Russian Chemical Reviews **83** (4) 281 – 298 (2014) © 2014 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2014v083n04ABEH004383

Synthesis of hydroxy derivatives of limonene

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Synthetic routes to mono-, di- and trihydroxy derivatives of limonene are presented. Emphasis is given to the problems of regio- and stereoselectivity of transformations. Data on the isolation from natural sources and on the biological activities of the title compounds are given.
The bibliography includes 107 references.

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I. Introduction

Limonene (*p*-mentha-1,8-diene, **1**) and its hydroxy derivatives are widely distributed in nature. Limonene (**1**) is the major component of many essential oils.[1] Although alcohols with the *p*-mentha-1,8-diene carbon skeleton were identified in many natural sources, except for carveol (**2**) and perillyl alcohol (**3**), they occur in plants in minor amounts, and, hence, development of methods for the selective synthesis of these products from available compounds is a topical task.

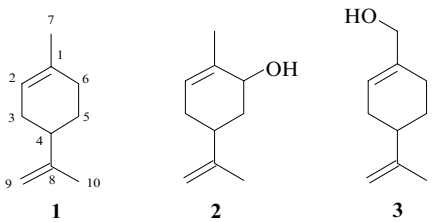
The interest in these alcohols is due to the broad spectrum of biological activities they have including antitumour,[2–4] anti-Parkinsonian,[5] antimicrobial,[6] antiparasitic,[7] anticonvulsant[8] activities and so on. It is noteworthy that the absolute configuration of the molecule often has a crucial influence on the biological activity.[5] Their molecules have two carbon–carbon double bonds with different reactivities and at least one hydroxy group; this enables various sorts of transformations and creation of new pharmaceutical drugs based on these compounds. Furthermore, owing to the possibility of being prepared in enantiomerically pure state and of being functionalized, alcohols with the *p*-mentha-1,8-diene carbon skeleton are employed as key building blocks in the asymmetric syntheses of intricate natural molecules.[9–11] Yet another characteristic feature of the title derivatives is relative structural simplicity. Nevertheless, asymmetric synthesis or interconversions involving hydroxy derivatives of *p*-mentha-1,8-dienes require, almost in all cases, thorough development of experimental procedures, including the adjustment of process conditions and application of modern highly effective reagents.

Despite numerous publications devoted to the monoterpene chemistry, including monographs,[12–14] no reviews covering limonene hydroxy derivatives have yet been published. The purpose of this review is to describe systematically the information available from the literature on the synthetic routes to these compounds. We considered in detail the approaches to the synthesis of alcohols with different numbers and positions of hydroxy groups, particular attention being devoted to regio- and stereoselectivity problems.

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Current research interests of the authors: chemistry of natural compounds, medical chemistry, asymmetric synthesis.

Received 14 March 2013
Uspekhi Khimii **83** (4) 281 – 298 (2014); translated by Z P Svitanko

Structures 1 – 3



1 **2** **3**

Different nomenclatures and atom numberings based on either cyclohexane or *p*-menthane carbon skeleton are used for these compounds in the literature. For the sake of simplicity, from here on, we adhere to a common numbering accepted for *p*-mentha-1,8-diene (**1**) and allowed by the IUPAC rules for derivatives of natural terpenoids.

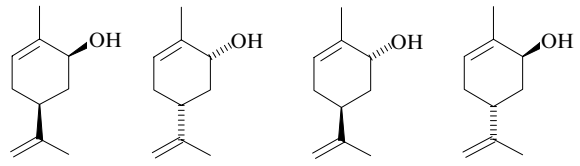
II. Synthesis of limonene derivatives containing one hydroxy group

1. Carveol

a. *cis*-Isomer

Both enantiomers of *cis*- [(4*S*,6*S*)-**2** and (4*R*,6*R*)-**2**] and *trans*-carveols [(4*S*,6*R*)-**2** and (4*R*,6*S*)-**2**] were found in natural specimens, their content in some essential oils being rather high. For example, in the essential oil of the flowers of lemon balm (*Melissa officinalis* L.), the proportion of *trans*-carveol reaches 28.9%,[15] while the essential oil of the *Peucedanum rutenicum* M. Bieb. fruits contains 6.9% of *cis*- and 4.0% of *trans*-isomers.[16]

Structures 2



(4*S*,6*S*)-**2** (4*R*,6*R*)-**2** (4*S*,6*R*)-**2** (4*R*,6*S*)-**2**

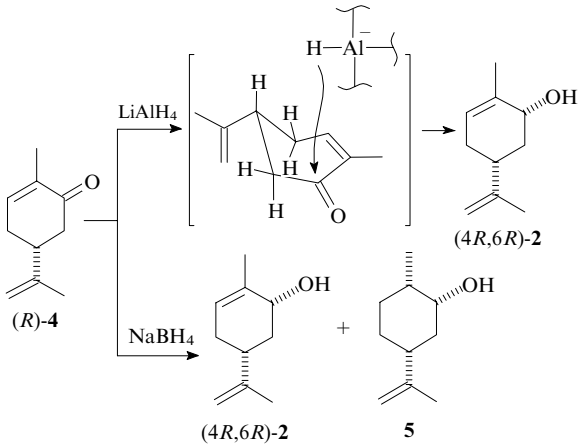
Nevertheless, the major sources of carveol stereoisomers are synthetic transformations of much more readily available monoterpenoids. (*R*)- and (*S*)-Carvones **4** are among the most naturally abundant compounds with the *p*-mentha-1,8-diene carbon skeleton.[14] These compounds of high optical purity are commercially available chemicals; they are rather easily reduced to *cis*-carveols with high stereoselectivity. A great number of studies were devoted to this reaction, largely due to the fact that carvones containing a keto group, non-conjugated and conjugated C=C double bonds and an asymmetric centre of a definite configuration are good model objects for studying regio- and stereoselectivities of a large number of reactions that form the basis of the methods being developed for reduction of carbonyl compounds and alkenes.

Most often, $LiAlH_4$ serves as the reducing agent, reactions are stereoselective and products are formed in high yields. For example, reduction of (−)-(*R*)-carvone [(*R*)-**4**] by treatment with $LiAlH_4$ in Et_2O at −78,[17] −70[18] and −50 °C[19] or at room temperature in CH_2Cl_2[20] furnishes the corresponding (−)-*cis*-carveol [(4*R*,6*R*)-**2**] in 96%–99% yield (Scheme 1). Also, noteworthy is the paper[21] in which the composition of the reaction products formed upon (*R*)-carvone reduction with $LiAlH_4$ at −78 °C in Et_2O was studied in detail. The authors obtained (−)-*cis*-carveol [(4*R*,6*R*)-**2**] in 94% yield and with a diastereomeric excess (*de*) of 95%. Thus, the calculated yield of the (−)-*cis*-isomer (4*R*,6*R*)-**2** in this reaction is 92%, and (−)-*trans*-carveol [(4*R*,6*S*)-**2**] accounts for 2%.

This high stereoselectivity of reduction of carvones (**4**) by $LiAlH_4$ can be attributed to the concerted influence of the kinetic and thermodynamic factors (see Scheme 1). First, the reagent attacks from the sterically less hindered side to give the alcoholate, which exists in the energetically most favourable 'pseudo-chair' conformation. Second, from the thermodynamic standpoint, beneficial is the fact that both the hydroxyl and isopropenyl groups in the final *cis*-carveol are in pseudo-equatorial positions.

The reduction of carvones (**4**) with $NaBH_4$ is less selective. For example, (−)-(*R*)-carvone [(*R*)-**4**] reacts with 1 equiv. of $NaBH_4$ to give a mixture containing, according to GLC data, 16% of the starting carvone [(*R*)-**4**], 71% of *cis*-carveol [(4*R*,6*R*)-**2**] and 13% of compound **5** in which the endocyclic double bond has also been reduced (see Scheme 1).[22]

Scheme 1



The situation was improved by adding 1 equiv. of $CeCl_3 \cdot 5H_2O$ to the reaction mixture (so-called Luche reduction).[22] In this case, the reaction proceeded over a period of 5 min, the yield of (−)-*cis*-carveol [(4*R*,6*R*)-**4**] increased to 98%, while the fraction of compound **5** decreased to 2%. Note that in another study,[23] the reduction of (*R*)-carvone [(*R*)-**4**] under Luche conditions afforded (−)-*cis*-carveol [(4*R*,6*R*)-**2**] in a 92% yield but with a diastereomeric excess of only 85%.

An alternative and cheaper synthetic route to *cis*-carveols **2** is the use of a reducing system with $CaCl_2$ instead of $CeCl_3$.[24] Calcium chloride is added to a solution of carvone **4** in MeOH and the mixture is stirred for 30 min until a transparent solution is formed, then $NaBH_4$ is added and the mixture is kept for 1 h at 0 °C. The workup gave rise to a mixture (97% yield) containing at least 99% of the corresponding *cis*-carveol **2**. A similar reduction procedure implies the use of the $NaBH_4$–$Ca(OTf)_2$ system in MeOH (Tf is trifluoromethanesulfonate, triflate).[25] Using this method, (−)-(*R*)-carvone [(*R*)-**4**] can be converted to the corresponding (−)-*cis*-carveol [(4*R*,6*R*)-**2**] with a minor impurity of compound **5** (97 : 3 ratio) in a total yield of 96%.

The reduction of carvone (the stereochemistry is not indicated in the original publication) with magnesium metal in the presence of $CdCl_2$ in aqueous tetrahydrofuran for 15 min furnished the corresponding stereoisomer of *cis*-carveol (**2**) in 95% yield.[26]

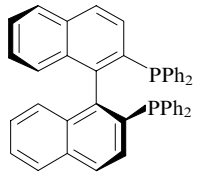
A 100% selectivity was observed for 1,2-reduction of carvone (**4**) to *cis*-carveol (**2**) on treatment with Bu^i_2AlH in a toluene–hexane mixture (4 : 1) at −78 °C, the product yield being 94%.[27]

Lithium pyrrolidinoborohydride ($LiPyrBH_3$) obtained by the reaction of the pyrrolidinoborane complex with Bu^nLi in THF at 0 °C proved to be a selective reagent for

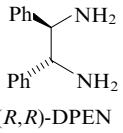
the reduction of (−)-(*R*)-carvone [(*R*)-**4**] to (−)-*cis*-carveol [(4*R*,6*R*)-**2**]. A solution of this reagent was added to a solution of (−)-(*R*)-carvone in THF, and the mixture was kept at room temperature for 3 h. The yield of (−)-*cis*-carveol [(4*R*,6*R*)-**2**] was 96%.[28]

Finally, catalytic hydrogenation of (−)-(*R*)-carvone [(R)-**4**] in the presence of $RuCl_2$[(*S*)-BINAP](DMF)$_n$ (BINAP is 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), (*R*,*R*)-DPEN (DPEN is 1,2-diphenylethylenediamine) and KOH at a 500 : 1 : 1 : 2 reactant molar ratio in isopropyl alcohol at a hydrogen pressure of 4 atm produced (−)-*cis*-carveol [(4*R*,6*R*)-**2**] in a quantitative yield and with 100% *de*.[29]

Ligands



(*S*)-BINAP

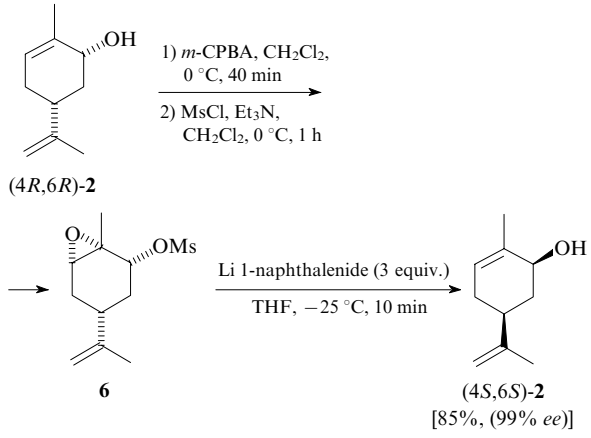


(*R*,*R*)-DPEN

For comparison, when the achiral complex of $RuCl_2(PPh_3)_3$ and ethylenediamine is used, the reaction affords a product mixture containing 93% of (−)-*cis* [(4*R*,6*R*)-**2**] and (−)-*trans* [(4*R*,6*S*)-**2**] carveols in a 81 : 19 ratio. The ratio changes in favour of (−)-*trans*-carveol to 34 : 66 (99% total yield) when the ligands (*R*)-BINAP and (*S*,*S*)-DPEN are used. In the case of hydrogenation of racemic carvone [(±)-**4**] in the presence of the system comprising $RuCl_2$[(*S*)-BINAP](DMF)$_n$, (*R*,*R*)-DPEN and KOH (1000 : 1 : 1 : 2 reactant ratio) at a hydrogen pressure of 4 atm, kinetic resolution takes place, 46% of (*S*)-carvone [(*S*)-**4**] [the enantiomeric excess (*ee*) was 94%] and 50% of (−)-*cis*-carveol [(4*R*,6*R*)-**2**] (93% *ee*) being isolated from the reaction mixture.

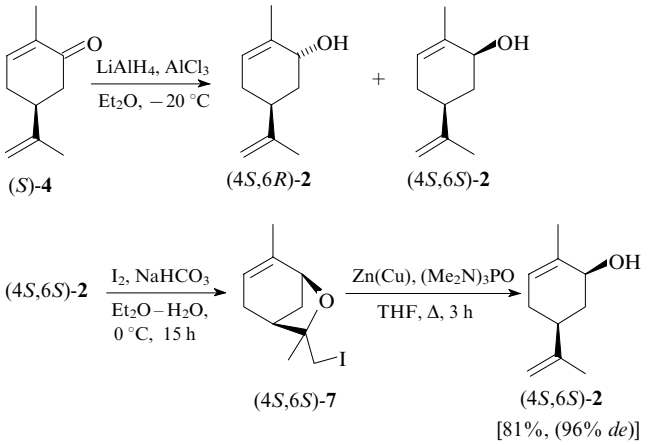
Transition from (−)-*cis*-carveol [(4*R*,6*R*)-**2**] to the (+)-*cis*-carveol enantiomer [(4*S*,6*S*)-**2**] is possible *via* a sequence of transformations comprising epoxidation with *m*-chloroperoxybenzoic acid (*m*-CPBA), reaction with MsCl (Ms is methanesulfonyl, mesyl) and treatment of epoxy mesylate **6** with lithium naphthalenide (Scheme 2).[30] This process is highly stereoselective.

Scheme 2



An effective chemical method for the separation of (+)-*cis* [(4*S*,6*S*)-**2**] and (+)-*trans* [(4*S*,6*R*)-**2**] carveols was reported.[31] (+)-(*S*)-Carvone [(*S*)-**4**] was reduced with a $LiAlH_4 – AlCl_3$ system in diethyl ether at −20 °C for 40 min to form a mixture of alcohols (4*S*,6*S*)-**2** and (4*S*,6*R*)-**2** in a 86 : 14 ratio in 95% overall yield. Treatment of this mixture with iodine in a basic medium induced intramolecular cyclization of the (+)-*cis*-isomer (4*S*,6*S*)-**2** to give compound (4*S*,6*S*)-**7** in a quantitative yield (Scheme 3). After separation of the (+)-*trans*-carveol [(4*S*,6*R*)-**2**], compound (4*S*,6*S*)-**7** was reduced with a zinc–copper pair with a recovery of (+)-*cis*-carveol [(4*S*,6*S*)-**2**] the yield of which was 81%. The product contained 2% of the *trans*-isomer impurity, the formation of which remained obscure. Note that the authors performed a similar process for individual *cis*-carveol [(4*S*,6*S*)-**2**]; a 2% – 3% of the (+)-*trans*-carveol [(4*S*,6*R*)-**2**] impurity always formed.

Scheme 3



Thus, a number of methods for selective preparation of (+)- and (−)-*cis*-carveols from appropriate carvones in good yields have been developed. This makes these alcohols with the *p*-menthadiene carbon skeleton available. Conversely, the preparation of *trans*-carveols is a more complicated and non-trivial task. Below we present a number of interesting approaches in which both more readily accessible *cis*-stereoisomers and other derivatives were used as the starting compounds.

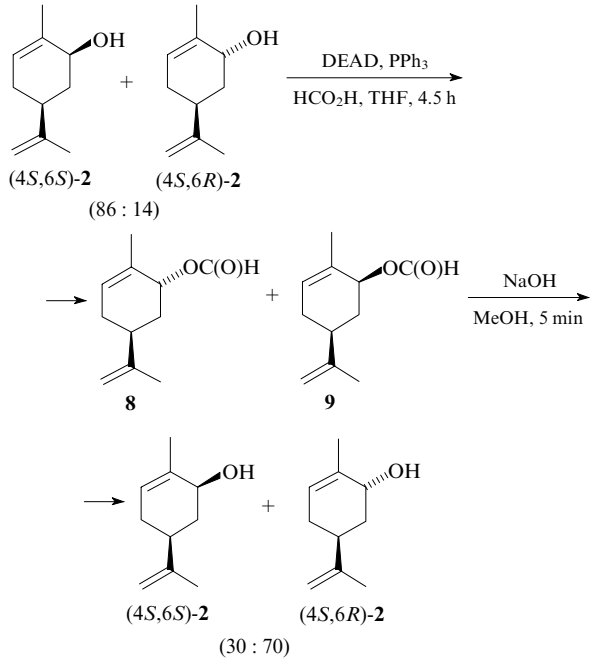
b. *trans*-Isomer

A relatively effective method for the preparation of (+)-*trans*-carveol [(4*S*,6*R*)-**2**] from (+)-*cis*-carveol [(4*S*,6*S*)-**2**] is the Mitsunobu reaction [reaction of the substrate with PPh_3, diethyl azodicarboxylate (DEAD) and carboxylic acid], which provides activation and nucleophilic displacement of the hydroxy group with inversion of the configuration.[32] By saponification of the resulting ester, the stereoisomeric alcohol can be prepared.

Thus, a 86 : 14 mixture of alcohols (4*S*,6*S*)-**2** and (4*S*,6*R*)-**2** resulting from the reduction of carvone [(*S*)-4] reacts with PPh_3, DEAD and formic acid yielding a mixture of formates **8** and **9**, which are saponified to afford a mixture of alcohols (4*S*,6*S*)-**2** and (4*S*,6*R*)-**2**, their ratio now being 30 : 70 and the total yield being 85% (Scheme 4).[32] By using the procedure described above (see Scheme 3), after column chromatography and vacuum distillation, (+)-*trans*-carveol [(4*S*,6*R*)-**2**] is formed in 29% yield (out of the theoretically possible 70% corresponding to the content of this compound in the reaction mixture)

and compound (4*S*,6*S*)-**7** is formed in 30% yield (out of the theoretically possible 30%).

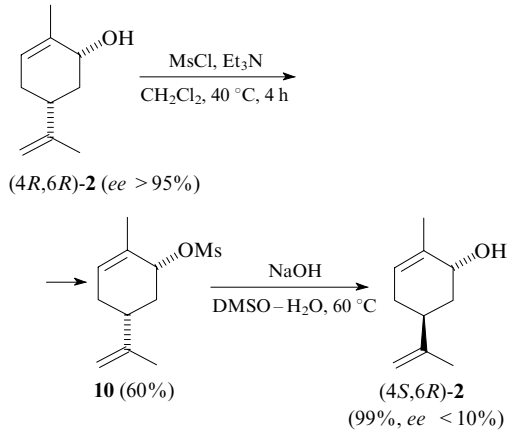
Scheme 4



In other studies using the Mitsunobu reaction to invert the configuration of C(6) in (−)-*cis*-carveol [(4*R*,6*R*)-**2**], benzoic[9] and *p*-nitrobenzoic acids[33] were used instead of formic acid; the yields of (−)-*trans*-carveol (4*R*,6*S*)-**2** were 72% and 60%, respectively.

Yet another approach to transition from (−)-*cis*-carveol [(4*R*,6*R*)-**2**] to the *trans*-diastereomer is to use mesylate **10**. On treatment with a solution of NaOH in aqueous DMSO at 60 °C, mesylate **10** is converted to (+)-*trans*-carveol [(4*S*,6*R*)-**2**] in 99% yield; however, its optical purity is < 10% due to competition of S_N2 and S_N2' nucleophilic substitution reactions (Scheme 5).[34]

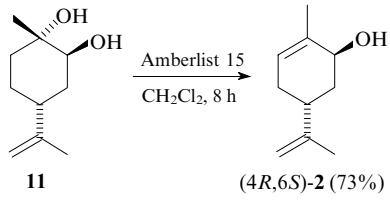
Scheme 5



Diol **11** can also be mentioned as a precursor of (−)-*trans*-carveol [(4*R*,6*S*)-**2**]. Compound **11** is dehydrated in the presence of Amberlist 15 ion exchange resin.[35] The product yield was 73% (Scheme 6).

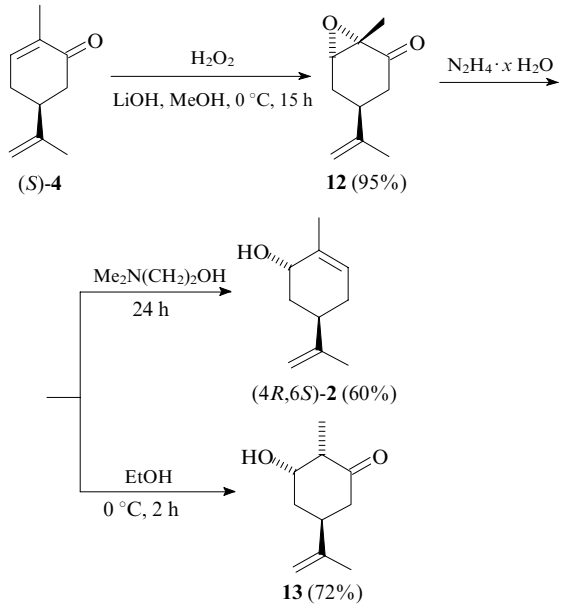
An interesting method for the preparation of *trans*-carveols is the Wharton reaction in which *trans*-carvone

Scheme 6



epoxide **12** serves as the starting compound. This compound is prepared by oxidation of (+)-(*S*)-carvone [(*S*)-**4**] with 30% hydrogen peroxide in the presence of LiOH (Scheme 7). Epoxide **12** reacts with hydrazine hydrate in $Me_2N(CH_2)_2OH$ at room temperature to give (−)-*trans*-carveol [(4*R*,6*S*)-**2**] in 60% yield.[10]

Scheme 7

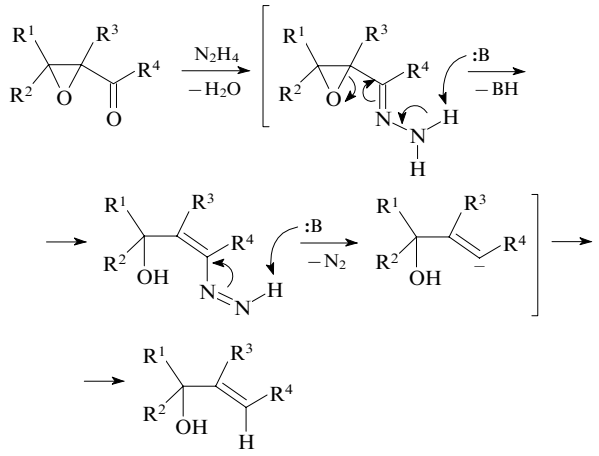


The commonly accepted mechanism of the Wharton reaction is presented in Scheme 8.[36] An important step is evolution of a nitrogen molecule after proton elimination induced by a base (**:B**). The evolution of nitrogen may also be due to homolytic processes; the free radicals thus generated are mainly responsible for the formation of by-products. Therefore, an improved procedure for the Wharton reaction was developed, which implies the addition of a base (Et_3N) and the use of a hydrazine salt instead of hydrazine hydrate. In the presence of Et_3N and $N_2H_4 \cdot HCl$, the yield of (−)-*trans*-carveol [(4*R*,6*S*)-**2**] increased to 71%.[36]

It is noteworthy that the replacement of the basic solvent, dimethylaminoethanol, by EtOH resulted in β-hydroxy ketone **13** being formed in 72% yield instead of (−)-*trans*-carveol [(4*R*,6*S*)-**2**] (see Scheme 7),[37] which demonstrates how important is the thorough selection of the reaction conditions.

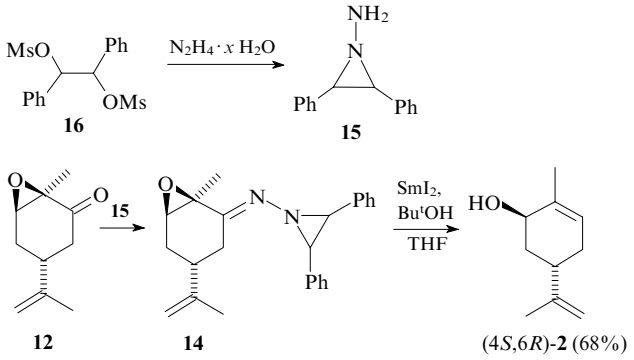
A modification of the Wharton reaction using samarium(II) iodide was reported.[38] First, epoxide **12** was converted to hydrazone **14** by the reaction with aziridine **15**

Scheme 8



that was formed in the reaction of hydrazine hydrate with dimesylate **16** (Scheme 9).[39] Then hydrazone **14** was treated with samarium(II) iodide in THF in the presence of *tert*-butyl alcohol. This gave (+)-*trans*-carveol [(4*S*,6*R*)-**2**] in 68% yield.

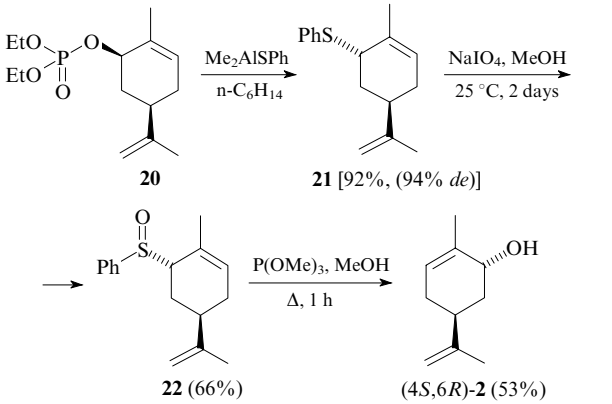
Scheme 9



The *trans*-epoxides of *cis*- and *trans*-carveols [(1*S*,2*R*,4*S*,6*R*)-**17** and (1*S*,2*R*,4*S*,6*S*)-**17**] can be converted to (+)-*trans*-carveol [(4*S*,6*R*)-**2**] by treatment with a Ti^{III} compound, Cp_2TiCl,[40] generated *in situ* upon the reduction of Cp_2TiCl_2 (Cp is cyclopentadienyl) with zinc. The Luche reduction of (−)-carvone epoxide **12** gives (1*S*,2*R*,4*S*,6*R*)-**17** in 91% yield. On treatment with a solution of Cp_2TiCl in THF, the latter is converted to a mixture of (+)-*trans*-carveol [(4*S*,6*R*)-**2**] and diol (2*R*,4*S*,6*R*)-**18** in a 88 : 12 ratio and in 91% total yield. Presumably, the reaction involves the intermediate formation of radical **19**. The epimeric epoxide (1*S*,2*R*,4*S*,6*S*)-**17** is formed in 94% yield upon the reduction of compound **12** with the organoboron reagent $Li[Bu^s_3BH]$ (L-selectride). The reaction of epoxide (1*S*,2*R*,4*S*,6*S*)-**17** with Cp_2TiCl gave a mixture of (+)-*trans*-carveol [(4*S*,6*R*)-**2**] and compound (2*R*,4*S*,6*S*)-**18** in a 94 : 6 ratio and a total yield of 80% (Scheme 10).

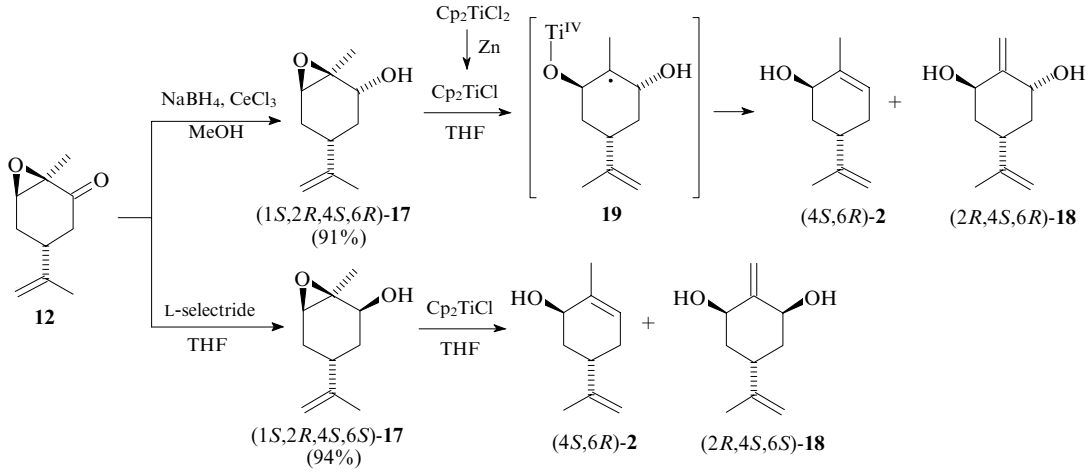
(−)-*cis*-Carveol diethyl phosphate **20** was also used to prepare (+)-*trans*-carveol [(4*S*,6*R*)-**2**].[41] The first stage was the treatment of compound **20** with Me_2AlSPh, resulting in the formation of sulfide **21** in 92% yield, the diastereomeric excess being 94%. Compound **21** was then oxidized with sodium periodate in methanol (Scheme 11). The yield of allyl sulfoxide **22** was 66%. The rearrangement of compound **22** was induced by refluxing in MeOH in the presence of $P(OMe)_3$, and this gave the desired (+)-*trans*-carveol [(4*S*,6*R*)-**2**] in 53% yield.

Scheme 11

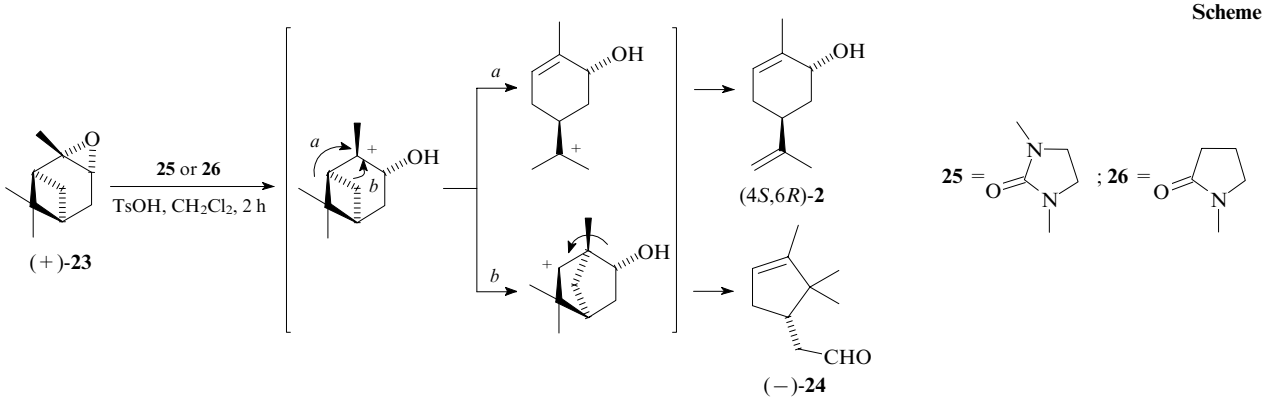


Another large group of synthetic methods for the preparation of *trans*-carveol is based on the use of α-pinene epoxide (**23**) as the starting compound (Scheme 12). Usually, the acid-induced rearrangements of compound **23** give campholenic aldehyde (**24**) as the major product;[42] however, several catalysts have been found for the synthesis of another isomerization product, *trans*-carveol (**2**), in good yields.

Scheme 10



Scheme 12



For instance, isomerization of (+)-α-pinene epoxide [(+)-**23**] in CH_2Cl_2 in the presence of the catalyst obtained by reaction of 1,3-dimethylimidazolidin-2-one (**25**) with *p*-toluenesulfonic acid (TsOH) gives, as the major products, (+)-*trans*-carveol [(4*S*,6*R*)-**2**] and (−)-campholenic aldehyde [(−)-**24**], which were isolated in 45% and 35% yields, respectively.[43] The replacement of compound **25** by *N*-methyl-2-pyrrolidone (**26**) for isomerization of (−)-α-pinene [(−)-**23**] resulted in the formation of the other enantiomer of carveol **2** and changed the product ratio towards aldehyde **24** (35%); the isolated yield of (−)-*trans*-carveol (4*R*,6*S*)-**2** was 17%.[44]

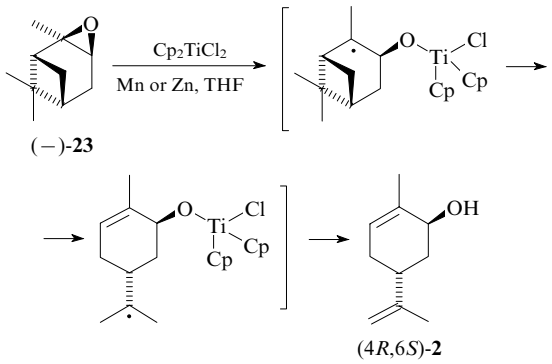
Yet another approach is the use of trimethylsilyl triflate (Me_3SiOTf) as the Lewis acid and 2,6-lutidine (2,6-Lu) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base. In this case, the yield of (+)-*trans*-carveol [(4*S*,6*R*)-**2**] with respect to the starting (+)-α-pinene epoxide [(+)-**23**] is up to 72%.[45]

When isomerization of (−)-α-pinene epoxide [(−)-**23**] is carried out at 140 °C in dimethylacetamide (DMA) in the presence of a number of catalysts ($SnCl_2$, Sn/SiO_2, Ce/SiO_2), the selectivity to (−)-*trans*-carveol [(4*R*,6*S*)-**2**] may be as high as 73%.[46] A substantial drawback of this procedure is the difficulty associated with the removal of a large excess of the high-boiling DMA solvent.

Apart from the cationoid rearrangements of the pinene skeleton to the *p*-menthane skeleton, the radical version of this process was described.[47] Treatment of (−)-α-pinene epoxide [(−)-**23**] with 0.2 equiv. of Cp_2TiCl_2 in the presence of manganese dust in THF affords (−)-*trans*-carveol [(4*R*,6*S*)-**2**] in 64% yield. The role of manganese is to reduce Cp_2TiCl_2 to Cp_2TiCl, which is then coordinated to the oxygen atom of the epoxide ring, and the ring is opened to give a tertiary radical (Scheme 13). This radical then rearranges with opening of the four-membered ring and, finally, gives off a hydrogen atom to Cp_2TiCl, being converted to the target product. It was shown[48] that when isomerization of (−)-α-pinene epoxide [(−)-**23**] is conducted in the presence of 2 equiv. of Cp_2TiCl and zinc is used as the reducing agent, the yield of (−)-*trans*-carveol [(4*R*,6*S*)-**2**] increases to 89%.

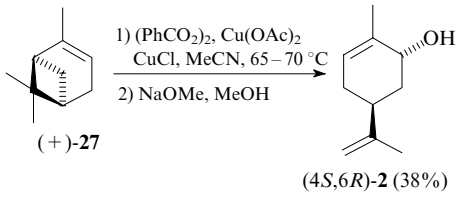
The isomerization of epoxide (−)-**23** in complex supercritical solvents containing lower alcohols (ethanol, isopropyl alcohol), CO_2 and water in a flow type reactor affords carveol **2** with a selectivity of up to 23%, although the major reaction product (content of up to 59%) is campholenic aldehyde **24**.[49]

Scheme 13



The synthesis of *trans*-carveols directly from α-pinene (**27**) is also possible. For example, the reaction of (+)-α-pinene [(+)-**27**] with benzoyl peroxide on heating in acetonitrile for 24 h in the presence of a catalytic amount of $Cu(OAc)_2$ and CuCl followed by saponification of the intermediate (+)-*trans*-carveol benzoate furnished (4*S*,6*R*)-**2** in an overall yield of 38% (Scheme 14).[50]

Scheme 14

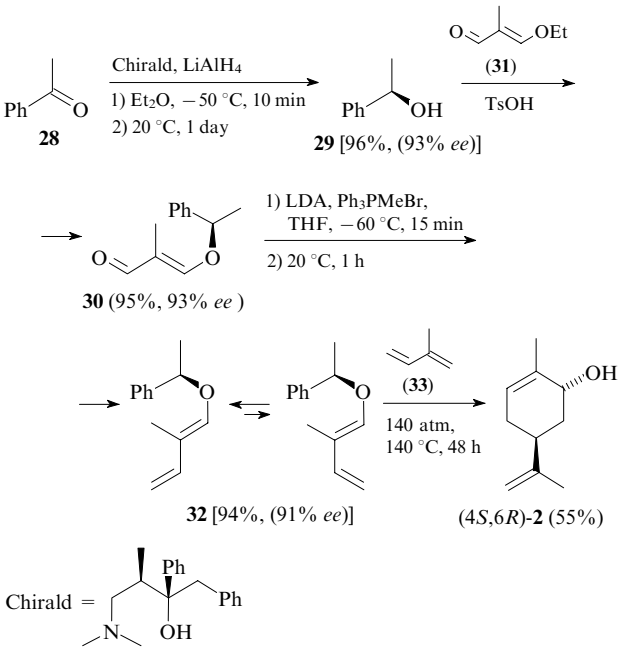


There are several other methods for the synthesis of carveols (**2**), for example, various sorts of oxidation of limonene (**1**) with oxygen and selenium dioxide, resulting in complex mixtures of products (the content of compound **2** in the mixtures did not exceed 22%),[51–56] and biochemical oxidation of (+)-(*R*)-limonene [(*R*)-**1**] to (+)-*trans*-carveol [(4*S*,6*R*)-**2**] by the cells of *Rhodococcus opacus* PWD4 (2.5 h, 94%–97% yield)[57] or *Cellulosimicrobium cellulans* EB-8-4 (12 h, 69% yield).[58]

To conclude the section, we will cite the example of (+)-*trans*-carveol [(4*S*,6*R*)-**2**] synthesis based on the Diels–Alder reaction.[59] Acetophenone (**28**) was reduced by $LiAlH_4$ in the presence of (2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenylbutan-2-ol (Chirald reagent) to give alcohol **29** in 96% yield and with enantiomeric excess of 93% (Scheme 15). Then alcohol **29** was converted to com-

pound **30** upon the reaction with 3-ethoxy-2-methylacrolein (**31**) in the presence of *p*-toluenesulfonic acid, and this was followed by the Wittig reaction. Chiral diene **32** was thus formed in 94% yield, *ee* being 91%. The Diels–Alder reaction of diene **32** with isoprene **33** proceeded under drastic conditions: a pressure of 140 atm and a temperature of 140 °C. This was also accompanied by elimination of the phenylethyl group as styrene to give the desired (+)-*trans*-carveol [(4*S*,6*R*)-**2**] in 55% yield.

Scheme 15

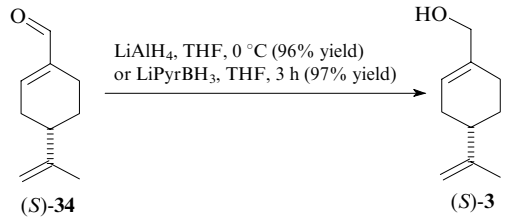


2. Perillyl alcohol

Perillyl alcohol (**3**) has been isolated from various natural sources. For example, its content in the essential oils of the flowers and leaves of *Cymbopogon densiflorus* Stapf.[60] and *Cymbopogon caesius* (Nees) Stapf.[61] may reach 27%.

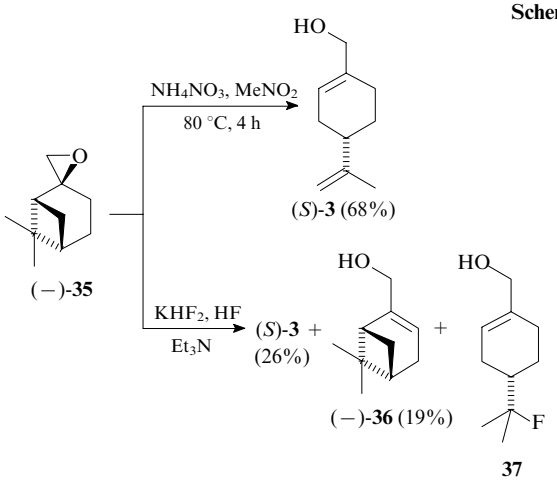
Compound (*S*)-**3** was prepared by reduction of (−)-perillaldehyde [(*S*)-**34**] with $LiAlH_4$ (see Ref. 62) or lithium pyrrolidinoborohydride[28] in 96% or 97% yield (Scheme 16). However, it should be noted that compound (*S*)-**34** is less accessible than alcohol (*S*)-**3**.

Scheme 16



A number of procedures for the synthesis of alcohol **3** from compounds with the pinane carbon skeleton were proposed. For example, rearrangement of (−)-β-pinene epoxide [(−)-**35**] in the presence of ammonium nitrate on heating in nitromethane affords (−)-(*S*)-perillyl alcohol [(*S*)-**3**], which was isolated in 68% yield (Scheme 17).[63] Likewise, the rearrangement of much less accessible enantiomeric epoxide (+)-**35** under the same conditions produces (+)-(*R*)-perillyl alcohol [(*R*)-**3**].[63]

Scheme 17

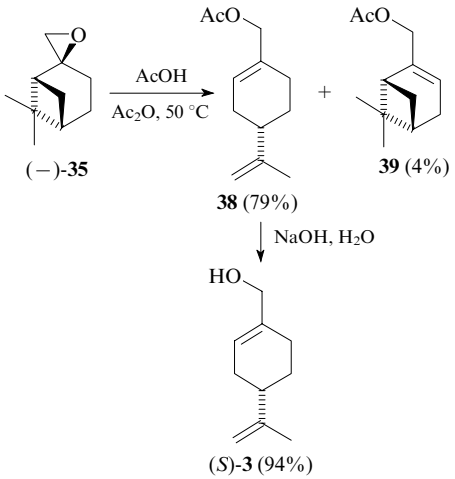


Yet another sort of such transformation is isomerization of epoxide (−)-**35** in a system containing potassium hydrogen fluoride, hydrofluoric acid and triethylamine. In this case, the reaction products are (−)-(*S*)-perillyl alcohol [(*S*)-**3**] formed in 26% yield, (−)-myrtenol [(−)-**36**] and a fluoro derivative with the *p*-menthane carbon skeleton **37**.[64]

Finally, the highest yields were attained using Cp_2TiCl formed *in situ* upon the reduction of Cp_2TiCl_2 with manganese dust[47] or granular zinc.[48] The isomerization of (−)-β-pinene epoxide [(−)-**35**] induced by this reagent in THF gives rise to (−)-(*S*)-perillyl alcohol [(*S*)-**3**] in 76%–80% yields.

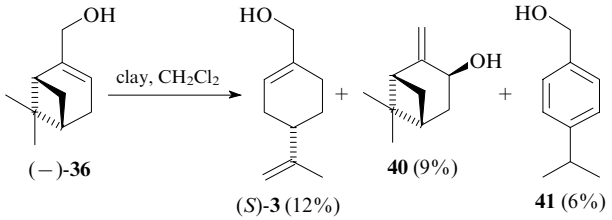
A two-stage transformation of (−)-β-pinene epoxide [(−)-**35**] into (−)-(*S*)-perillyl alcohol [(*S*)-**3**] comprises isomerization of monoterpenoid (−)-**35** in the presence of 1 equiv. of AcOH in Ac_2O, resulting in acetates **38** and **39** (the yields are 79% and 4%, respectively). The conversion of the starting epoxide **35** is 94%, while the yield of acetate **38** after distillation is 67%. Saponification of compound **38** by aqueous NaOH to give the target product (*S*)-**3** occurs in 94% yield (Scheme 18).[65]

Scheme 18



The isomerization of (−)-myrtenol [(−)-**36**] in the presence of acidic montmorillonite clay gave (−)-(*S*)-perillyl alcohol [(*S*)-**3**], the isolated yield being 12%. Other reaction products were (+)-*trans*-pinocarveol (**40**) and 1-hydroxymethyl-4-isopropylbenzene (**41**) (Scheme 19).[66]

Scheme 19

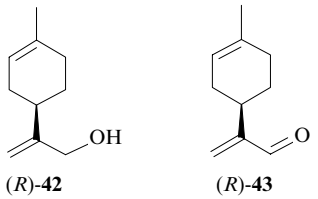


In conclusion, it should be mentioned that some microbial processes are suitable for selective oxidation of limonene (**1**) to (*S*)-perillyl alcohol [(*S*)-**3**] (for example, in the presence of *Mycobacterium* sp. HXN-1500)[67] or to (*R*)-perillyl alcohol [(*R*)-**3**] (for example, *Bacillus stearothermophilus* BR388).[68] Yet another biochemical approach suitable to achieve a 97% selectivity to (*R*)-perillyl alcohol is the use of the CYP102A1 mutant of cytochrome from *Bacillus megaterius* (A328VL/437F/A264V) for the oxidation of (*R*)-limonene [(*R*)-**1**].[69]

3. *p*-Mentha-1,8-dien-10-ol

(*R*)-*p*-Mentha-1,8-dien-10-ol [(*R*)-**42**] is present in plants, for example, in *Dracocephalum kotschyi*,[70] most often, as a minor component. Meanwhile, compound (*R*)-**42** can be obtained by the lithium aluminium hydride reduction of aldehyde (*R*)-**43**, which is the major component of the essential oil of the above-ground part of the plant *Dracocephalum foetidum* Bge. of the *Labiatae* family (the content is 67%).[71]

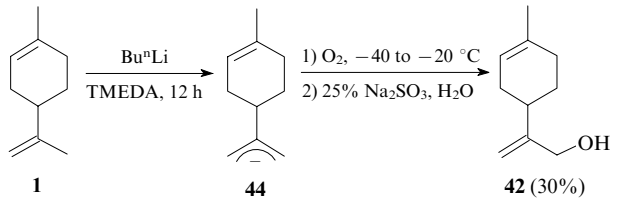
Structures 42, 43



An important circumstance, which allowed for the development of the key preparative routes to compound **42**, was the fact that formation of the allyl carbanion from limonene (**1**), unlike transformations that follow radical or cationoid pathways, occurs selectively for steric reasons with proton abstraction from the methyl group at C(10). Carbanion **44** resulting from the action of the Bu^nLi–*N*,*N*,*N*′*N*′-tetramethylethylenediamine (TMEDA) system can be further converted to alcohol **42**, for example, by the oxidation by atmospheric oxygen, the intermediate peroxide being then reduced by sodium sulfite.[72] Using this procedure, racemic limonene (**1**) was converted to racemic compound **42** in 30% yield (Scheme 20). A similar method was used more recently to synthesize optically active alcohols (*R*)-**42** (32% yield) and (*S*)-**42** (28% yield) from the corresponding limonenes (*R*)-**1** and (*S*)-**1**.[73,74]

A more efficient procedure is based on the synthesis and subsequent oxidation of organoboron compounds. In this case, limonene (**1**) (the stereochemistry is not indicated in the publication) was first stirred with 1.1 equiv. of TMEDA and 1 equiv. of Bu^nLi for 60 h, then cooled down to −78 °C and treated with 1.4 equiv. of trimethyl borate for 1.5 h. Finally, the temperature of the reaction mixture was raised to −30 °C and the resulting organoboron compounds were oxidized with 30% H_2O_2 for 2 h. This gave compound **42** in 94% yield with respect to the converted limonene (**1**), the degree of conversion being 68%.[6]

Scheme 20



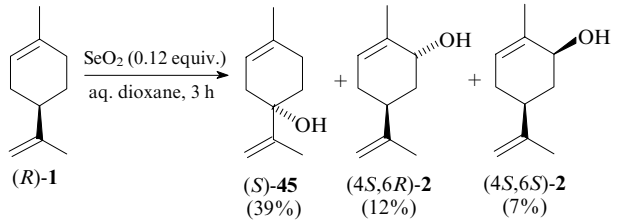
A detailed study of the process demonstrated that, along with compound **42**, perillyl alcohol (**3**) is also formed. Indeed, the reaction of (*R*)-limonene [(*R*)-**1**] with 0.67 equiv. of Bu^nLi, 0.73 equiv. of TMEDA and 0.73 equiv. of trimethyl borate under conditions similar to those described above and subsequent hydrogen peroxide oxidation gave a mixture of (*R*)-**42** and (*R*)-**3** in a 9 : 1 ratio and 64% yield with respect to the converted (*R*)-limonene. The degree of conversion of the starting compound (*R*)-**1** was 57%. The reaction with (*S*)-limonene [(*S*)-**1**] proceeded in a similar way.[75]

4. *p*-Mentha-1,8-dien-4-ol

p-Mentha-1,8-dien-4-ol (**45**) occurs in small quantities in some plants, for example, in the essential oil of the fruits of Japanese pepper *Zanthoxylum piperitum* DC.[76]

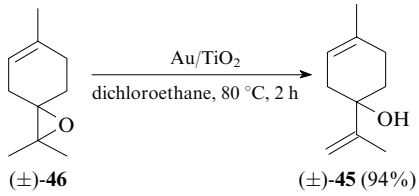
The enantiomers of **45** can be synthesized by oxidation of the corresponding limonenes (**1**) with selenium dioxide in aqueous dioxane.[56] Dropwise addition of a solution of 0.12 equiv. of SeO_2 in a dioxane–water mixture (5 : 1) to a solution of (+)-limonene [(*R*)-**1**] in dioxane at room temperature gives, after 3 h, a mixture of products containing (GLC data) (+)-*p*-mentha-1,8-dien-4-ol [(*S*)-**45**], 39%; (+)-*trans*-carveol [(4*S*,6*R*)-**2**], 12%; and (+)-*cis*-carveol [(4*S*,6*S*)-**2**], 7%. The degree of conversion of (+)-limonene [(*R*)-**1**] was 15% (Scheme 21).[55]

Scheme 21



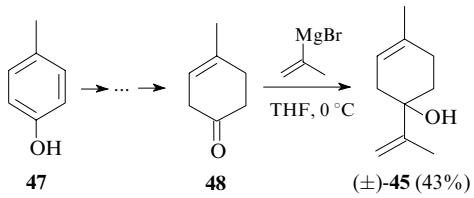
One more method provides the high-yield synthesis of alcohol (±)-**45** from racemic terpinolene epoxide (**46**). Isomerization of epoxide (±)-**46** catalyzed by 1.5% Au/TiO_2 at 80 °C in dichloroethane for 2 h affords (±)-*p*-mentha-1,8-dien-4-ol [(±)-**45**] in 94% yield (Scheme 22).[77] The use of this approach to prepare enantiomers of **45** is hampered by much lower accessibility of the required epoxides (+)-**46** and (−)-**46**.[78]

Scheme 22



As a conclusion of the section, consider an example of the preparation of compound (±)-**45** by means of a Grignard reagent (Scheme 23). First, *p*-cresol (**47**) is converted to ketone **48**, which then reacts with isopropenylmagnesium bromide in THF at 0 °C to give alcohol **45** in a moderate yield.[79]

Scheme 23



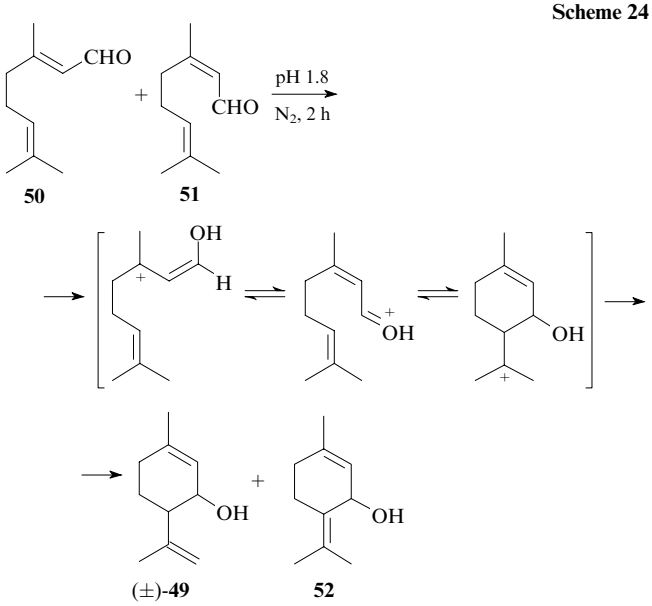
5. Isopiperitenol

Isopiperitenol [(±)-**49**] is formed in small quantities upon acid-catalyzed cyclization of citral — a mixture of *cis*- and *trans*-isomers of terpene aldehydes [geranial (**50**) and neral (**51**)] in comparable proportions (Scheme 24).[80]

The highest content of compound (±)-**49** equal to 10% was obtained by keeping citral at pH 1.8 for 2 h under a nitrogen atmosphere; the resulting fraction of piperitenol **52** was 20%, while the recovered starting aldehydes **50** and **51** accounted for 42% and 8%, respectively. Thus, the calculated yield of alcohol (±)-**49** was 20% for a 50% degree of conversion of citral.[80]

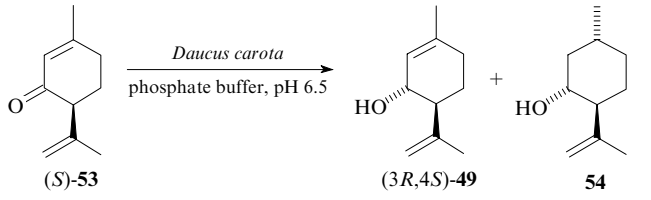
A more efficient approach is reduction of isopiperitenone **53**, which can in turn be prepared by oxidation and cyclization of geraniol under the action of the oxoammonium resin.[81] The reduction of (*S*)-isopiperitenone [(*S*)-**53**] to (−)-*trans*-isopiperitenol [(3*R*,4*S*)-**49**] is accomplished using the homogenate of the *Daucus carota* roots.

Scheme 24



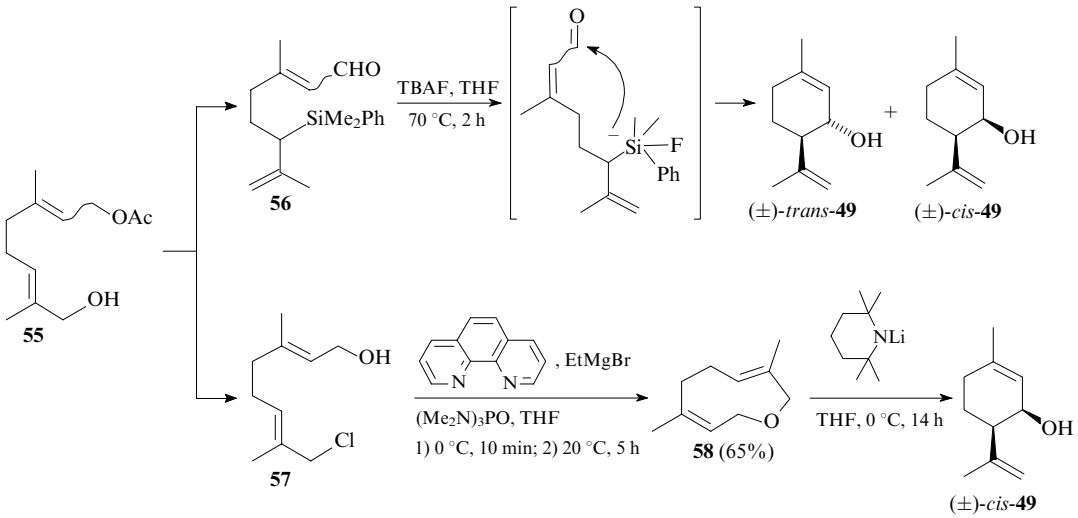
Note that the reduction does not stop after the formation of compound (3*R*,4*S*)-**49** and proceeds further to alcohol **54**; therefore, it is necessary to adjust the reaction time as to ensure the highest content of the desired product (3*R*,4*S*)-**49** (Scheme 25).[82]

Scheme 25



The anionic type of cyclization was implemented in the synthesis of isopiperitenol (**49**) from terpenoid **55** (Scheme 26). First, aldehyde **56** was obtained *via* a multistage synthesis and then it was made to cyclize by the action of tetra-n-butylammonium fluoride (TBAF) in THF at 70 °C during 2 h. This gave a mixture of racemic *trans*- and *cis*-isopiperitenols **49** in a 9 : 1 ratio and in a total yield of 46%.[83]

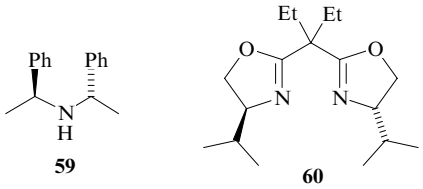
Scheme 26



Yet another approach to the preparation of isopiperitenol (**49**) from terpenoid **55** comprises the synthesis of compound **57**, its cyclization induced by lithium 2,2,6,6-tetramethylpiperidide (LiTMP) to give ether **58** and the subsequent [2,3]-Wittig rearrangement leading to racemic (±)-*cis*-isopiperitenol [(±)-*cis*-**49**] (Scheme 26).[84] When the Bu^nLi–chiral bis[(*S*)-1-phenylethyl)amine (**59**) system in THF is used instead of LiTMP, the reaction at 25 °C gives within 36 h (3*R*,4*R*)-isopiperitenol [(3*R*,4*R*)-**49**] in 58% yield with respect to the converted compound **58** (the degree of conversion is 90%), the enantiomeric excess being 25%.[84]

In a similar way, the use of the Bu^tLi–bis(oxazoline) **60** system for the rearrangement in hexane at −78 °C results in the formation of alcohol (3*R*,4*R*)-**49** in a 20% yield with a diastereomer ratio (*dr*) of >98% and 94% *ee* for 78% degree of conversion of compound **58**.[85]

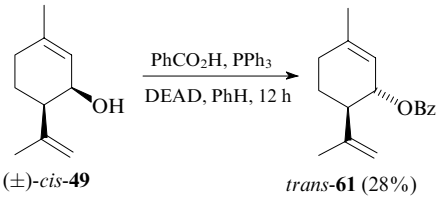
Structures 59, 60



59 **60**

The possibility of conversion of (±)-*cis*-isopiperitenol [(±)-*cis*-**49**] to the (±)-*trans*-isomer by means of the Mitsunobu reaction was demonstrated.[84] The yield of the corresponding *trans*-benzoate **61** was 28% (Scheme 27).

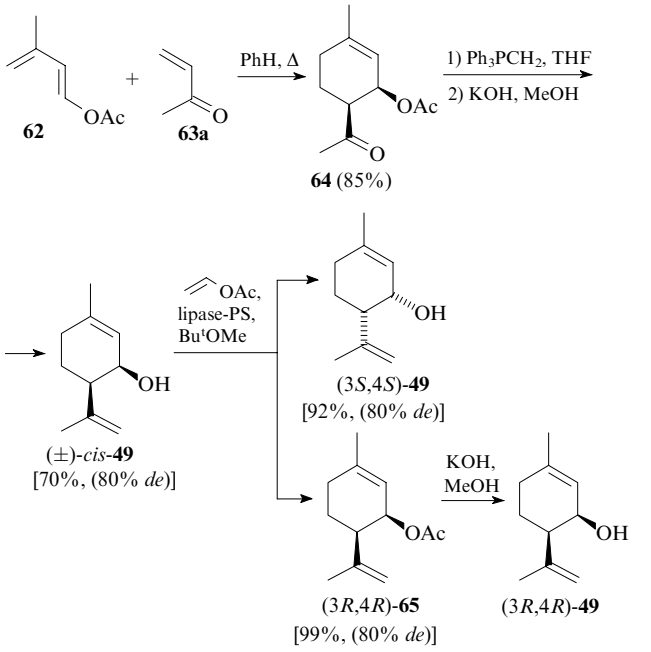
Scheme 27



(±)-*cis*-**49** *trans*-**61** (28%)

The use of the Diels–Alder reaction and the biochemical separation methods for the preparation of individual enantiomers of alcohol *cis*-**49** have been reported.[86] The Diels–Alder adduct formed from diene **62** and methyl vinyl ketone **63a** — ketoacetate **64** — was converted to alcohol (±)-*cis*-**49** (80% *de*) by a sequence of the Wittig reaction and saponification. Selective acylation of *cis*-isopiperitenol [(±)-*cis*-**49**] with vinyl acetate in the presence of lipase-PS results in the formation of acetate (3*R*,4*R*)-**65** (80% *de*, 99% *ee*) and (3*S*,4*S*)-isopiperitenol [(3*S*,4*S*)-**49**] (80% *de*, 92% *ee*). Finally, saponification of acetate (3*R*,4*R*)-**65** yields stereoisomer (3*R*,4*R*)-**49** (Scheme 28).

Scheme 28



62 **63a** **64** (85%)

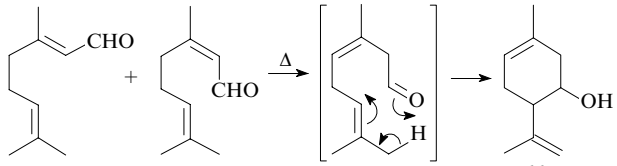
(±)-*cis*-**49** [70%, (80% *de*)] (3*S*,4*S*)-**49** [92%, (80% *de*)] (3*R*,4*R*)-**65** [99%, (80% *de*)] (3*R*,4*R*)-**49**

6. *p*-Mentha-1,8-dien-5-ol

p-Mentha-1,8-dien-5-ol (**66**) is present in the essential oil of lemongrass *Cymbopogon flexuosus*, from which it was isolated in a yield of 21%.[87]

A mixture of stereoisomers **66** is formed upon thermal cyclization of citral [a mixture of geranial (**50**) and neral (**51**)]. The content of alcohols **66** in the reaction mixture is determined by the temperature. At 205 °C, only the reaction products are present in the mixture (Scheme 29).[88]

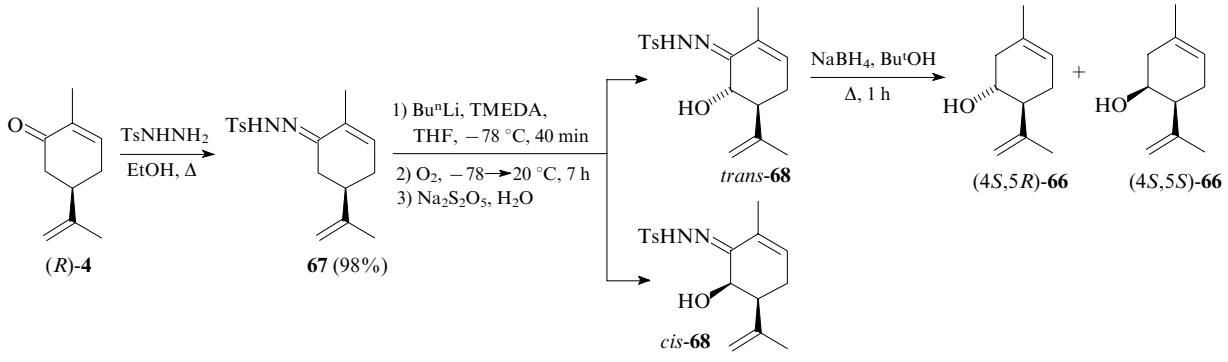
Scheme 29



50 **51** **66**

Individual stereoisomers of alcohols **66** can be synthesized from carvone (**4**). (−)-(*R*)-Carvone [(*R*)-**4**] reacts with *p*-toluenesulfonic acid hydrazide on refluxing in ethanol being converted to hydrazone **67** in a yield of 98% (Scheme 30). α-Hydroxylation of compound **67** was performed by a sequence of reactions with Bu^nLi in the presence of TMEDA in THF, oxygen and a saturated solution of $Na_2S_2O_5$. As a result, a 3 : 1 mixture of *trans*-

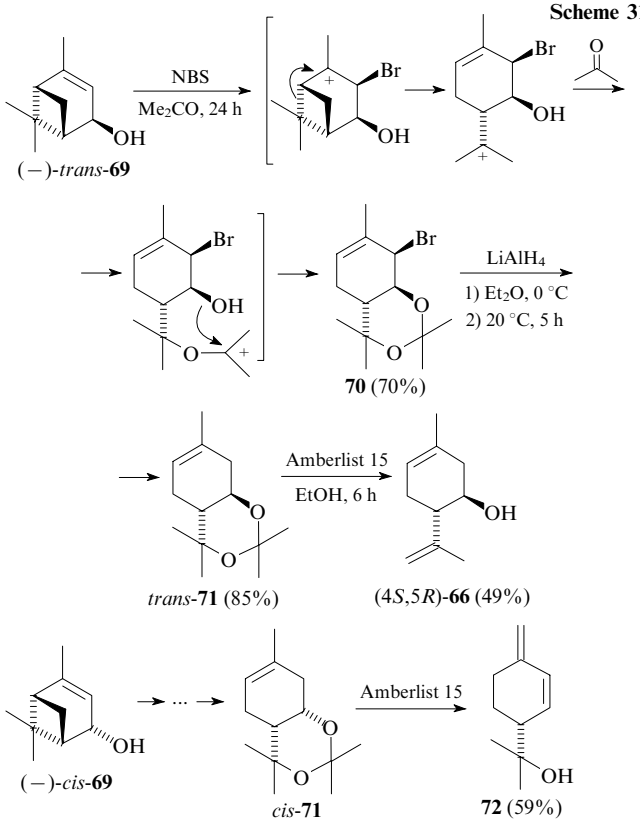
Scheme 30



(*R*)-**4** **67** (98%) *trans*-**68** *cis*-**68** (4*S*,5*R*)-**66** (4*S*,5*S*)-**66**

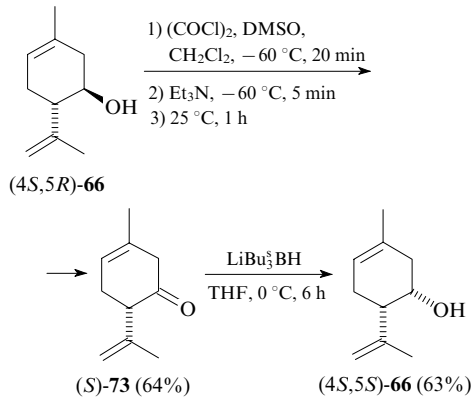
and *cis*-hydroxytosylhydrazones **68** is formed in an overall yield of 85%; from the mixture, individual stereoisomers were isolated in 57% and 19% yields, respectively. Finally, the $NaBH_4$ reduction of *trans*-hydroxytosylhydrazone of *trans*-**68** gave a mixture of desired alcohols (4*S*,5*R*)-**66** and (4*S*,5*S*)-**66** (the total yield was 83%, the diastereomer ratio was not presented in the publication).[89]

Scheme 31



Yet another method for the synthesis of individual stereoisomers of alcohol **66** employs (−)-*trans*-verbenol [(−)-*trans*-**69**] as the starting compound (Scheme 31).[90] The bromination of compound (−)-**69** with *N*-bromosuccinimide (NBS) in acetone was accompanied by cleavage of the pinane skeleton and furnished acetonide **70**, which was reduced by $LiAlH_4$ to give compound **71** in a yield of 85%. The deprotection of compound **71** on treatment with the resin Amberlist 15 produced alcohol (4*S*,5*R*)-**66** in a yield of 49%.

Scheme 32

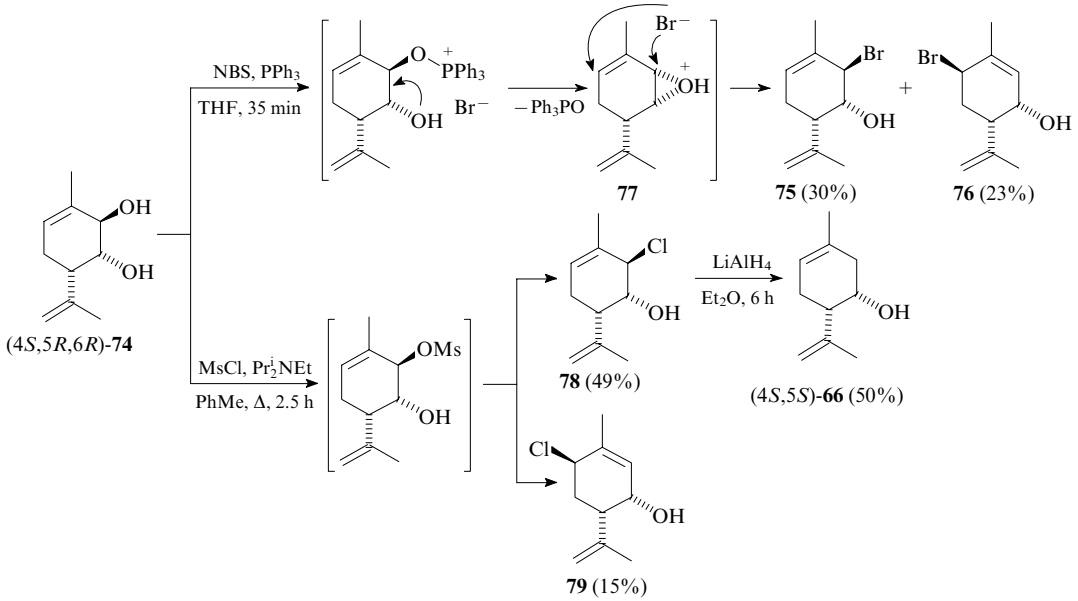


Similarly, (−)-*cis*-verbenol [(−)-*cis*-**69**] was converted to acetonide *cis*-**71**. However, the attempt to prepare the expected alcohol (4*S*,5*S*)-**66** from this compound by Amberlist 15 failed; instead, diene **72** was formed in a yield of 59% (see Scheme 31).[90]

Hydroxy derivative (4*S*,5*S*)-**66** was obtained from epimer (4*S*,5*R*)-**66** by Swern oxidation giving ketone (*S*)-**73** followed by reduction with lithium tri-*sec*-butylhydroborate (Scheme 32).[90]

Yet another approach to the preparation of alcohol (4*S*,5*R*)-**66** implies the use of diol (4*S*,5*R*,6*R*)-**74** as the starting compound. This is a fairly readily accessible compound (the methods for its preparation are discussed below in Section III.2). Diol (4*S*,5*R*,6*R*)-**74** reacts with *N*-bromosuccinimide and PPh_3 giving regioisomeric bromohydrins **75** and **76**, the yields of which after chromatographic separation were 30% and 23%, respectively (Scheme 33).[44] Probably, the reaction involves the formation of intermediate **77**, which is responsible for retention of the configurations of stereocentres in bromohydrins. However, compounds **75** and **76** can be interconverted, in particular,

Scheme 33

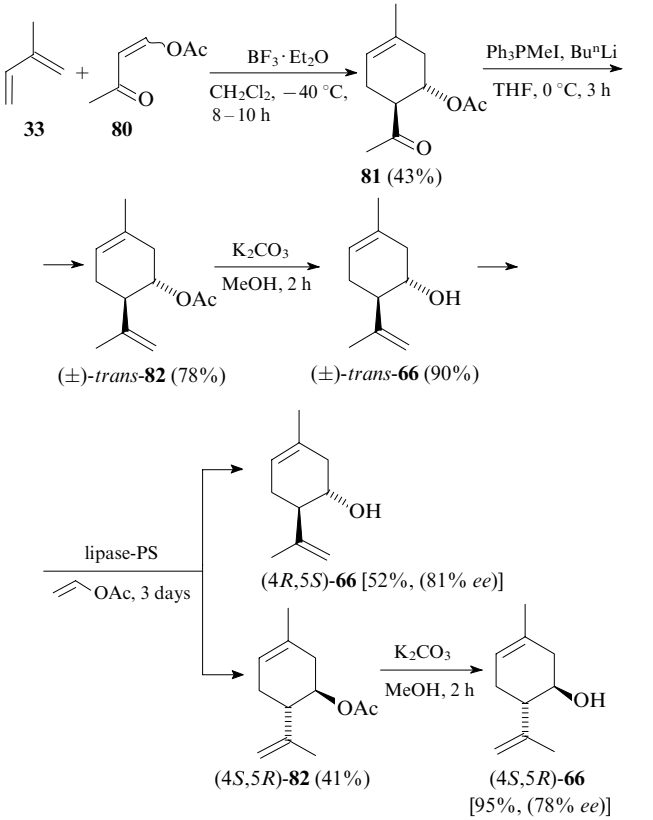


during the reduction, thus giving a mixture of isomeric alcohols, which makes this route little efficient.

This problem was solved by replacing bromohydrin **75** with the chlorine-containing analogue **78** (see Scheme 33). On refluxing of diol (4*S*,5*R*,6*R*)-**74** with MsCl in toluene in the presence of Pr^i_2NEt, both the formation of mesylate and replacement of the MsO group by the chlorine atom take place. As a result, a mixture of compounds **78** and **79** was obtained in yields of 49% and 15%, respectively. The reduction of chlorohydrin **78** with lithium aluminium hydride gave product (4*S*,5*S*)-**66** in a yield of 50%.[44]

In conclusion, we will present the procedure for the synthesis of racemic alcohol (±)-*trans*-**66**. First, the Diels–Alder reaction catalyzed by boron trifluoride etherate was carried out between isoprene **33** and compound **80** (Scheme 34).[91] The resulting *trans*-ketoacetate **81** formed in a yield of 43% was subjected to the Wittig reaction to give acetate (±)-*trans*-**82** (78% yield), which was saponified to give alcohol (±)-*trans*-**66**. The enantiomers of *trans*-**66** were separated by enzyme- (lipase-PS-) catalyzed selective acylation with vinyl acetate in *tert*-butyl methyl ether. The unreacted alcohol (4*R*,5*S*)-**66** was isolated in a yield of 52% with enantiomeric excess of 81% and acetate (4*S*,5*R*)-**82** was obtained in a yield of 41%; the latter was saponified to give alcohol (4*S*,5*R*)-**66** in 95% yield with enantiomeric excess of 78%.

Scheme 34

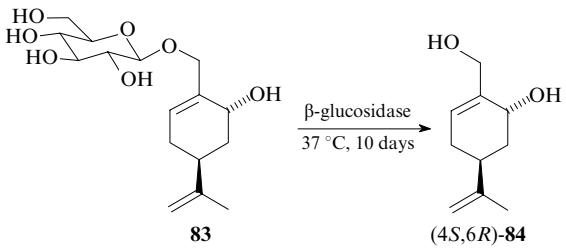


III. Synthesis of dihydroxy derivatives of limonene

1. *p*-Mentha-1,8-diene-6,7-diol

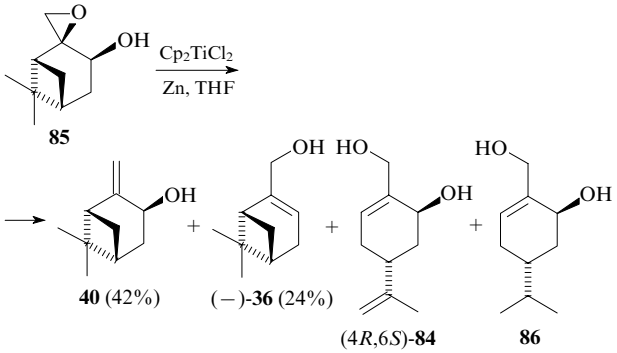
Before considering the synthetic routes to diols having the *p*-mentha-1,8-diene carbon skeleton available from the literature, we would like to note that the detection and isolation of compounds of this type in plant sources are very complicated. For example, column chromatography and HPLC treatment of 2 kg of a methanol extract of caraway (*Carum carvi* LINN fruits, *Umbelliferae*) gave only 8 mg β-glucoside **83** as one of the components.[92] Enzymatic hydrolysis of 6 mg of compound **83** afforded 3 mg of (4*S*,6*R*)-*p*-mentha-1,8-diene-6,7-diol [(4*S*,6*R*)-**84**] (Scheme 35).

Scheme 35



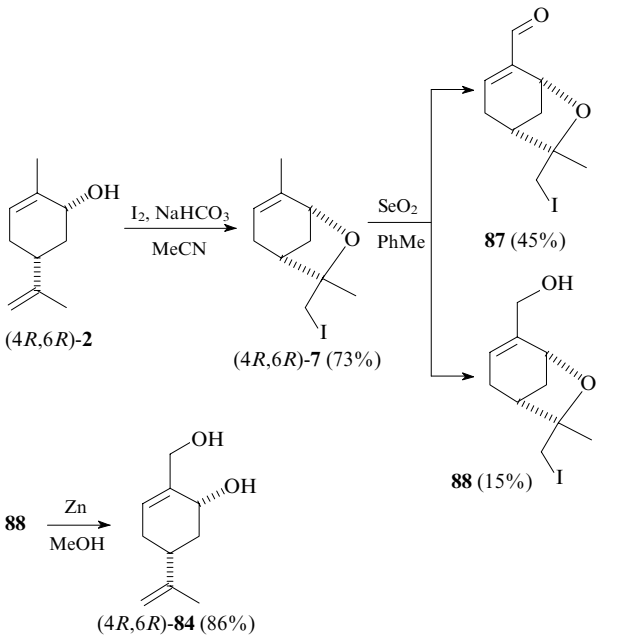
Dihydroxy derivative **84** is one of the minor products of isomerization of *trans*-pinocarveol epoxide (**85**) in the presence of Cp_2TiCl. Compound **84** was isolated as a difficult-to-separate mixture with diol **86** in a 1 : 4 ratio and in 18% total yield (Scheme 36).[48]

Scheme 36



(−)-*cis*-Carveol [(4*R*,6*R*)-**2**] was used as the starting compound to prepare (4*R*,6*R*)-*p*-mentha-1,8-diene-6,7-diol [(4*R*,6*R*)-**84**).[93] First, compound **2** was made to react with I_2 in the presence of $NaHCO_3$ to give bicyclic product

Scheme 37

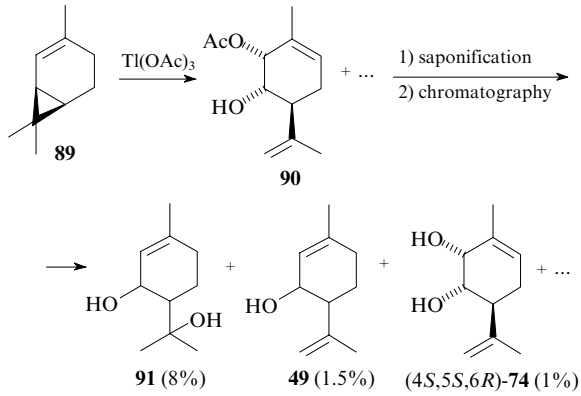


(4*R*,6*R*)-**7** (Scheme 37). The latter was oxidized by treatment with SeO_2 to give bicyclic compounds **87** and **88** in 45% and 15% yields, respectively. The reduction of bicyclic compound **88** with activated zinc led to the target diol (4*R*,6*R*)-**84** in high yield.[94]

2. *p*-Mentha-1,8-diene-5,6-diol

Compound **74** is the best studied diol with the *p*-mentha-1,8-diene carbon skeleton, which is largely obliged to its anti-Parkinsonian, anticonvulsant and analgesic activities.[5,8,95] Diol **74** was first obtained by the reaction of 2-carene (**89**) with thallium acetate followed by saponification of monacetate **90** in a yield as low as 1% (Scheme 38).[96] Note that the yield of the major product **91** in this process did not exceed 8%. Isopiperitenol **49** was also isolated in this process as an isomer mixture.

Scheme 38



An efficient method for the stereospecific synthesis of the (4*S*,5*R*,6*R*)-stereoisomer of diol **74** is isomerization of (−)-*cis*-verbenol epoxide [(−)-*cis*-**92**] in the presence of acidic montmorillonite clay. In this case, the mutual arrangement of all three substituents in the cyclohexene moiety of product **74**, which was formed in 44% – 47% yield, was unambiguously pre-determined by the stereochemistry of the starting epoxide (−)-*cis*-**92** (Scheme 39).[66,97] Hydroxy ketone (*S*)-**93** was the major by-product of this reaction (5% – 16% yield). Subsequently it was demonstrated that the use of Co^{2+}-containing montmorillonite clay to catalyze this transformation may substantially (up to 1.5-fold) increase the content of the target compound (4*S*,5*R*,6*R*)-**74** in the reaction mixture as compared with that attained for acidic clay.[98] The isomerization of epoxide (−)-*cis*-**92** in the presence of Cp_2TiCl afforded a difficult-to-separate mixture of diol (4*S*,5*R*,6*R*)-**74** and its dihydro derivative **94** in a 2 : 3 ratio and in a total yield of 78%.[48]

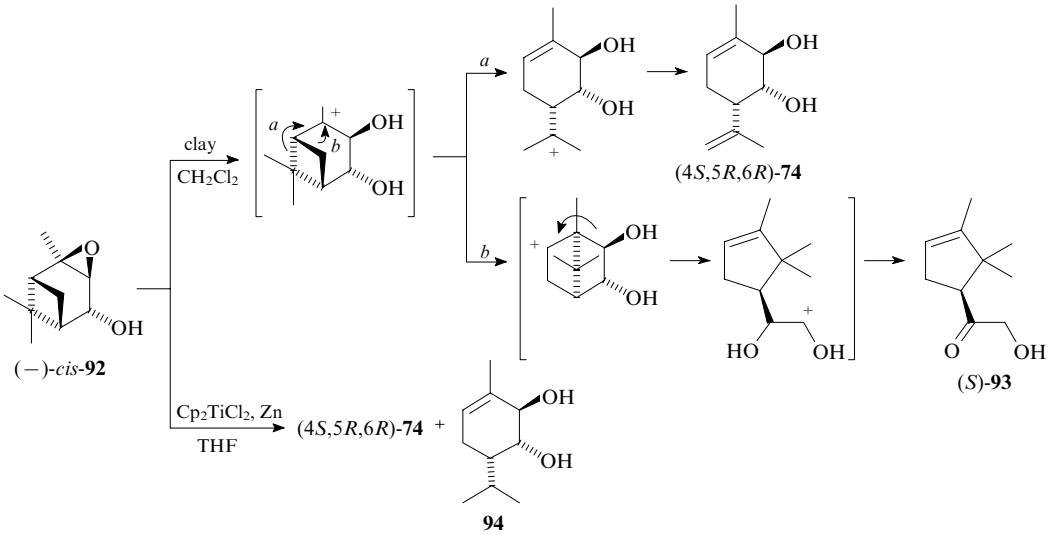
Non-catalyzed isomerization of (−)-*cis*-verbenol epoxide [(−)-*cis*-**92**] was implemented using a flow type reactor and a mixed supercritical solvent containing isopropyl alcohol and CO_2.[99] The conversion of epoxide **92** proved to be quantitative even at 140 °C and a contact time of only 2 min; the content of compound (4*S*,5*R*,6*R*)-**74** in the reaction mixture was up to 30%, and compound **93** was the major reaction product formed in a yield of up to 49%.

The synthesis of all of the eight possible stereoisomers of compound **74** has been reported.[5] The enantiomer pairs (4*S*,5*R*,6*R*)-**74**/(4*R*,5*S*,6*S*)-**74** and (4*S*,5*S*,6*R*)-**74**/(4*R*,5*R*,6*S*)-**74** were prepared from (−)- and (+)-α -pinenes (**27**) with high optical purity. The key stages of these synthetic routes include the formation of stereoisomeric epoxides **92** and isomerization of these epoxides to diols **74** (Scheme 40).

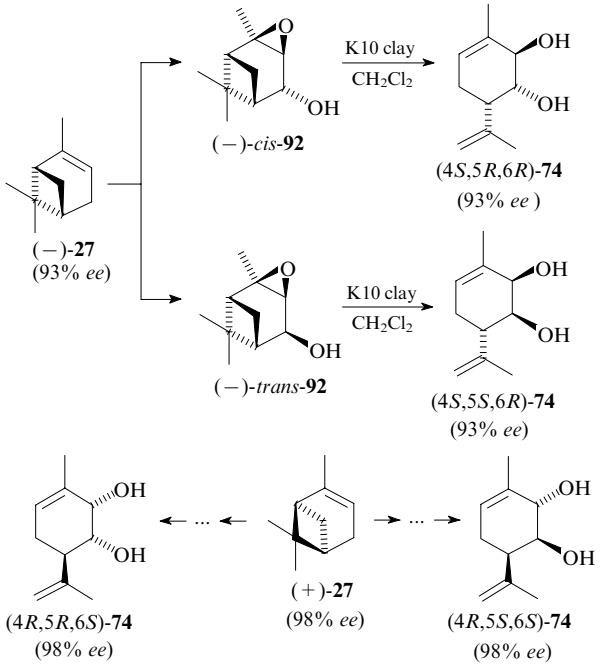
Starting from diols (4*S*,5*R*,6*R*)-**74** and (4*R* ,5*S*,6*S*)-**74**, which were subjected to Swern oxidation of the allylic hydroxyl group, and subsequent reduction of the resulting oxo group in compound **95**, two more diol stereoisomers — (4*S*,5*R*,6*S*)-**74** and (4*R*,5*S*,6*R*)-**74** — were prepared (Scheme 41).[5]

The last stereoisomer pair, (4*S*,5*S*,6*S*)-**74** and (4*R*,5*R*,6*R*)-**74**, was obtained from (+)-(*S*)- and (−)-(*R*)-carvones [(*S*)-**4** and (*R*)-**4**] as shown in Scheme 42.[5] (−)-(*R*)-Carvone [(*R*)-**4**] reacted with lithium diisopropylamide and trimethylchlorosilane (TMSCl) to give Si-enolate (*R*)-**96** (93% yield), which was oxidized by *m*-chloroperoxybenzoic acid. After separation, product (−)-*trans*-**97** was obtained in 38% yield together with diastereomer (−)-*cis*-**97** formed in 15% yield. The removal of the trimethylsilyl group by treatment with $NH_4F \cdot HF$, the reduction of the ketone group in compound (4*S*,5*S*)-**95** followed by separation of diastereomers gave compound (4*S*,5*S*,6*S*)-**74** in 68%

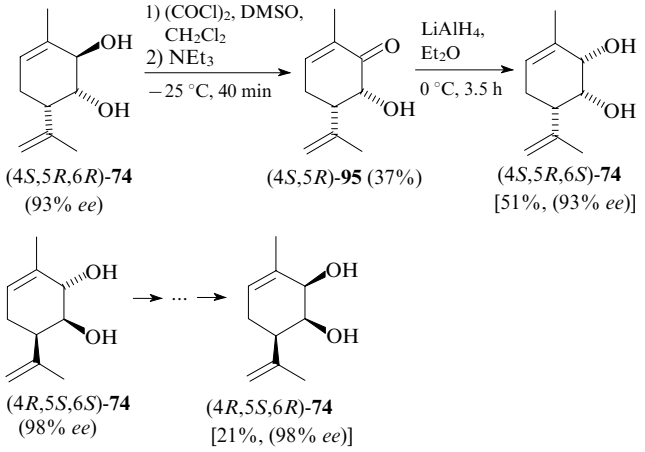
Scheme 39



Scheme 40



Scheme 41



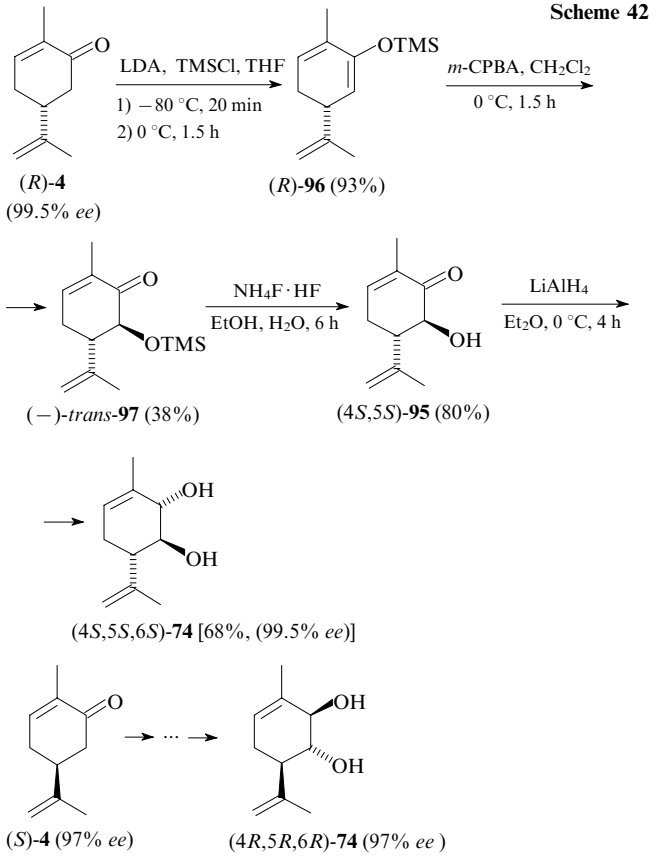
yield. The epimeric (4*S*,5*S*,6*R*)-**74** was isolated in a yield of 32%.

Using the same sequence of reactions, (+)-(*S*)-carvone [(*S*)-**4**] (97% *ee*) was converted to diol (4*R*,5*R*,6*R*)-**74** in an overall yield of 17%.[5]

The absolute configuration of compound **74** was found to have a crucial impact on its biological activity: dihydroxy derivative (4*S*,5*R*,6*R*)-**74** has a high anti-Pakinsonian activity on models with the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), whereas its epimer (4*S*,5*R*,6*S*)-**74** has a clear-cut opposite effect *i.e.*, enhances the action of the neurotoxin.[5]

A similar approach was reported for the synthesis of four stereoisomers of diol **74** from (*R*)-carvone [(*R*)-**4**].[100] The reaction of (*R*)-**4** with lithium diisopropylamide and trimethylchlorosilane was used to obtain trimethylsilyl derivative (*R*)-**96**. The latter was oxidized by peroxyphthalic

Scheme 42



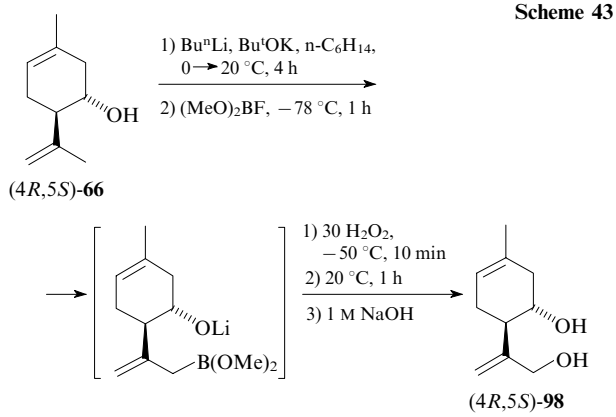
acid, which was formed *in situ* upon the oxidation of phthalic anhydride by a complex of urea with hydrogen peroxide. A mixture of hydroxy ketones (4*S*,5*S*)-**95** and (4*S*,5*R*)-**95** was thus obtained; the products were isolated in 61% and 31% yields with respect to (*R*)-carvone [(*R*)-**4**], respectively. It is of interest that in this case, no additional stage for removal of the TMS group was required. The reduction of *trans*-hydroxy ketone (4*S*,5*S*)-**95** by $LiAlH_4$ provided the synthesis of the (4*S*,5*S*,6*R*)- and (4*S*,5*S*,6*S*)-stereoisomers of diol **74** in 53% and 34% yields, respectively, while the reduction of *cis*-hydroxy ketone (4*S*,5*R*)-**95** afforded the other two stereoisomers, (4*S*,5*R*,6*S*)-**74** and (4*S* ,5*R*,6*R*)-**74**, in 48% and 36% yields.

3. *p*-Mentha-1,8-diene-5,10-diols

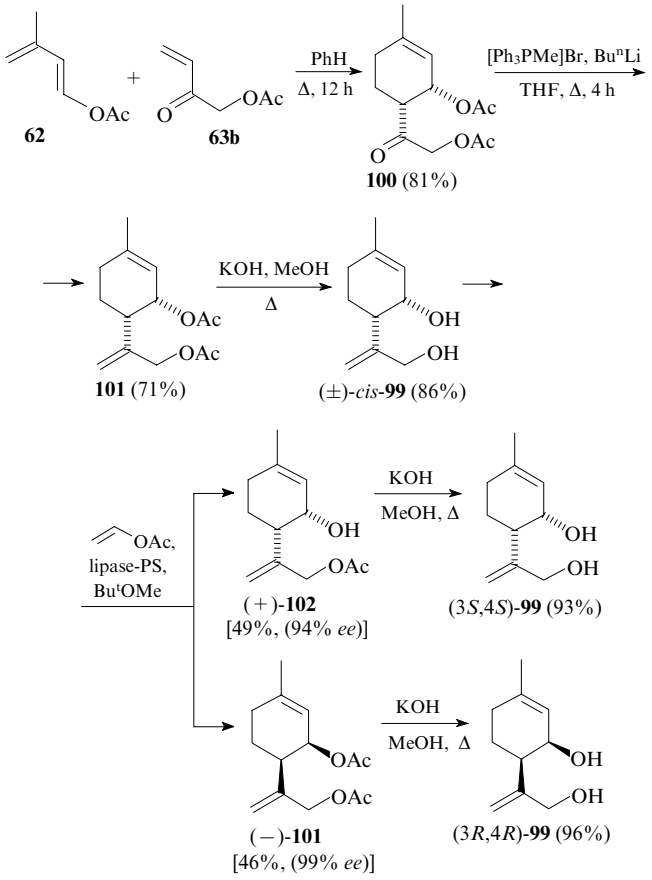
(4*R*,5*S*)-*p*-Mentha-1,8-diene-5,10-diol (**98**) was synthesized from alcohol (4*R*,5*S*)-**66** by successive reactions with Bu^nLi and Bu^tOK, then with $(MeO)_2BF$ followed by oxidation of the resulting organoboron compound and hydrolysis of the borate (Scheme 43).[11] The product yield was 63% after column chromatography and 41% after recrystallization from a hexane–diethyl ether mixture.

The synthetic route to diol (±)-*cis*-**99** was based on the Diels–Alder reaction of compounds **62** and **63b**, which gave adduct **100** in a yield of 81% (Scheme 44).[101] Ketone **100** was subjected to the Wittig reaction to be converted to diacetate **101**, which was hydrolyzed to diol (±)-*cis*-**99**. Then the authors performed kinetic resolution of the enantiomers of diol (±)-*cis*-**99** by lipase-PS-catalyzed acylation by vinyl acetate, which produced monoacetate (+)-**102** in 49% yield and 94% *ee* and diacetate (−)-**101** in 46%

Scheme 43



Scheme 44



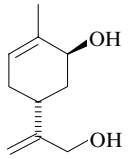
yield and 99% *ee*.[101] The corresponding (3*S*,4*S*)- and (3*R*,4*R*)-enantiomers of diol *cis*-**99** were isolated as the products of saponification of (+)-**102** and (−)-**101**.

4. *p*-Mentha-1,8-dienediols with hydroxy groups in positions 6,10, 7,10 or 4,6

The preparation of diols with the *p*-mentha-1,8-diene carbon skeleton containing hydroxy groups in positions other than the positions described above has received quite little attention; examples of isolation of these derivatives from natural sources are also very rare.

For example, diol (4*R*,6*S*)-**103** was detected in small amounts in the plant *Hyssopus cuspidatus*.[102] Currently, several approaches to its synthesis have been developed.

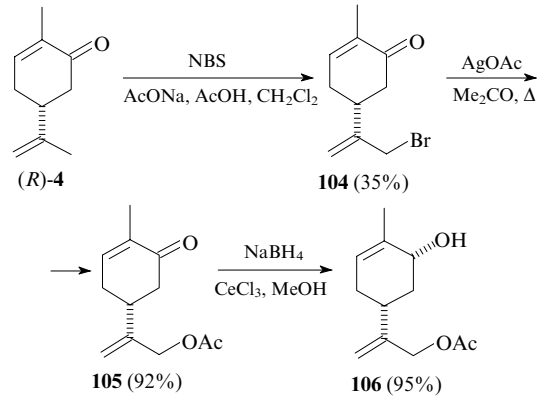
Structure 103



Allylic bromination of (−)-(*R*)-carvone [(*R*)-**4**] in dichloromethane in the presence of sodium acetate and acetic acid resulted in the synthesis of bromide **104** in 35% yield (Scheme 45).[103] It was found that, despite the presence of sodium acetate in the reaction mixture, no keto acetate **105** was formed.[103] To replace the bromine atom in bromide **104** by an acetate group, refluxing in acetone in the presence of silver acetate was necessary.

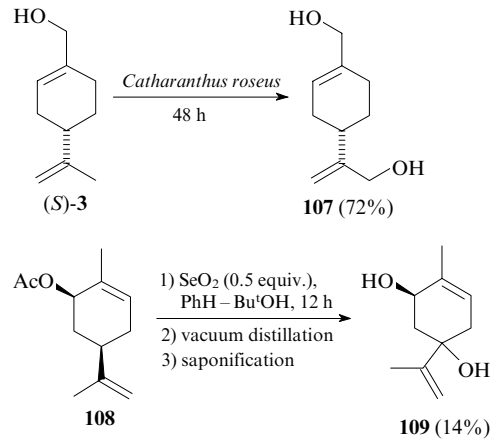
Finally, the Luche reduction of keto acetate **105** by $NaBH_4$ in the presence of $CeCl_3$ gave hydroxy acetate **106**, the monoacetylated derivative of diol (4*R*,6*R*)-**103**, in 95% yield.

Scheme 45



The oxidation of (−)-(*S*)-perillyl alcohol [(*S*)-**3**] by cultured *Catharanthus roseus* cells provided selective synthesis of diol **107** in a yield of 72% (Scheme 46).[104]

Scheme 46



The reaction of (−)-*cis*-carvyl acetate **108** with selenium dioxide in a benzene – *tert*-butyl alcohol mixture with subsequent saponification of the intermediate acetates furnished a mixture of epimers *trans*-**109** and *cis*-**109** in 14% isolated yield with respect to the converted acetate **108** (the degree of conversion was 71%) (see Scheme 46).[105]

IV. Synthesis of trihydroxy derivatives of limonene

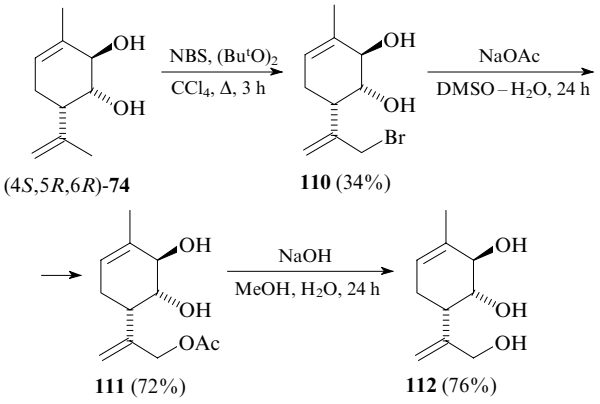
1. *p*-Mentha-1,8-diene-5,6,10-triol

We found only two reported examples of the synthesis of triols with the *p*-mentha-1,8-diene carbon skeleton. This is attributable, at least partly, to numerous difficulties faced by their synthesis.

For example, the oxidation of diol (4*S*,5*R*,6*R*)-**74** induced by SeO_2, which could directly lead to the triol, is non-selective. According to GLC, this reaction affords four major products in approximately equal amounts and a number of minor products.[106]

Allylic bromination of diol (4*S*,5*R*,6*R*)-**74** proved to be more efficient (probably, for steric reasons). This diol reacted with NBS in CCl_4 in the presence of $(Bu^tO)_2$ on refluxing for 3 h, the reaction mixture was applied without workup onto a column with silica gel, and the chromatography gave bromide **110** (Scheme 47).[106] For comparison, in the case of the standard workup of the reaction mixture comprising washing with a solution of Na_2SO_3, drying of the organic phase, collection and separation by column chromatography, the yield of bromide **110** was only 10%. It is noteworthy that the use of diacetate instead of diol (4*S*,5*R*,6*R*)-**74** in the allylic bromination decreased the reaction selectivity and gave rise to a complex mixture of products. The reaction of bromide **110** with NaOAc in aqueous DMSO followed by saponification of acetate **111** furnished *p*-mentha-1,8-diene-5,6,10-triol (**112**) in an overall yield of 55%.

Scheme 47



(4*S*,5*R*,6*R*)-**74**; **110** (34%); **111** (72%); **112** (76%)

2. *p*-Mentha-1,8-diene-5,6,7-triol

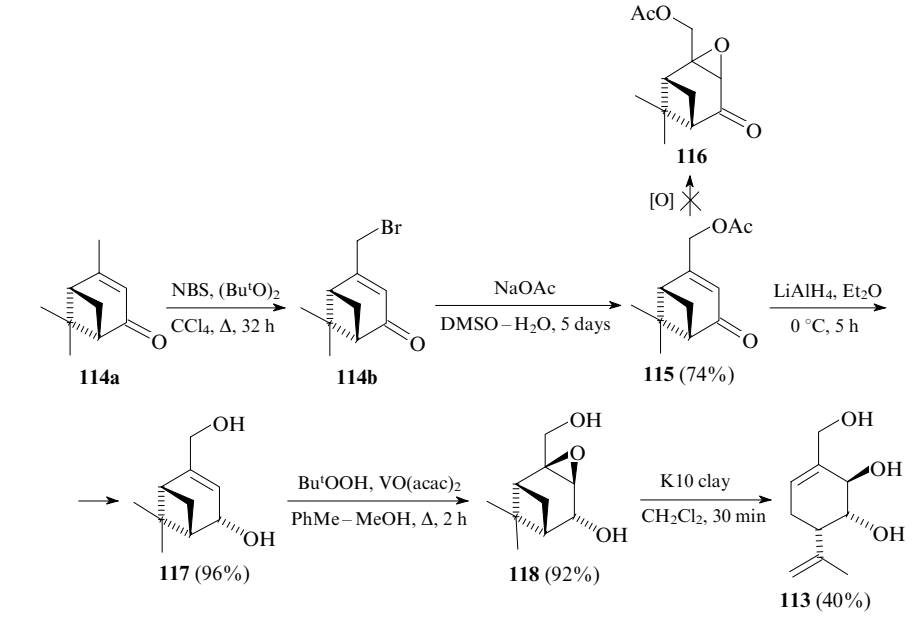
p-Mentha-1,8-diene-5,6,7-triol (**113**) was prepared from (−)-verbenone [(−)-**114a**].[107] In the first stage, allylic bromination of compound (−)-**114a** by NBS in the presence of $(Bu^tO)_2$ gave bromide **114b**, which was converted, without isolation, to acetate **115** by the reaction with sodium acetate in aqueous DMSO (Scheme 48). The yield of compound **115** was 74% with respect to converted (−)-verbenone [(−)-**114a**].

According to the proposed retro-synthetic route, the oxidation of keto acetate **115** to epoxide **116** was supposed to be the next stage in the synthesis of triol **113**. However, all attempts at epoxidation of compound **115** failed: depending on the epoxidating agent used, either the initial compound was recovered or a complex mixture of products was formed.[107] Much more successful was the bypass route comprising reduction of the keto group in compound **115** by $LiAlH_4$, which was accompanied by ester bond hydrolysis. Then compound **117** was made to react with Bu^tOOH in the presence of $VO(acac)_2$ on refluxing in a toluene–MeOH mixture to give epoxide **118** in 92% yield. Finally, isomerization of compound **118** in the presence of K10 clay gave rise to triol **113** in 40% yield (see Scheme 48). The overall yield of trihydroxy derivative **113** with respect to (−)-verbenone [(−)-**114a**] was 26%.

V. Conclusion

Thus, we discussed synthetic routes to alcohols with the *p*-mentha-1,8-diene carbon skeleton and associated regio- and stereoselectivity problems. Attention is drawn by the great diversity of the described methods, which imply the use of radical, anionic and cationoid reactions, concerted cycloaddition reactions and various rearrangements, the use

Scheme 48



116; **114a**; **114b**; **115** (74%); **117** (96%); **118** (92%); **113** (40%)

acac is acetylacetonate

of reagents based on transition metals, both stoichiometric and catalytic procedures, processes using reagents supported on solids, in particular polymers, and structured acid catalysts — montmorillonite clays. Also, various biochemical processes that enable some enantioselective transformations or separation of racemic products were described.

Nevertheless, problems of regio-, stereo- and enantioselectivity of reactions are still at the forefront and require further elaboration and search for new solution methods. Here hydroxy derivatives of limonene will long remain attractive subjects for specialists.

The selectivity problems are manifested especially clearly and vividly in the development of synthetic routes to diols and polyhydroxy compounds with the *p*-mentha-1,8-diene carbon skeleton. This field of chemistry is currently little studied but obviously it is fairly promising both from the standpoint of mechanistic studies of organic reactions and in relation to the preparation of new biologically active compounds.

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