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
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: *atlantica*, *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 Grimali. Pfau and Plattner showed the existence of two sesquiterpene ketones: α- and γ-Atlantone 2 and 3. Teisseire and Plattier 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. isolated other sesquiterpenoid compounds, such as allohimachalol 7 and (+)-longiborneol 8 (Scheme 1).

![Chemical structure of compounds isolated from essential oil of cedar.](image)

**Scheme 1.** Compounds isolated from essential oil of cedar.
Ruzička et al.\textsuperscript{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.\textsuperscript{9} isolated two bicyclic optically active sesquiterpene hydrocarbons named α- and β-himachalene, 9 and 10 respectively (Scheme 1).\textsuperscript{9} The structures of these two sesquiterpenes were identified and confirmed by Joseph and Dev.\textsuperscript{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.\textsuperscript{11} Moreover, Teisseire and Plattier\textsuperscript{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, deodorone 25, deodorantine 24,\textsuperscript{13-17} centdarol 15, isocentdarol 16,\textsuperscript{18,19} α-torsol 18, β-torsol 19, andirolactone 28,\textsuperscript{20} α-trans-atlantone 20, γ-atlantone 21,\textsuperscript{21} himasecolone 23,\textsuperscript{22} acetyldipentene 26 and limonene carboxylic acid 27 (Scheme 1).\textsuperscript{17} In addition, the products mentioned above, recent studies have been discovered the existence of other compounds.\textsuperscript{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.\textsuperscript{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\textsubscript{2}O/dioxane gave a tricyclic ketone 32 in 35\% yield based on 31. The action of CH\textsubscript{3}Mgl followed by treatment with the Simmons-Smith reagent gave after hydrolysis a product 33 with a cyclopropane moiety. Then, alkylation was conducted with CH\textsubscript{3}/(CH\textsubscript{3})\textsubscript{2}COK in t-butyl alcohol-benzene followed by hydrogenation with (Pt/Rh) catalyst to gave 34. Reduction of 34 with LiAIH\textsubscript{4} gave a separable mixture of diols 35 and 36. Finally, dehydration in pyridine in presence of POCl\textsubscript{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.\textsuperscript{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\textsubscript{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.\textsuperscript{31} This derivative is successfully prepared by addition [1,2] of the enolate ester 43 with 3,3-dimethylacrolein 44 in THF at −78 °C. 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 LiAIH\textsubscript{4} provided the corresponding alcohol, which is oxidized in its turn by PCC at 25 °C to obtain dienal 47 (82\%) (Scheme 4). Reaction of product 47 with complex 48 in THF at -78 °C followed by protection of the alcohol formed with diethyl phosphochloridate CIPO(OEt)\textsubscript{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.
Scheme 2. Total synthesis of α-trans and β-himachalenes developed by De Mayo.


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 ZnBr2 provides the product 54, which was converted into an 5-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
Another synthesis in seven steps was carried out by Mehta and Kapoor starting from the tricyclic
esesquiterpene longifolene. This strategy allowed synthesis of (+)-himachalene dihydrochloride which is an
intermediate that gave access to trans-himachalene derivatives and (+)-ar-himachalene (Scheme 6).

![Scheme 6](https://example.com/scheme6.png)

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

The key step is the preparation of a bifunctional longiborne 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. Thus, Wolff-Kishner
reduction of 59 and purification (AgNO₃-silica gel) gave the himachalene isomer 60. A stream of HCl gas
through an acetic acid solution of 60 gave (+)-himachalene dihydrochloride 37. 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 showed that α- and β-himachalene can be obtained by
Wagner-Meerwein rearrangement of longipinene with a variety of acids (BF₃·Et₂O, HClO₄ in aqueous dioxane,
H₂NSO₂OH in acetone, and H₂SO₄ in glacial acetic acid).

Piers and Ruediger\textsuperscript{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 \textit{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 \textit{n}BuLi/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.\textsuperscript{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. \(^{30,36,43,44}\)

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 (15,2R)-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\(_2\)SiCHN\(_2\) 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\(_4\)NF 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).

![Chemical structure](image)

**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 dehydrochlorination/isomerization in pyridine or filtering on alumina.\(^6,29,39,50,51\)
Scheme 10. Enantiospecific synthesis of (+)-trans-α-himachalene.

Dufour et al.\textsuperscript{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\textsubscript{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,\textsuperscript{53} which underwent Wittig reaction to give triene 105 (43% 2 steps).
The Diels-Alder cyclization catalyzed by different Lewis acids (SnCl₄·5H₂O, ZnCl₂ or ZnBr₂), which all gave only one regioisomer and good diastereoselectivity. The best results were obtained with ZnCl₂ 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 methylation with Tebbe reagent to obtain a desired 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 MeMgl 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 H₂ provided the required product 12.
Scheme 12. Synthesis of \textit{ar}-himachalene from \textit{m}-methylacetophenone 111.

A shorter and more efficient method was described by Sonawane \textit{et al.} \textsuperscript{55} (Scheme 13).

Scheme 13. Synthesis of \textit{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. \textsuperscript{56,57} The resulting product undergoes an acid-catalyzed rearrangement to give the ketone.
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. provides a series of sesquiterpenes including ar-himachalene. The route involved ten steps from cycloheptanone 128. Firstly, the latter was dimethylated with Mel and t-BuOK in t-BuOH under Ireland-Marshall conditions. Bromination of the resulting product 129 followed by HBr elimination using LiBr–Li$_2$CO$_3$ in DMF, provided enone 131. Interaction of the latter with Me$_2$CuLi followed by Michael addition in the presence of silyl ketone 132 gave silyl diketone 133. 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).


Another method was reported by Mori et al. 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,2S)-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)-citronellall (Scheme 15).

![Chemical diagram](Image)

\[\text{a) PDC, DMF, O C to room temp.; b) K}_2\text{CO}_3, \text{EtI, DMF, O C to room temp. (74%, 2 steps); c) O}_3, \text{MeOH, 78 C; then Me}_2\text{SO (72%); d) (EIO)\text{P(O)}\text{CHMeCO}_2\text{Et, NaH, THF, 30 C (96%); e) H}_2, \text{P} (\text{O}_2) \text{EtOAc, room temp. (quanti.); f) 1BuOK, m-xylene, 150 C; 2) diluted HCl (79%); g) 1} \text{NaOH, MeOH, H}_2\text{O, reflux; 2) diluted HCl (85%); h) 1BuOK, tBuOK, Mel, O C to room temp. (88% based on consumed 142); i) 1} \text{LDA, TMSCI, THF, 78 C; 2) MeLi, CH}_2\text{C(TMS)COMe, THF; 3) NaOMe, MeOH, room temp. (44% based on consumed 143), i)Wittig reaction; k) chloranil T}\]

**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-ethylidisopropylamine. Treatment of the resulting amide 161 with the Grignard reagent 2-methylpropenylmagnesium bromide afforded (R)-ar-turmerone 162 (Scheme 16). Finally, (R)-ar-turmerone was converted into ar-himachalene in two steps: intramolecular cyclization in the presence of AlCl₃ and CS₂, then the bicyclic ketone (R)-163 formed was reduced with N₂H₄·H₂O 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 [α]D²³⁺ = +3.8 while in chloroform [α]D²³⁻ = -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.


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 H₂ 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 Me₂C=CHMgBr. The latter was converted into (+)-bisacumol 168 by hydrogenation of the carbonyl function, or ar-himachalene 12 by Friedel-Crafts cyclization.

\[
\begin{align*}
\text{164} & \xrightarrow{a} \text{165} & \text{166} \\
\text{(+)-bisacumol 168} & \xrightarrow{b} \text{or} \xrightarrow{d} \\
\text{12 ar-himachalene} &
\end{align*}
\]

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.\textsuperscript{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\textsubscript{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 benzyl position. The best result was obtained with Pd/C in ethanol under pressure of H₂ (60 psi) at room temperature. The iodo derivative (R)-172 was obtained by treatment of the alcohol with iodine in the presence of PPh\textsubscript{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\textsuperscript{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\textsubscript{2} and BF\textsubscript{3}OEt\textsubscript{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).\textsuperscript{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.\textsuperscript{76}
Enantioselective synthesis of ar-himachalene starting from α,4-dimethylstyrene.

Campagne et al.\textsuperscript{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\textsubscript{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\textsubscript{2}O\textsubscript{5} in MeSO\textsubscript{3}H), 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 Me₂TiCl₂ Reetz reagent 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, chloranil, palladium, Raney nickel, bromine, DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone). The selectivity and yield of this transformation is dependent on the reagent employed and the operating conditions.


3.3 Synthesis of α-atlantones

Atlantones represent the major ketone 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). 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 (4R,8S) p-menth-1-en-9-al 185, which transformed into cyanohyrdrins derivatives 186 using potassium cyanide and acetic acid. Dehydration of cyanohyrdrins 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-isolantone 188a and cis-isolantone 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-dihydroatlanlone 189a and 189b (Scheme 21).

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-bisabololone 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-bisabololone 194 (55%) followed by dehydorination 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. 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 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 (trimethylstanny)limonene.

Another method, developed by Cookson and Parsons, involves a synthesis of allenyl sulfoxide made from propynyl alcohol 197 and benzenesulfenyl chloride. 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 P2S5 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 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.\(^9\) 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)\(_2\)SO\(_4\) to give 208. Electrolytic reduction provided access to deodarone 209 as a mixture of two diasteroisomers (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. described a new brief synthesis of (±)-\(\alpha\)-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 (±)-\(\alpha\)-atlantone or (±)-ar-turmerone 162 according to the ketone used.

![Scheme 26. Synthesis of (±)-\(\alpha\)-atlantone and (±)-ar-turmerone.](image)

The same intermediate dimethyl (2-oxo-4-methyl-3-pentenyl)phosphonate 212 was synthesized by Blouin and Friesen from a tertiary \(\alpha\)-allenic alcohol in four steps. This was used in the synthesis of (Z)- and (E)-\(\alpha\)-atlantone by condensation with acetone in presence of Na\(\text{N(TMS)}_2\) in THF.

Recently, a new strategy for synthesizing ar-atlantone and \(\alpha\)-atlantone was developed by Nakajima et al. This method is based on a sequential TiCl\(_4\)-promoted aldol reaction to simple ketones and base-promoted elimination to obtain \(\beta,\beta\)-substituted and \(\alpha,\beta\)-unsaturated carbonyl compounds. Treatment of 4-methylpent-3-en-2-one with TiCl\(_4\) and Bu\(_3\)N 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 \(\alpha\)-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. 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).
Scheme 27. Hydrochlorination and dehydrochlorination of himachalene.

4.2 dehydrohalogenation
Benharref et al.\textsuperscript{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 \textit{trans}. (Scheme 28).


4.3 Oxidation of himachalenes
4.3.1 Oxidation with KMnO\textsubscript{4}. Oxidation of β-himachalene 10 was carried out by Benharref \textit{et al.}\textsuperscript{99,100} using KMnO\textsubscript{4}. The authors showed that the tetrasubstituted double bond reacted easily with KMnO\textsubscript{4}. Indeed, treatment of β-himachalene with a stoichiometric quantity of KMnO\textsubscript{4} quantitatively produced a diol, 220. However, with an excess of KMnO\textsubscript{4} (3 eq) in a mixture of acetone/water (9/1) the product 221 was regioselectively formed in 30% yield (Scheme 29).
Scheme 29. Oxidation of β-himachalene with KMnO₄.

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 6α,7α-epoxyhimachalene 5 by action of m-chloroperbenzoic acid on β-himachalene (10) (Scheme 30).¹⁰¹ The same epoxide 5 was prepared chemoselectively 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).

Scheme 30. Epoxidation of β-himachalene.
Metal-ion-catalyzed epoxidation of olefinic substrates has been exploited with β-himachalene (Scheme 30). 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 Ag₃CO₃-celite led to 5% of oxygenated product containing 21% of 17 and 19% of 5. A similar conversion was obtained using H₂O₂ under UV light. When β-himachalene in EtOAc containing H₂O₂ (90%) was irradiated, 12% of oxygenated products were formed with 13% of oxydohimachalene 17.

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 [RuCl₂(p-cymene)]₂ in the presence of 2-methyl-5-oxo-7-phenyl-3-thioxo-3,4,5,6-tetrahydro-2H-1,2,4-triazepine (HTAZO) and 2-methyl-7-phenyl-3,5-dithioxo-3,4,5,6-tetrahydro-2H-1,2,4-triazepine (H₂TAZS) respectively. Good stereoselectivity was observed using complexes C1 which allowed isolation of the 6α,7α-epoxyhimachal-2-ene 5 with a chemoselectivity greater than 96% after 7h of reaction.

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.

![Scheme 31. Epoxidation of α-himachalene.](image)

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.
**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 \([\text{MoO}_2(\text{SAP})]\)_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.** \([\text{MoO}_2(\text{SAP})]\)_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 \([\text{MoO}_2(\text{SAP})]\) 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 \([\text{MoO}_2(\text{SAP})]/\text{TBHP}\) 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 \(\text{m-ClO}_2\text{H}_{8}\) under the same conditions as above, provided two diastereoisomers 229 and 230 in 85/15 ratio (Scheme 34).\(^{110}\)

**Scheme 34.** Epoxidation of chlorohimachalene 215.
Treatment of \((1S,3R,8R)-2,2\text{-dichloro-3,7,7,10-}
\text{tetramethyltricyclo}[6,4,0,0^{1,3}]\text{dodec-9-ene} \ 231\) with a stoichiometric amount of 2-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.\(^ {110}\)

![Scheme 35. Epoxidation of compound 231.](image)

### 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).\(^ {112}\)

![Scheme 36. Synthesis of di- and tetra-halo-cyclopropahimachalenes.](image)

Oukhrib \textit{et al.}\(^{113,114}\) found 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/H₂O 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).
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. 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-diepox-himachalene 223 was performed by bubbling HCl gas for one minute in chloroform (Scheme 38). The formation of the tricyclic derivative 245 can be explained by double $S_n$2 type reactions. After the protonation of epoxide at position 6-7, anti nucleophilic attack of Cl$^-$ 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 tetrahydrofuranc ring.

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

Rearrangement of α-epoxyhimachalene 224 was studied by El Haib et al. 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$_3$Et$_2$O, BF$_3$MeOH, 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$_3$Et$_2$O and BF$_3$MeOH, 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$_3$Et$_2$O in dichloromethane, gave ketone 248 and α-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$_3$MeOH 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 $\alpha$-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 $\beta$-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 Br2/DCM, Br2/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/H2O (1:1, v/v) for 5 h at room temperature provided a compound 254 as a major product, which was found 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 K2CO3 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.

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 NaIO4 and OsO4 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.
Scheme 41. Synthesis of amino-dehydro-ar-himachalenes.

Other amino-himachalene derivatives was reported by Auhmani et al.\(^\text{125}\) Firstly, (1S,3R,8R)-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 \(\beta\)-enaminone 261 with 2-hydrizinopyridine (Scheme 42).

Scheme 42. Synthesis of enaminones and fused pyrazoles.
Aziridines 264 were formed by treatment of epoxide 242 with an excess of NaN₃ and NH₄Cl 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 PPh₃ 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 (1S,6S)-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 NaN₃ 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.

Ourhriess 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 ¹³C NMR spectroscopy and its absolute configuration established by single-crystal X ray diffraction analysis.
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 AlCl₃ at room temperature. Under these conditions the reaction produced one product: 1-(3,5,5-tetramethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-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.

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.

Recently, similar results were obtained by a catalytic route. Catalytic nitration of ar-himachalene was studied with complexes based on transition metals. In fact, a practical system of metal (2,4-pentanediolate)
(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 α-himachalene to the mononitro-α-himachalene in moderate to good yields under mild conditions. It was found 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-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-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.

\[\text{Z- & E-atlantones 20/21} \xrightarrow{a} \text{277} \xrightarrow{b} \text{278, 279} \]

\(a)\) Pd/C, Reflux. \(b)\) thiosemicarbazone

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).\(^{134}\)
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 283 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 AlCl₃ in dichloromethane. 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 AlCl₃ 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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