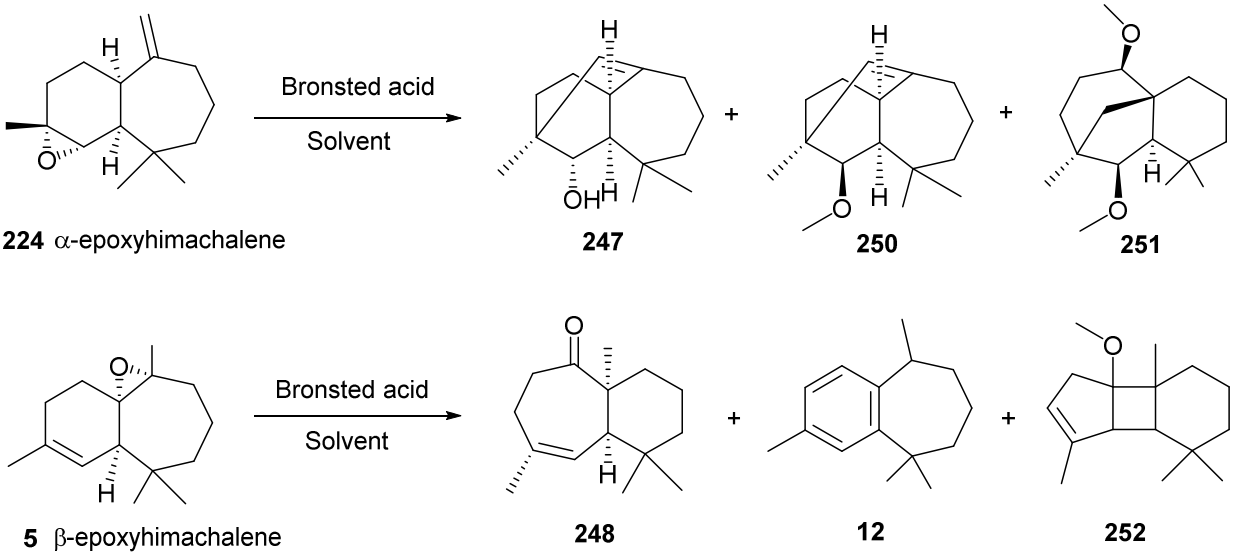
The ketone was the product formed predominantly, using (BF_3Et_2O, BF_3MeOH, $InCl_3$, $FeCl_3$) except in the case of $Bi(OTf)_3$ since the alcohol was the main product produced. The comparisons of the various results obtained showed the effect of the Lewis acid on the kinetic and the selectivity of the reaction. With BF_3Et_2O and BF_3MeOH, a rapid and complete conversion of the epoxide was observed while the reaction time must be increased to 6 hours or 9h 30min to achieve complete conversion of substrate with $FeCl_3$ and $InCl_3$ respectively. Rearrangement of β-epoxyhimachalene **5** in the presence of BF_3Et_2O in dichloromethane, gave ketone **248** and *ar*-himachalene **12**, the two products can be isolated in 62% and 16% yield respectively

(Scheme 39). However, the compound **249** with cyclobutane motif could be isolated using BF_3MeOH as catalyst.[123]



Scheme 39. Rearrangement of epoxy-himachalene by Lewis acid.

Brønsted acids have also been used as catalysts in order to compare their activity and selectivity to those of Lewis acids. Rearrangement of *α*-epoxyhimachalene **224** was studied in the presence of a catalytic amount of methanesulfonic acid (MSA) or *p*-toluenesulfonic acid (PTSA). It led to the formation of alcohol **247** and/or **250** and/or **251.** In the same way, the β-epoxy-himachalene **5** gave ketone **248** and/or *ar*-himachalene **12** and/or compound **252** (Scheme 40).



Scheme 40. Rearrangement of epoxy-himachalene by Brønsted acid.

Several experiments were conducted using different solvents and temperatures. The results showed that the total conversion of epoxide requires larger amount of Brønsted acids (1%) and longer reaction times. Unidentifiable by-products in small quantities were observed by gas chromatography as with Lewis acids. The

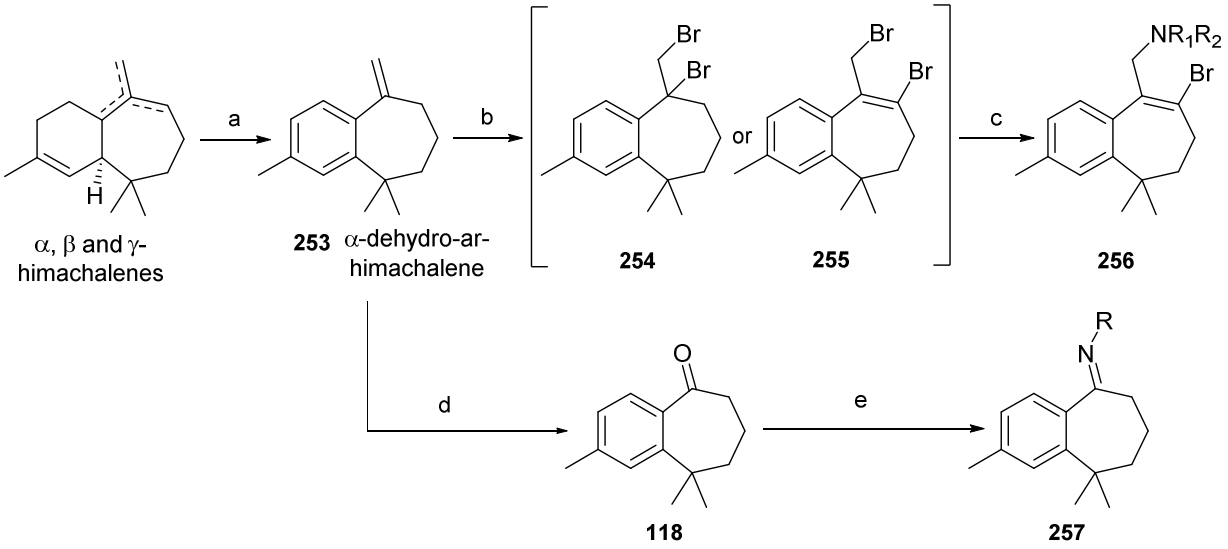
chemoselectivity of the reaction depends on the solvent, temperature, and catalyst used. In methanol, MSA and PTSA catalysts promoted the rearrangement of α-epoxyhimachalene **224** into alcohol **247** and methoxy derivative **250** as a new product. However, in the case of epoxyhimachalene **5**, a compound **252** was isolated besides the ketone **248** and *ar*-himachalene **12**. In addition, the selectivity in favor of alcohol **247** at room temperature was switched and in favor of methoxy compound **250** by heating at 60°C. With PTSA, compound **250** could be obtained in 63% yield. However, using MSA, the epoxide rearrangement afforded a mixture of three products, **247**, **250** and **251** in 35%, 44%, and 10% respectively.

4.6 Amination of himachalenes

Benzocycloheptene and their derivatives are a biologically potent class of bicyclic frameworks and are attractive synthetic targets for organic and medicinal chemistry. A new series of benzocycloheptene amino vinyl bromide derivatives were synthesized from the mixture of α, β and γ-himachalenes through two steps: The mixture of three isomers α, β and γ-himachalenes was treated with DDQ in dry benzene under nitrogen at reflux. In these conditions, the reaction gave *α*-dehydro-*ar*-himachalene **253** as major product (Scheme 41). Optimization of the bromination of *α*-dehydro-*ar*-himachalene **253** with Br_2/DCM, Br_2/AcOH and NBS all led to the formation of mixture of dibrominated products. Finally, bromination using KBr (4 equiv) and ceric ammonium nitrate (CAN, 3 equiv) in DCM/H_2O (1:1, v/v) for 5 h at room temperature provided a compound **254** as a major product, which was founded to be unstable during its purification by column chromatography.

Mechanistically, the alkene reacted with bromide radicals to form a dibromo intermediate **254** which rearranged to product **255**. The intermediate **255** was further treated with 1.5 equiv of amine in the presence of 2 equiv of K_2CO_3 in DMF at 90 °C for 15 h to produce benzocycloheptenamino derivative **256** as major product. This reaction was investigated using different aromatic and aliphatic amines. Several secondary amines such as morpholine, piperidine, piperazine, pyrrolidine, and diethylamine were used giving satisfactory yields ranging from 62% to 76%. Different primary amines such as cyclohexyl-, benzyl-, *iso*-butyl-, *t*-butyl-amine, and phenylethyl-amines were also tested in the same reaction. Good yields were founded, ranging from 50 to 72% according to the amine used. The structures of the various products were confirmed by NMR and X-ray crystallographic analyses. The new products were further evaluated for their antidepressant activities and it was observed that the piperazine substituted derivative showed good activity. Thus, the piperazine derivative was considered as a lead entity selected for further modifications to obtain more efficacious and potent antidepressant drugs.[124]

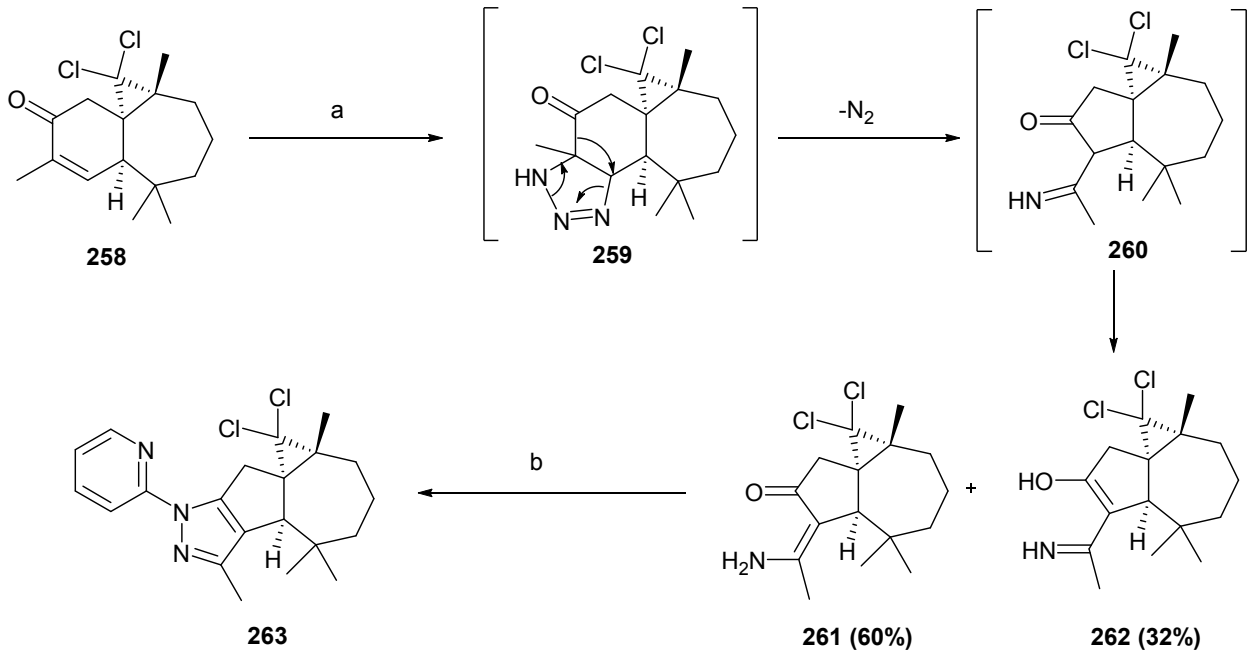
Recently, five new 2,9,9-trimethyl-6,7,8,9-tetrahydro-benzocyclohepten-5-ylidene imine derivatives were synthesized by Chaudhary *et al.*[84] Starting from the same substrate α-dehydro-*ar*-himachalene **253.** Oxidation of the exocyclic double bond with $NaIO_4$ and OsO_4 in a mixture of water/THF (1:1, v/v) for 20 h at room temperature produced a corresponding benzocycloheptenone **118** in 73 % yield. Finally, using dry silica gel (H) as a Lewis acid and an appropriate amine gave good conversions to the corresponding imines. Different imines **257** were obtained with good yields up to 79% according to the amine used (Scheme 41). The prepared compounds were tested against a group of sixteen organisms including gram positive and gram negative bacterial and fungal strains. The imine containing an isobutyl group showed the highest activity amongst tested compounds.



a) DDQ, dry benzene, reflux, 24 h, N_2; b) CAN, KBr, DCM/H_2O, r.t, 5 h; c) Amine,K_2CO_3, DMF, 80-90 °C. d) OsO_4, $NaIO_4$, H_2O:THF (1:1), 20 h, r.t. e) Amine, silica gel, H, 4-7 h

Scheme 41. Synthesis of amino-dehydro-*ar*-himachalenes.

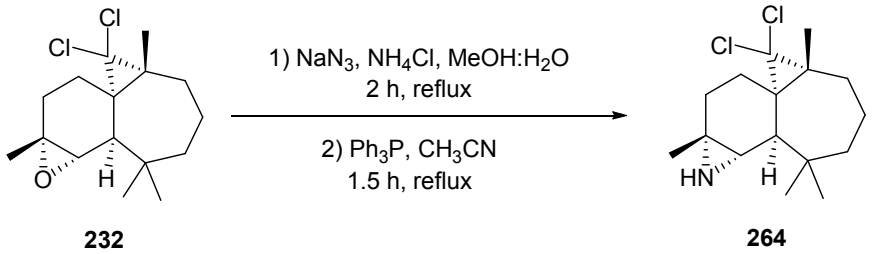
Other amino-himachalene derivatives was reported by Auhmani *et al.*[125] Firstly, (1*S*,3*R*,8*R*)-2,2-dichloro-3,7,7,10-tetramethyltricyclo[6,4,0,$0^{1,3}$]-dodec-9-en-11-one **258** was prepared in good yield from **231** by allylic oxidation with *N*-bromosuccinimide (NBS). When a compound **258** treated with sodium azide in trifluoroacetic acid medium, the enone **258** was easily transformed into enaminone **261** and iminol **262**. Formation of enaminone **248** and iminol **249** proceeded by a [3+2] cycloaddition with HN_3, generated *in situ* from sodium azide and trifluoroacetic acid. The *N*-substituted pyrazole **263** was formed regiospecifically by treatment of β-enaminone **261** with 2-hydrazinopyridine (Scheme 42).



a) HN_3, b) Py-NH-NH_2, AcOH, reflux

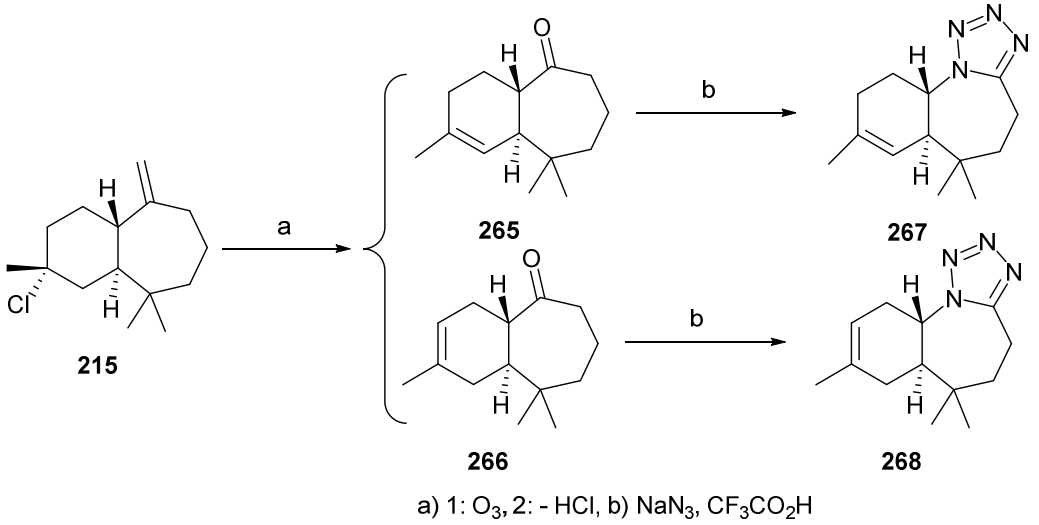
Scheme 42. Synthesis of enaminones and fused pyrazoles.

Aziridines **264** were formed by treatment of epoxide **242** with an excess of NaN_3 and NH_4Cl in a mixture of methanol/water (15/1) at reflux for 2 hours. Under these conditions the reaction led to a mixture of azido-alcohol derivatives. They were purified by column chromatography and then treated with an excess of PPh_3 in acetonitrile under reflux for 1.5h. The product **264** was obtained with 82% yield from azido alcohol after purification by column chromatography (Scheme 43). The structure was determined by X-ray diffraction analysis.[126]



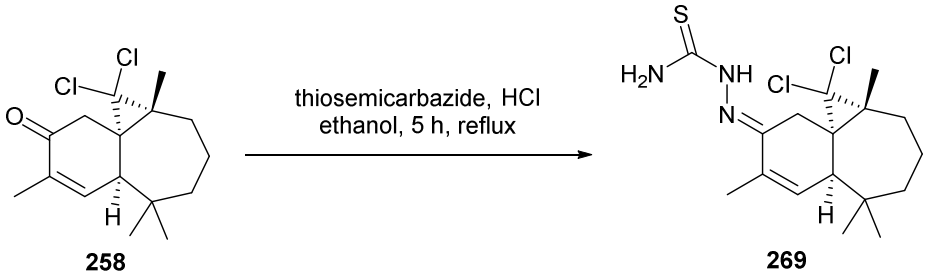
Scheme 43. Aziridination of **232**.

Lassaba *et al.* reported the synthesis of (1*S*,6*S*)-tetrazolo[1,5-*g*]-7-aza-*trans*-himachal-2-ene by ozonolysis of **215** followed by a dehydrohalogenation to give two sesquiterpenic ketones **265** and **266**.[118] Then, action of two equivalents of NaN_3 on **265** and **266** in presence of trifluoroacetic acid provided **267** and **268** in 75% and 70% yield respectively (Scheme 44).



Scheme 44. Synthesis of tetrazolo-himachalenes **267** and **266**.

Ourhriss *et al.*[127] have described the synthesis of tricyclic thiosemicarbazone derivative of β-himachalene. Dichlorocyclopropanation of β-himachalene, from essential oil of Atlas cedar, followed by allylic oxidation using *N*-bromosuccinimide and condensation with thiosemicarbazide, gave a compound **269** (Scheme 43). The structure was elucidated by ^1H and ^{13}C NMR spectroscopy and its absolute configuration established by single-crystal X ray diffraction analysis.

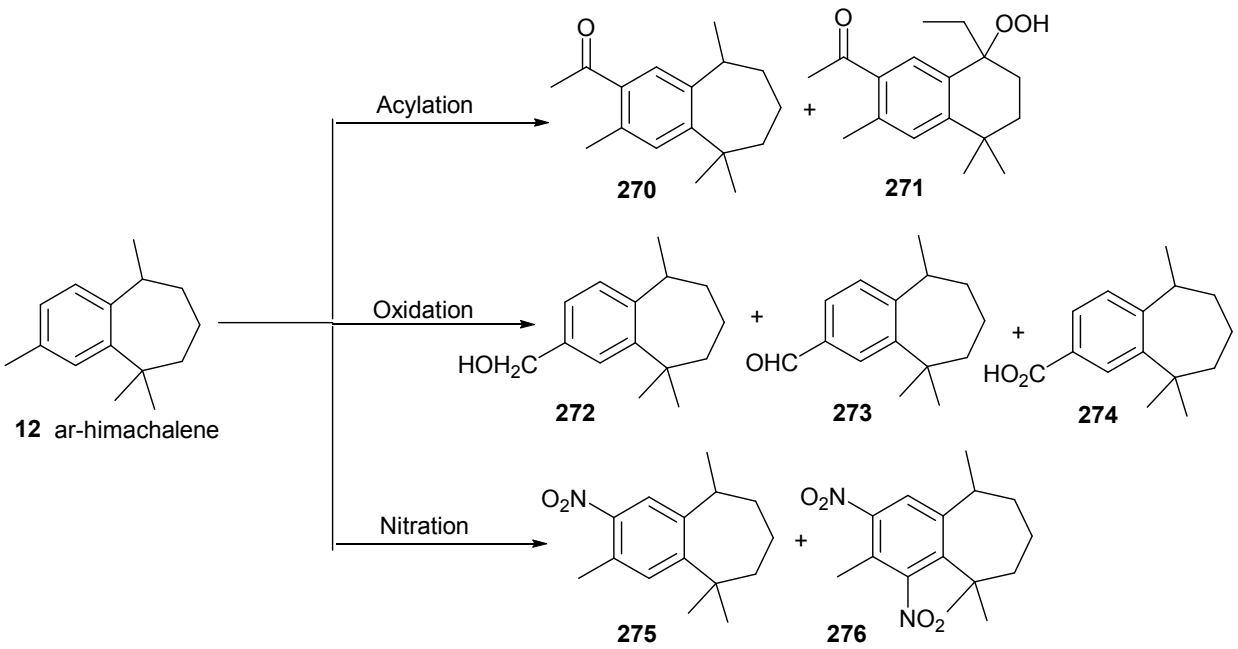


258 **269**

Scheme 45. Condensation of enone **258** with thiosemicarbazide.

5. Synthesis of *ar*-Himachalene Derivatives

The Friedel Craft acylation of *ar*-himachalene obtained by dehydrogenation of a mixture of the three isomers α-,β- and γ-himachalene was carried out with acetyl chloride and $AlCl_3$ at room temperature.[128] Under these conditions the reaction produced one product: 1-(3,5,5,9-tetramethyl-6,7,8,9-tetrahydro-5*H*-benzocyclo-hepten-2-yl)ethanone **270**. The study also showed that with increasing the temperature from 25 to 100 °C the reaction gave a mixture of the acylated compound **270** as major product (69%) and 1-(8-ethyl-8-hydroperoxy-3,5,5-trimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethanone **271** (21%) (Scheme 46**).** The formation of the acyl hydroperoxide **271** could be explained by oxyfunctionalization of the acyl-*ar*-himachalene with molecular oxygen when exposed to air. Its structure was confirmed by X-ray diffraction.



12 ar-himachalene **270** **271** **272** **273** **274** **275** **276**

Scheme 46. Synthesis of *ar*-himachalene derivatives.

Nitration of *ar*-himachalene with nitric acid in a mixture of acetic anhydride and acetic acid produced two products, **275** and **276**. When the reaction was performed in sulfuric acid medium, only the dinitrate compound was obtained.[129]

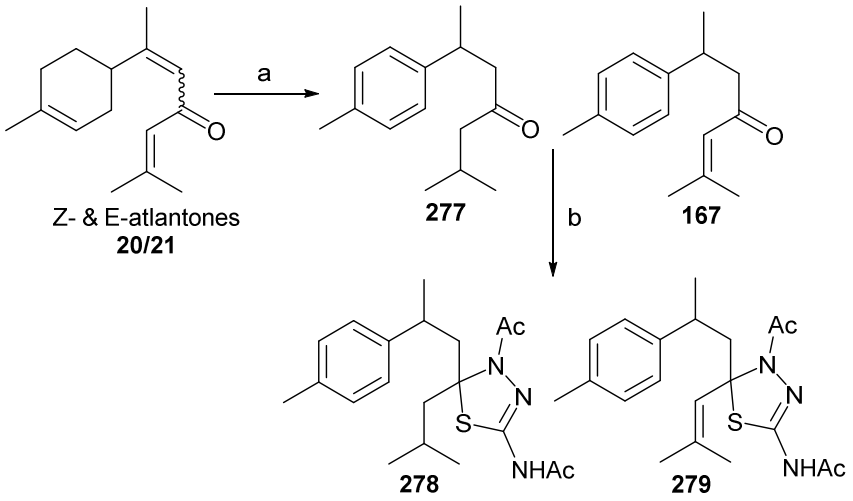
Recently, similar results were obtained by a catalytic route. Catalytic nitration of *ar*-himachalene was studied with complexes based on transition metals.[130] In fact, a practical system of metal (2,4-pentanedionate)

($M(acac)_n$ (M = Fe, Zn, Co and V)) with phosphorus pentoxide (P_2O_5) in the presence of nitric acid, catalyzed regioselective nitration of *ar*-himachalene to the mononitro-*ar*-himachalene in moderate to good yields under mild conditions. It was founded that the reaction selectivity was excellent if the mononitrate was required, compared with the classical method using HNO_3/H_2SO_4.

6. Reactivity of α-Atlantones

6.1 Aromatization/condensation with thiosemicarbazone

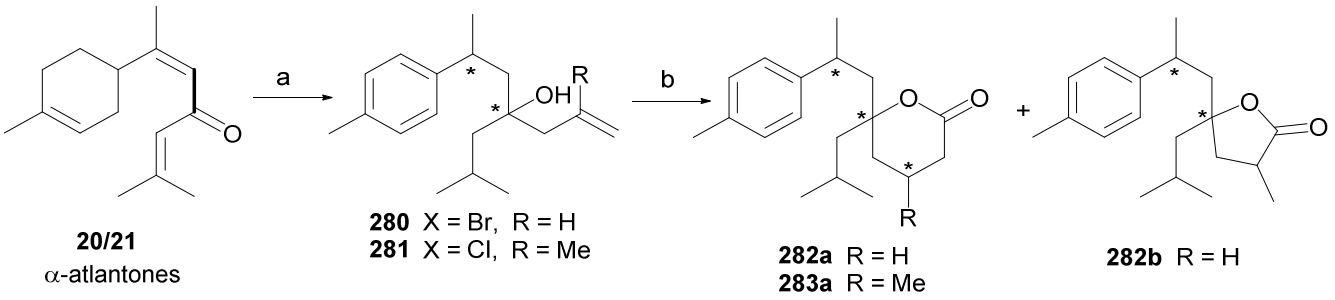
Both isomeric (*Z*)- and (*E*)-*α*-atlantones **20** and **21** were quantitatively converted into *N*-[4-acetyl-5-isobutyl-5-(2-*p*-tolylpropyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]acetamide[131] **278** or to *N*-[4-acetyl-5-(2-methylprop-1-enyl)-5-(2-*p*-tolylpropyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]acetamide[132,133] **279** (Scheme 47). The reaction was carried out in two steps: firstly a treatment with Pd/C and by adjusting the temperature conditions, aromatic ketone intermediate **277** and **167** could be obtained selectively. Reaction with thiosemicarbazone resulted in formation of products **278** and **279** in good yields.



Scheme 47. Aromatization of atlantones followed by condensation with thiosemicarbazone.

6.2 Cyclocarbonylation of atlantone derivatives

Cyclocarbonylation is an alkoxycarbonylation reaction of a substrate containing both olefin and -ZH function (Z = O, N) which will react with the acyl intermediate formed during the catalytic cycle. Cyclocarbonylation of allylic alcohols **280** and **281** obtained from *Z* and *E*-*α*-atlantones after aromatization with Pd/C followed by Grignard reaction was studied in the presence of catalyst [$PdCl_2L_2/SnCl_2.2H_2O$] with L = monophosphine or diphosphine ligand (Scheme **48**).[134]



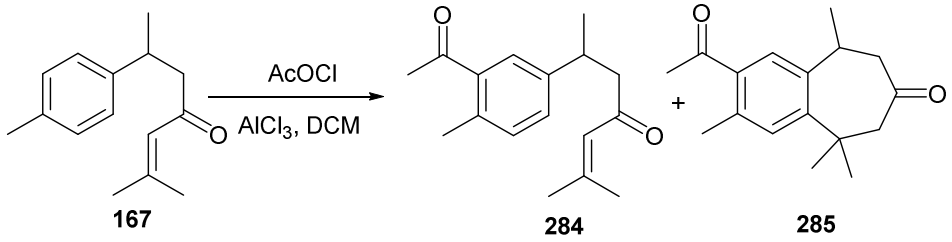
a) 1: Pd/C, 160°C, 2: CH_2CRCH_2MgX, THF, 0°C. b) $PdCl_2L_2$ / $SnCl_2.2H_2O$, CO

Scheme 48. Cyclocarbonylation of homoallylic alcohols derived from (*E*)- and (*Z*)-α-atlantones.

Alcohol **280** was transformed into lactones **282a** and **282b** with a selectivity ranging from 78 to 82%. This study showed that the regioselectivity depends heavily on the nature of the ligand used. Indeed, using monophosphine ligand mainly promoted the formation of the lactone five-membered ring **282b**, whereas in the case of diphosphines, the regioselectivity was reversed in favor of the six-membered lactone **282a**. Similarly, cyclocarbonylation of alcohol **281** was performed under the same catalytic and experimental conditions. Introduction of a methyl group in position γ resulted in a lower conversion but the regioselectivity to form the six-membered lactone **283a** was excellent since the latter was formed exclusively. This result showed that this reaction does not depend only on the nature of the ligand used, but also on the nature of the substrate.

6.3 Acylation of atlantone derivatives

The acylation of 2-methyl-6-(4-methylphenyl)hept-2-en-4-one **167** was performed in the presence of acetyl chloride and $AlCl_3$ in dichloromethane.[135] The reaction led to the formation of two acylated compounds **284** and **285** with an overall yield of 90%, in a ratio **284/285** of 55/35 (Scheme 47). Formation of product **285** can be explained by activation of the double bond in the presence of $AlCl_3$ which generates a positive partial charge on the C2 carbon, leading to an intramolecular Friedel-Crafts reaction.



Scheme 49. Acylation of atlantone derivative **167.**

7. Conclusions

Chemists have a compelling curiosity to discover what compounds nature provides, but to obtain this information it is necessary to isolate compounds from their natural source and to determine their structures. This is seldom an easy task, especially when the compound of interest is present at low concentrations. In this circumstance a high degree of skill and technology is required in both the isolation procedures and the subsequent investigations to establish the chemical structure. A second objective is the total synthesis of the

compound from smaller molecules. Indeed, in the classical approach to structure determination, a structure was assigned to a natural product through chemical degradation studies to smaller, identifiable molecules. However, the assigned structure was not regarded as fully confirmed until the compound was synthesized and shown to be identical in all respects (composition, configuration, conformation) with the natural compound. This approach persists, although the enormous impact of modern methods of separation and spectroscopic analysis has made it possible to determine structure beyond a reasonable doubt in almost all cases without recourse to synthesis. Nevertheless, despite the problems of stereoselectivity and the high number of steps, the synthesis of natural products continues to be important. It provides new methodology, new reactions and techniques. It also provides alternative sources of natural compounds and offers routes to related but unnatural analogs. In the case of a useful drug, the synthetic objective is to find a related structure that is more potent at lower dosages with fewer side effects than the natural compound. This review provides an overview of research concerning the upgrading of essential oil of cedar. Firstly we showed the different work cited in the literature on the chemical constituents of these essences and the different methods that allow synthesis of the main constituents from commercial products. We have also reviewed the significant contributions of various research groups on the chemical transformation of the main sesquiterpenes in order to increase the biological activity of the molecule or to discover new activities. This inexhaustible source allows the identification of several products to achieve a range of activities of growing potential and targeted to cover a broad spectrum of diseases.

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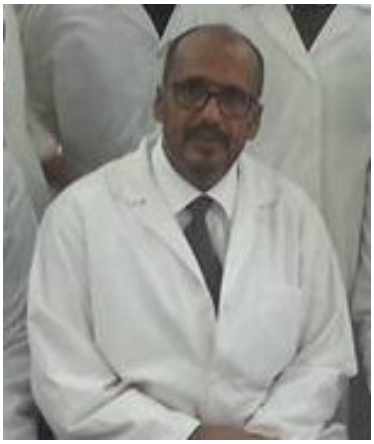
Authors' Biographies



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