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# Synthesis of oxygen-containing heterocyclic compounds based on monoterpenoids

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The review integrates data on the synthesis of chiral oxygen-containing heterocycles of various structural types by reactions of monoterpenoids with carbonyl compounds. Depending on the structure of the monoterpene and carbonyl components and the catalyst used, these reactions lead to mono-, bi-, tri- or tetracyclic products. The possible reaction mechanisms are discussed and data on the biological activities of the products are given.
The bibliography includes 125 references.

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## 1. Introduction

The synthesis of new products from natural compounds is an important area of modern organic chemistry. Owing to their unique structures and properties, natural molecules can be converted to compounds possessing pronounced biological activities.[1–3] It is known[4] that about a half of medications introduced into medical practice from 1981 to 2006 are based on natural products. It is pertinent to remind that the Nobel Prize in medicine of 2015 was awarded to William C. Campbell, Satoshi Ōmura and Youyou Tu for the discoveries of novel drugs against parasitic diseases particularly among compounds isolated from natural products.

An important group of natural compounds are monoterpenes composed of two isoprene moieties and their oxygen-containing derivatives, which are called monoterpenoids. These compounds often show various biological activities.[5–11] Many monoterpenes and their derivatives are available from plant sources as both enantiomers, which makes them unique building blocks for the preparation of various chiral compounds,[6,12–16] including heterocycles. It is known that the reactions of monoterpenoids with carbonyl compounds, mainly aldehydes, may yield chiral oxygen-containing heterocyclic systems with different skeletons.[17,18] These reactions can be carried out for naturally abundant monoterpenoids of various structural types. As a rule, these reactions are highly stereoselective, and using enantiomeric pairs of monoterpenoids as the starting compounds, it is possible to obtain both optical isomers of heterocyclic products; some of the products showed a pronounced biological activity.[5] Thus, these transformations constitute a new promising route to new types of physiologically active compounds based on accessible monoterpenoids.

Although the wide use of aldehydes in reactions with monoterpenoids for the preparation of heterocyclic compounds started approximately twenty years ago, research along this line is now actively developed. Only a few reviews on this subject have been published to date;[17–19] they are concerned with particular aspects of these reactions and are now largely obsolete.

The present review addresses the reactions of monoterpenoids with carbonyl compounds, resulting in the formation of oxygen-containing heterocycles with direct involvement of the monoterpenoid moiety, reported before

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the end of 2017. The mechanisms of these reactions are discussed and the data on the biological activities of the products are given. The text is arranged according to the number of fused rings in the heterocycles formed.

## 2. Monocyclic products of reactions between monoterpenoids and aldehydes

Compounds containing a heterocyclic moiety can be formed upon the reactions of acyclic monoterpenoids with aldehydes. The most abundant acyclic monoterpenoid is citral, which is present in the essential oils of lemongrass, lemon, eucalyptus and other. It is widely used as a supplement in food products, cosmetics and detergents.[20] Citral is a mixture of geranial (**1**, *E* isomer) and neral (**2**, *Z* isomer), with the former predominating. Geranial (**1**), which is obtained by kinetic resolution of citral,[21] and neral (**2**) can undergo homocoupling reactions catalyzed by bis(cyclopentadienyl)titanium(III) in the presence of water. This gives (4*S*,5*R*)- (**3**) and (4*R*,5*R*)-γ-lactols (**4**) as mixtures of diastereomers at position 2 in 5 : 1 ratio (the absolute configuration of the predominant diastereomer is not indicated in the publication) (Scheme 1).[22] Monoterpenoids **1** and **2** are cross-coupled with decanal (**5**) and 3-phenylpropanal (**6**) under similar conditions to give mixtures of isomers **7** and **8** or **9** and **10**, respectively. Among the products, *E*-isomers **7**, **9** predominate in the case of geranial (**1**) and *Z*-isomers **8**, **10** predominate for neral (**2**).[22]

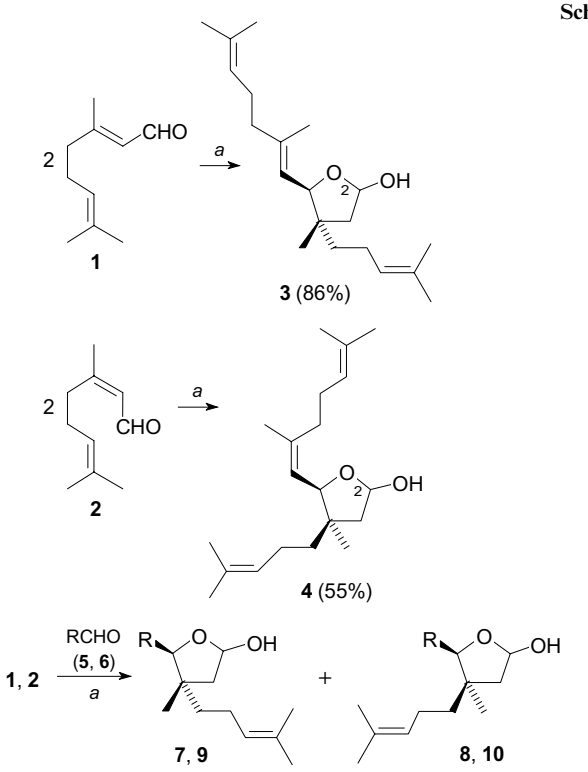
Presumably, the presence of water in the system leads to the formation of aqua complex **11** (see the mechanism in Scheme 1), the coordination of which to monoterpenoid **1** or **2** and electron transfer from $Ti^{III}$ may afford allylic radical **12**.[22] In the resulting titanium-oxy derivative, the $Ti^{IV}$ atom is coordinated by the aldehyde oxygen atom to give intermediate **13**. The favourable positions of the π-orbitals of the aldehyde carbonyl group and delocalized allyl group enable the cyclization.

Citronellal (**14**) has a distinct lemon odour and is contained in the essential oils of the plants *Eucalyptus citriodora*, *Cymbopogon nardus*, *Cymbopogon citratus* and *Cymbopogon winterianus*.[23,24] The *S*-enantiomer of citronellal [(*S*)-**14**] condenses with 1-amino-2,2-dimethylpropane-1,3-diol, which is formed *is situ* from 3-hydroxy-2,2-dimethylpropanal (**15**) and ammonia, to give diastereomeric 5,6-dihydro-2*H*-1,3-oxazines **16** and **17** in 2 : 1 ratio (Scheme 2).[25,26]

Geraniol (**18**) is the major component of the essential oils of several plants, including *Monarda fistulosa* (95%) and *Cymbopogon martinii* (54%), and rose oil (44%) and has a fruity-floral fragrance.[27] In the presence of $BF_3 \cdot Et_2O$, geraniol (**18**) can eliminate a water molecule to give allylic cation **19**, which can react with aliphatic aldehydes **20** – **24** to afford tetrahydropyran products **25a**,**b** – **29a**,**b** in moderate yields (Scheme 3, Table 1).[28] For steric reasons, the formation of isomers **25a** – **29a** is more favourable, irrespective of the structure of the used aldehyde. Bicyclic compounds **30** – **34**, which are formed as side products, are discussed in more detail in the next Section.

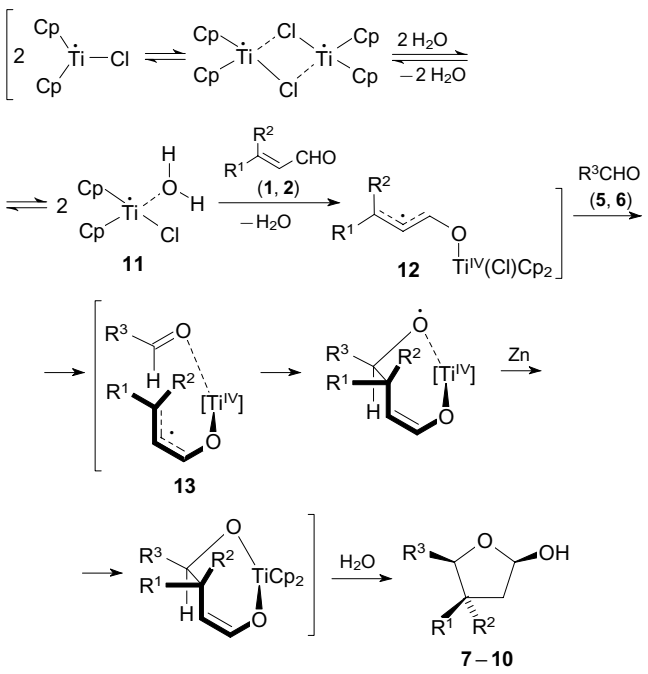
Saha *et al.*[28] noted that the tetrahydropyran products are formed predominantly when aliphatic (rather than aromatic) aldehydes are used. The authors attributed this to the fact that aliphatic aldehydes are more nucleophilic and have smaller molecule size than aromatic aldehydes, which facilitates their reaction with acyclic carbocation **19**

**Scheme 1**

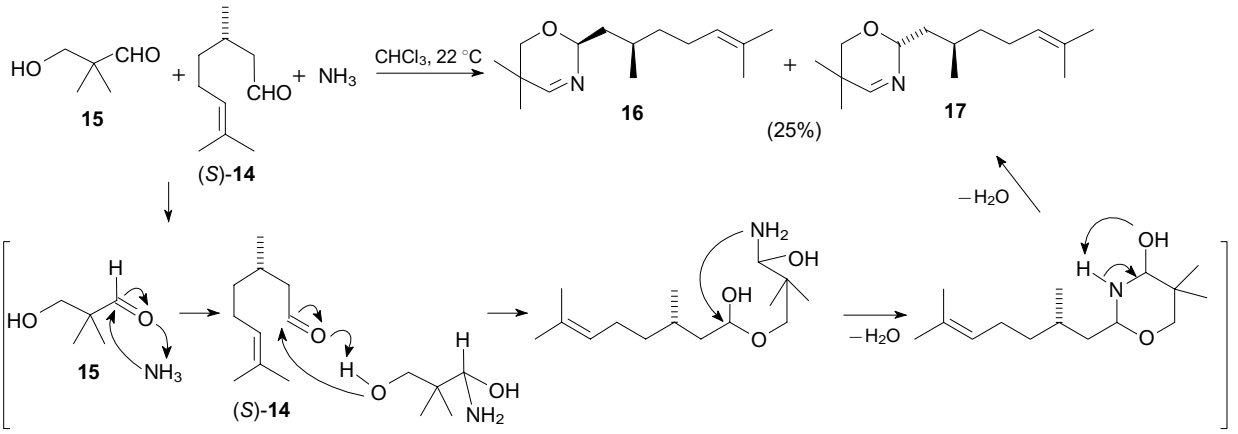



(*a*) $Cp_2TiCl$ (1 equiv.), $H_2O$ (100 equiv.), Zn (8 equiv.), THF; R = n-$C_9H_{19}$ (**5**, **7**, **8**), $Ph(CH_2)_2$ (**6**, **9**, **10**); Cp is cyclopentadienyl

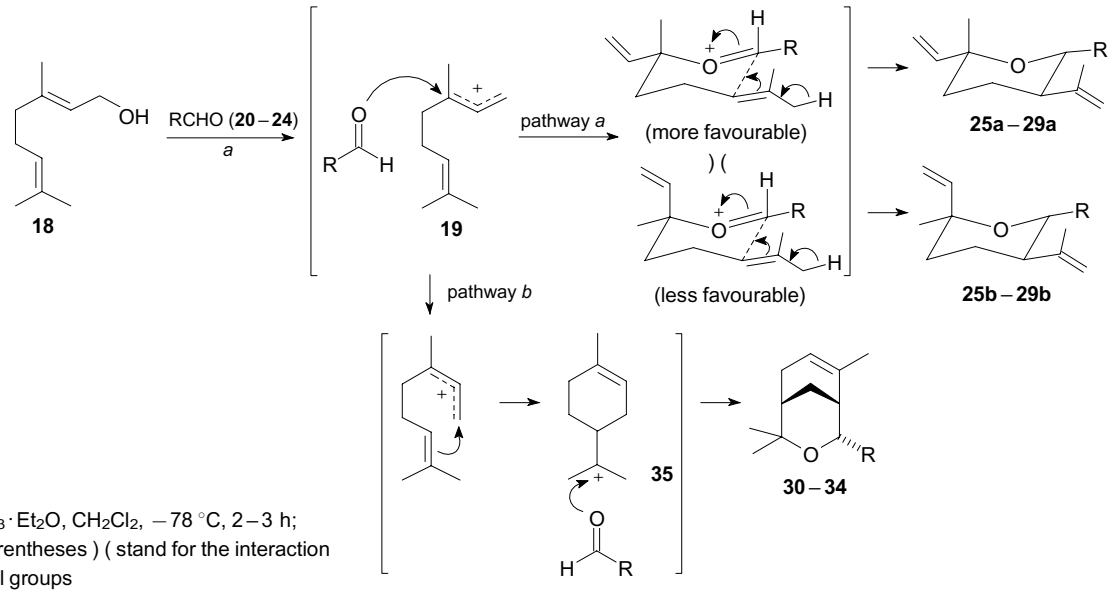
| Terpenoid | Yield (%) | | | |
|---|---|---|---|---|
| | **7** | **8** | **9** | **10** |
| **1** | 62 | 5 | 93 | 4 |
| **2** | 7 | 55 | 11 | 72 |



**Scheme 2**




**Scheme 3**




(*a*) $BF_3 \cdot Et_2O$, $CH_2Cl_2$, −78 °C, 2 – 3 h; the parentheses ) ( stand for the interaction of axial groups

**Table 1**. Synthesis of tetrahydropyrans from geraniol (**18**) (see Scheme 3).[28]

| Aldehyde | R | Pathway *a* | | Pathway *b* | |
|---|---|---|---|---|---|
| | | products | yield (%) | products | yield (%) |
| **20** | Et | **25a**,**b** | 65 | **30** | 8 |
| **21** | $Pr^n$ | **26a**,**b** | 65 | **31** | 8 |
| **22** | $Bu^i$ | **27a**,**b** | 67 | **32** | 10 |
| **23** | n-$C_6H_{13}$ | **28a**,**b** | 60 | **33** | 15 |
| **24** | n-$C_{15}H_{31}$ | **29a**,**b** | 62 | **34** | 10 |

(pathway *a* in Scheme 3), thus preventing its subsequent cyclization to α-terpinyl cation **35** (pathway *b*).

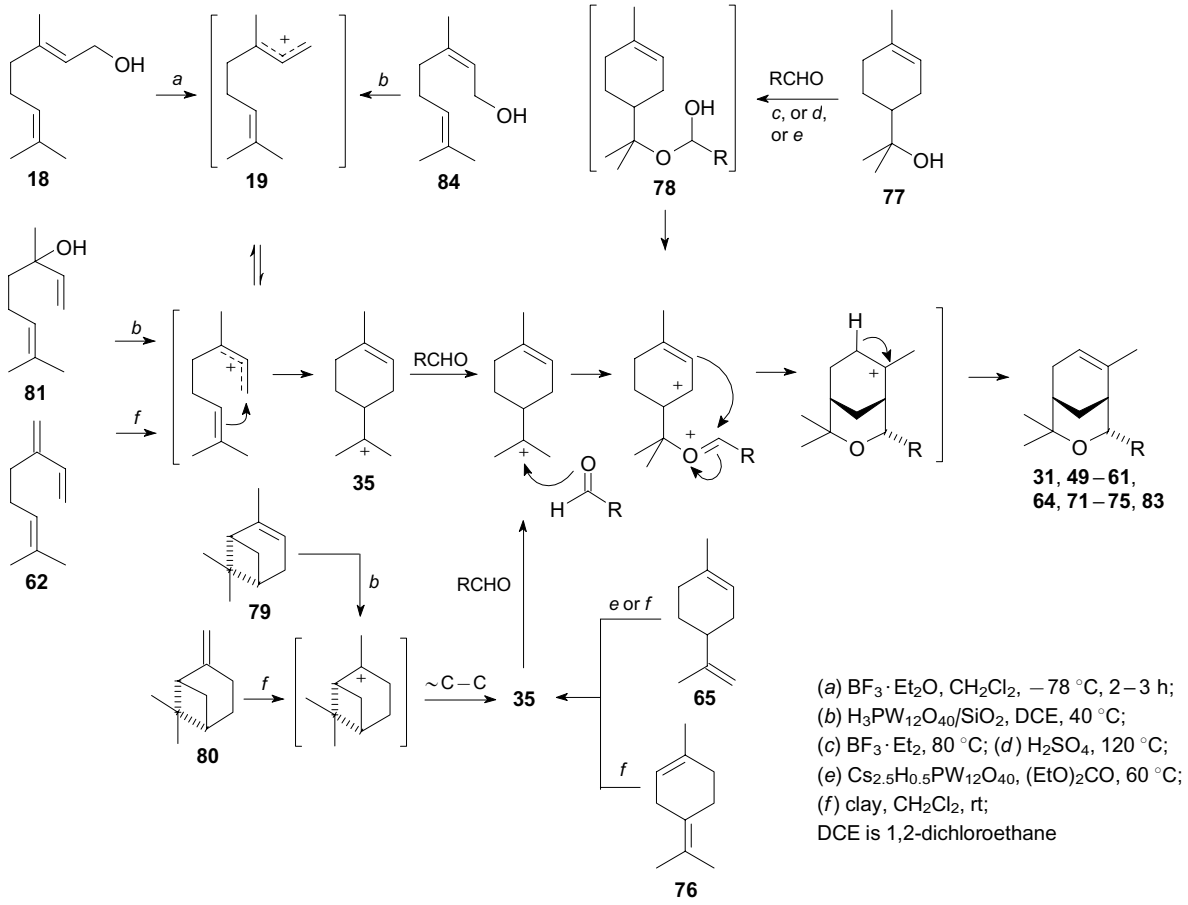
## 3. Bicyclic products of reactions between monoterpenoids and carbonyl compounds

### 3.1. Compounds with the 3-oxabicyclo[3.3.1]nonane skeleton

The reactions of geraniol (**18**) with aromatic aldehydes **36** – **48** in the presence of $BF_3 \cdot Et_2O$ afford bicyclic 3-oxabicyclo[3.3.1]nonenes **49** – **61** (Scheme 4) *via* the intermediate formation of carbocation **35**.[28] When benzaldehyde (**36**) or 4-nitrobenzaldehyde (**40**) is used as the carbonyl component, tetrahydropyran type minor products, which are discussed above, were isolated together with bicyclic compounds **49** and **53** (see Scheme 3).

The acyclic monoterpene myrcene (**62**) is present in the essential oil of *Cymbopogon citratus* (lemongrass)[29] and is a valuable reactant for the synthesis of fragrance compounds. It was found[30] that myrcene (**62**) reacts with butenal (**63**) in the presence of montmorillonite clay, which is often used to catalyze transformations of this type,[18,31] to give predominantly heterocyclic compound **64** with the 3-oxabicyclo[3.3.1]non-6-ene skeleton, similar to products **49** – **61** (see Scheme 4). It is noteworthy that conducting the same reaction in an autoclave at 200 °C or in the presence of $BF_3 \cdot Et_2O$ results in the formation of the monocyclic Diels – Alder adduct instead of bicyclic product **64**.[32,33] The reaction of monoterpene **62** with benzaldehyde (**36**) also affords bicyclic product **49**. The presumptive mechanism of this reaction includes cyclization and formation of intermediate *p*-menthane type cation **35**, which then reacts with the aldehyde.

**Scheme 4**




Among monocyclic monoterpenes, *p*-menthane derivatives are most naturally abundant. (*R*)-Limonene [(*R*)-**65**] is the major component of the essential oils of citrus plants (*Citrinae*)[34] and is present in the essential oils of the plants *Lippia alba*[35] and *Artemisia dracunculus*.[36] Limonene (**65**) reacts with aromatic and aliphatic aldehydes **66** – **70** in the presence of montmorillonite clay, which also results in heterocyclic products **31**, **49**, **64** and **71** – **75** with the 3-oxabicyclo[3.3.1]nonene skeleton. Evidently, this reaction proceeds *via* the same intermediate cation **35** (see Scheme 4).[37,38] Terpinolene (**76**), a positional isomer of limonene (**65**) with a different double bond position, reacts with benzaldehyde (**36**) in the presence of clay to afford the same bicyclic product **49**.[30]

3-Oxabicyclo[3.3.1]nonene compounds demonstrated a noticeable activity as α- and β-estrogen receptor agonists,[39 – 42] in particular, in *in vivo* experiments.[39]

α-Terpineol (**77**) is the major component of the essential oils of many plants, including *Ravensara aromatica*, *Melaleuca qinquenervia*, *Myrtus communis*, *Laurus nobilis*, *Croton sonderianus* and *Eucalyptus globulus*, which are widely used in folk medicine and aromatherapy.[43] Unlike monoterpenes **65** and **76**, α-terpineol (**77**) contains a hydroxy group in position 8 of the *p*-menthane moiety. However, the presence of a hydroxy group in monoterpenoid **77** does not affect the structure of bicyclic product **49** formed in the acid-catalyzed reaction with benzaldehyde (**36**). In the presence of acids ($BF_3 \cdot Et_2O$ or $H_2SO_4$), α-terpineol (**77**) is converted to hemiacetal **78** (see Scheme 4), although the alternative route with the intermediate formation of cation **35** cannot be ruled out either.[44,45]

α-(**79**) and β-Pinenes (**80**) are the major components of turpentine oils of coniferous trees. α-Pinene (**79**) is available from natural sources as two enantiomers, whereas for β-pinene (**80**), only one enantiomer, (−)-β-pinene, is present in considerable amounts.[46] Under acidic conditions, pinenes and their derivatives readily rearrange to give compounds with the *p*-menthane skeleton, which accounts for the formation of many identical products in the reactions of these two monoterpenes with aldehydes. β-Pinene (**80**) reacts with aliphatic aldehydes, butanal (**21**) and butenal (**63**), in the presence of clay to give 3-oxabicyclo[3.3.1]non-6-enes **31** and **64** (see Scheme 4).[47]

The reactions of a group of monoterpenes [limonene (**65**), α-pinene (**79**) and β-pinene (**80**)] and monoterpenoids [α-terpineol (**77**), linalool (**81**)] with benzaldehyde (**36**) and cuminaldehyde (4-isopropylbenzaldehyde, **82**) in the presence of the $SiO_2$-supported heteropoly acid $H_3PW_{12}O_{40}$ or heteropoly acid salt $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ have been studied.[48,49] It is noteworthy that linalool (**81**) (see Scheme 4) is widely present in the essential oils of fragrant plants such as *Citrus bergamia Risso*, *Melissa officinalis* L., *Rosmarinus officinalis* L., *Cymbopogon citratus* DC and *Mentha piperita* L.[50,51] In all cases, bicyclic compounds **49** and **83** were obtained as the major products. β-Nerol (**84**) also undergoes analogous reactions. The yields of products depicted in Scheme 4 are summarized in Table 2.

In some studies,[48 – 51] the products were not isolated in a pure state, but the conversion and selectivity were deter-

**Table 2**. Synthesis of 3-oxabicyclo[3.3.1]nonene type compounds from monoterpenoids **18** and **65** (see Scheme 4).

| Terpenoid | Aldehyde | R | Product | Yield (%) | Ref. |
|---|---|---|---|---|---|
| **18** | **36** | Ph | **49** | 52 | 28 |
| **18** | **37** | 4-$ClC_6H_4$ | **50** | 70 | 28 |
| **18** | **38** | 4-$BrC_6H_4$ | **51** | 70 | 28 |
| **18** | **39** | 4-$FC_6H_4$ | **52** | 68 | 28 |
| **18** | **40** | 4-$O_2NC_6H_4$ | **53** | 50 | 28 |
| **18** | **41** | 2-$O_2NC_6H_4$ | **54** | 54 | 28 |
| **18** | **42** | 2-Naph | **55** | 55 | 28 |
| **18** | **43** | PhCH=CH | **56** | 62 | 28 |
| **18** | **44** | 4-$O_2NC_6H_4CH$=CH | **57** | 55 | 28 |
| **18** | **45** | 4-$MeO_2CC_6H_4$ | **58** | 57 | 28 |
| **18** | **46** | 4-$HOC_6H_4$ | **59** | 69 | 28 |
| **18** | **47** | 4-$MeC_6H_4$ | **60** | 68 | 28 |
| **18** | **48** | cyclo-$C_6H_{11}$ | **61** | 62 | 28 |
| **65** | **21** | $Pr^n$ | **31** | 6 | 37 |
| **65** | **63** | All | **64** | 70 | 37 |
| **65** | **66** | 4-$MeOC_6H_4$ | **71** | 38 | 38 |
| **65** | **67** | $CH_2$=CH | **72** | 5 | 38 |
| **65** | **68** | $CH_2$=CMe | **73** | 5 | 38 |
| **65** | **69** | $C_6F_5$ | **74** | 3 | 38 |
| **65** | **70** | 3-Me-4-$HOC_6H_3$ | **75** | – | 49 |
| **65** | **82** | 4-$Pr^iC_6H_4$ | **83** | – | 49 |

**Note**. Geraniol (**18**) reacts in the presence of $BF_3 \cdot Et_2O$, and limonene (**65**) reacts in the presence of clay. A dash means that the yield is not indicated in the original publication. Naph is naphthyl, All is allyl.

mined from gas chromatography data. In the presence of the heteropoly acid $H_3PW_{12}O_{40}/SiO_2$, conduction of the reaction in 1,2-dichloroethane at 40 °C proved to be optimal, with the highest selectivity to product **49** being attained with limonene (**65**) (92%) or α-terpineol (**77**) (94%) as the starting compound.[48] The application of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ in diethyl carbonate at 50 – 60 °C yielded target product **83** with a selectivity of 70% – 93%; in this case, too, α-terpineol (**77**) was the most efficient substrate.[49]

As regards the spatial structure of 3-oxabicyclo[3.3.1]-nonenes formed in these reactions, there is no common opinion in the literature about the relative positions of the bridging methylene group and the substituent R derived from the aldehyde. A comparison of the $^1H$ NMR spectra for similar compounds reported in different literature sources attests to the identity of compounds obtained under different conditions from various monoterpenoids. Analysis

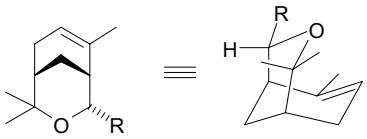



**Figure 1.** Spatial structure of 3-oxabicyclo[3.3.1]non-6-ene type products.

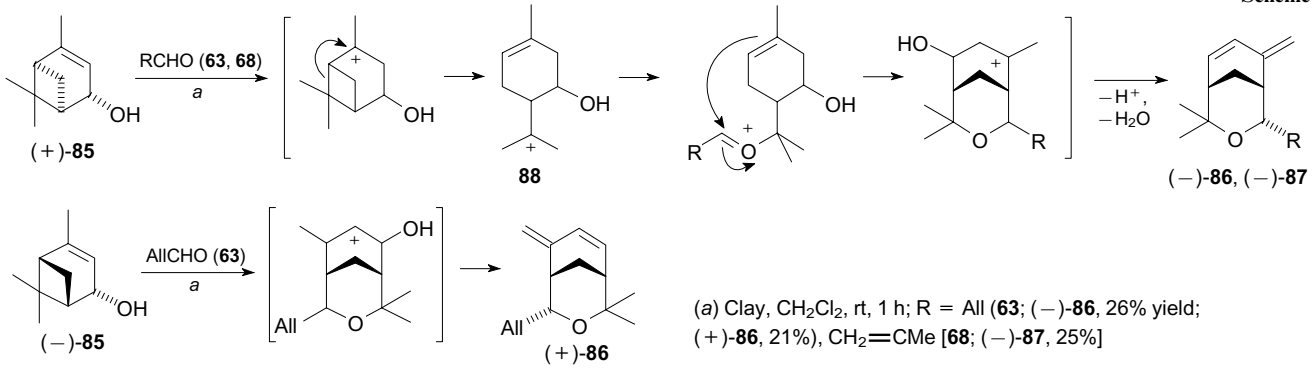
of the NMR chemical shifts indicates that these compounds have a *trans*-position of the bridging methylene group and the substituent R (Fig. 1).

Verbenol, a monoterpenoid with the pinane skeleton, possesses fresh pine smell and is contained in the essential oil of verbena;[52] this accounts for its name. The reaction of (+)-*trans*-verbenol [(+)-(**85**)] with butenal (**63**) and methacrolein (**68**) in the presence of montmorillonite clay furnishes bicyclic products (−)-**86** and (−)-**87**, respectively.[47, 53] Apparently, the transformation involves the formation of *p*-menthane type carbocation **88**; the presence of the hydroxy group in the starting monoterpenoid (+)-**85** and, hence, in the formed carbocation **88** gives rise to an additional double bond in products (−)-**86** and (−)-**87** (Scheme 5). The reaction of the stereoisomer of monoterpenoid (+)-**85**, (−)-*cis*-verbenol [(−)-**85**], with butenal (**63**) affords the enantiomeric product (+)-**86** under similar conditions.[54]

Unlike α-terpineol (**77**), *trans*-sobrerol (**89**) contains an additional hydroxy group in position 2 of *p*-menthane. This compound was found in considerable amounts in a number of plants, including the fruits of *Illicium lanceolatum* and the pine cones of *Pinus koraiensis*.[55, 56] The reaction of monoterpenoid **89** with various aldehydes, including phenylacetaldehyde (**90**), in the presence of $BF_3 \cdot Et_2O$ affords the corresponding oxabicyclo[3.3.1]nonane products **91** – **106**, but containing a keto group (Scheme 6, Table 3).[57] It is assumed that the first step affords carbocation **107**, which reacts with aldehyde to give oxonium ion **108** (see Scheme 6). The subsequent tautomerization of enol **109** gives a heterocyclic product. Note that in this case, the *trans*-arrangement of the methylene bridge and the aldehyde substituent R was unambiguously derived from X-ray diffraction data.[57]

The yields of products **101** – **104** and **106** in the reactions of sobrerol (**89**) with aliphatic aldehydes **20** – **23** and **48** proved to be markedly higher than those for aromatic aldehydes, except for benzaldehyde (**36**). It is noteworthy that the yield of heterocyclic products virtually did not

**Scheme 5**




(*a*) Clay, $CH_2Cl_2$, rt, 1 h; R = All (**63**; (−)-**86**, 26% yield; (+)-**86**, 21%), $CH_2$=CMe [**68**; (−)-**87**, 25%]

**Scheme 6**

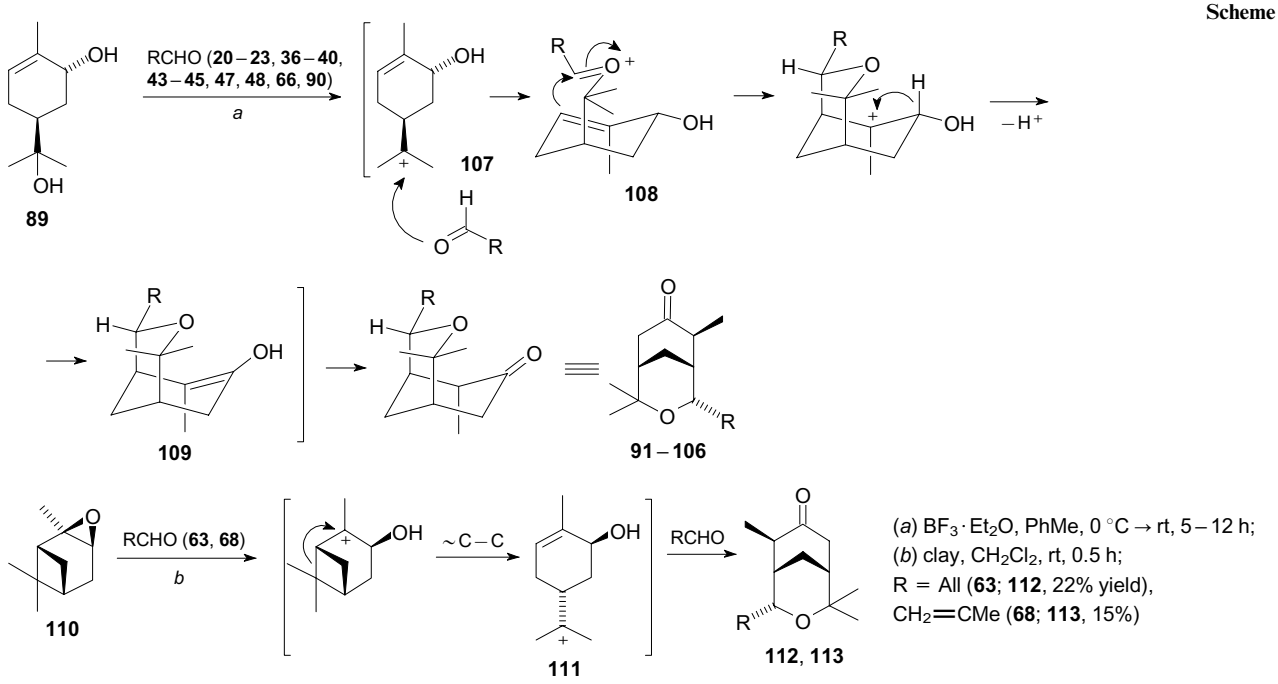



**Table 3**. Synthesis of 3-oxabicyclo[3.3.1]nonane type compounds from sobrerol (**89**) (see Scheme 6).[57]

| Aldehyde | R | Product | Yield (%) |
|---|---|---|---|
| **36** | Ph | **91** | 80 |
| **37** | 4-$ClC_6H_4$ | **92** | 50 |
| **38** | 4-$BrC_6H_4$ | **93** | 51 |
| **39** | 4-$FC_6H_4$ | **94** | 62 |
| **40** | 4-$O_2NC_6H_4$ | **95** | 50 |
| **43** | PhCH=CH | **96** | 57 |
| **44** | 4-$O_2NC_6H_4CH$=CH | **97** | 62 |
| **45** | 4-$MeO_2CC_6H_4$ | **98** | 52 |
| **47** | 4-$MeC_6H_4$ | **99** | 68 |
| **66** | 4-$MeOC_6H_4$ | **100** | 56 |
| **20** | Et | **101** | 98 |
| **21** | $Pr^n$ | **102** | 98 |
| **22** | $Bu^i$ | **103** | 82 |
| **23** | n-$C_6H_{13}$ | **104** | 80 |
| **90** | Bn | **105** | 50 |
| **48** | cyclo-$C_6H_{11}$ | **106** | 90 |

depend on the nature of substituents in the aldehyde aromatic ring. Probably, under these conditions, the product yields depend on the nucleophilicity of the starting aldehyde. The highest yield was attained for aliphatic aldehydes **20**, **21** and **48**. The increase in the aliphatic chain length (aldehyde **23**) or degree of branching (aldehyde **22**) leads to somewhat lower yields of the resulting oxabicyclo[3.3.1]nonanes.[57]

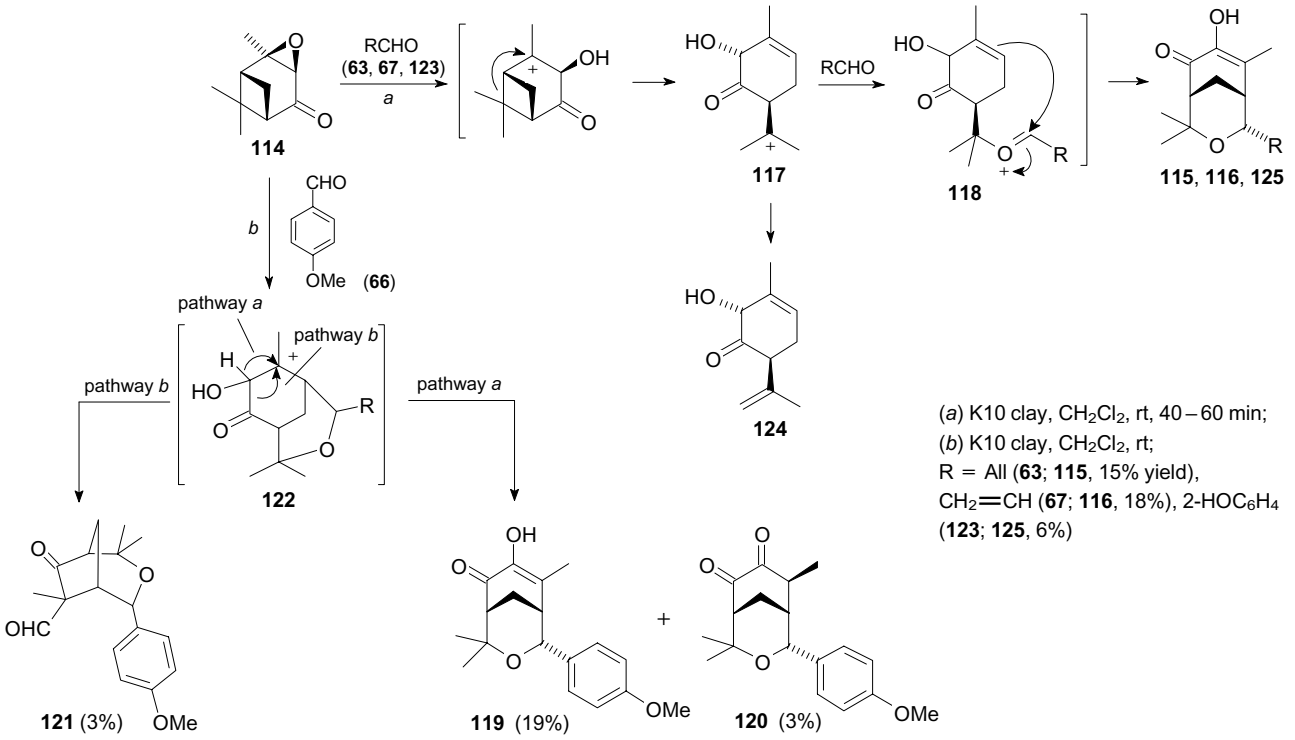
As noted above, pinane monoterpenoids can be rearranged to *p*-menthane type compounds under acidic conditions. Keeping (−)-α-pinene epoxide (**110**) in the presence of montmorillonite clay in dichloromethane induces epoxide ring opening and rearrangement to cation **111** with the *p*-menthane skeleton (see Scheme 6).[53] The carbocation **111** thus formed is an enantiomer of cation **107**; hence, it further reacts with aldehyde as described above for sobrerol (**89**) and gives compounds **112** and **113**.

In the case of verbenone epoxide (**114**), the structure of the starting monoterpenoid is complicated by the keto group. Compound **114** reacts with aliphatic aldehydes **63** and **67** in the presence of clay to afford 3-oxabicyclo[3.3.1]-non-6-ene type diketones **115** and **116** in the enol form (Scheme 7).[58] Apparently, *p*-menthane type carbocation **117** first reacts with aldehyde to generate cation **118**. The reaction of aromatic 4-methoxybenzaldehyde (**66**) with epoxide **114** in the presence of clay follows a more complex pathway, resulting in the formation of a mixture of bicyclic tautomers **119** and **120** with the 3-oxabicyclo[3.3.1]non-6-ene skeleton (pathway *a* in Scheme 7) and compound **121**, which is likely to result from ring contraction in cation **122** (pathway *b*).[58]

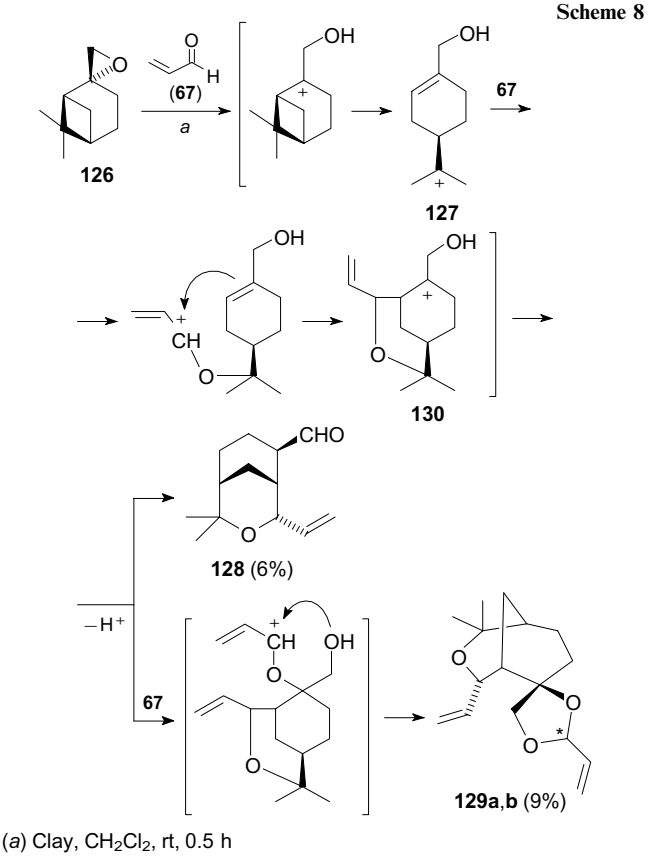
The clay-catalyzed reaction of verbenone epoxide (**114**) with 2-hydroxybenzaldehyde (**123**) containing a phenolic OH group in the *ortho*-position affords a mixture of hydroxy ketone (**124**), resulting from isomerization, and heterocyclic compound **125**, which resembles products **115**, **116** and **119**.[58] Note that the formation of compound **124** supports the reaction mechanism depicted in Scheme 7, in which cation **117** with the *p*-menthane skeleton is formed as an intermediate.

Isomerization of β-pinene epoxide (**126**) in the presence of montmorillonite clay affords carbocation **127** with a structure differing from those formed in the case of monoterpenoids **89** and **110**, and, hence, absolutely different products: 3-oxabicyclo[3.3.1]nonane type aldehyde **128** and tricyclic spiro compounds **129a**,**b** (Scheme 8).[53] A possible mechanism of these transformations includes the formation of *p*-menthane type cation **127** and its reaction with a propenal (**67**) molecule, giving rise to bicyclic carbocation **130**. Then cation **130** can either be converted to 3-oxabicyclo[3.3.1]nonane type aldehyde **128** or react with one more molecule of aldehyde **67** to give a mixture of diastereomeric

**Scheme 7**




**Scheme 8**




acetals **129a**,**b** (2 : 1 ratio), which differ in the configuration of the vinyl group in the dioxolane ring.

It can be seen that irrespective of the type of the starting monoterpenoid, reactions with carbonyl compounds in acid solutions proceed *via* the formation of intermediate cations with the *p*-menthane skeleton, which accounts for the formation of identical or structurally similar 3-oxabicyclo[3.3.1]nonane type products.

### 3.2. Compounds with the polyhydro-2*H*-chromene skeleton

Lewis and Brønsted acids, including $InCl_3$, $CeCl_3$, montmorillonite clays and so on, are known to catalyze the reaction of homoallylic alcohols with aldehydes (Prins reaction), furnishing a broad range of tetrahydropyran derivatives.[59 – 62] Chiral compounds containing a tetrahydropyran moiety can be obtained, for example, by using chiral ligands.[63] Another approach to the synthesis of chiral octahydropyrans implies the reaction of optically active monoterpene alcohols with carbonyl compounds. The homoallylic alcohol (–)-isopulegol (**131**) is often used in these reactions as the starting monoterpenoid, as it is commercially available and relatively cheap being formed as intermediate in the industrial synthesis of menthol.[64] (–)-Isopulegol (**131**) is a component of the essential oils of *Eucalyptus citriodora*,[65] *Corymbia citriodora*[66] and *Zanthoxylum schinifolium*[67] and has a fresh minty smell.

As the first reaction of this type, mention may be made of the formation of lactones **132a**,**b** in the palladium-catalyzed carbonylation of isopulegol (**131**) (Scheme 9).[68] The product is formed as a mixture of diastereomers in the **132a** : **132b** ratio of ~3 : 2.[69, 70] Presumably, stabilization of the palladium complex by the hydroxy group of isopulegol (**131**) is largely responsible for lactone ring closure.[69]

Isopulegol (**131**) reacts with various aromatic, heterocyclic and aliphatic aldehydes (compounds **21**, **36** – **39**, **42**, **47**, **66** and **133** – **141**) in the presence of acid-activated H-K10 montmorillonite clay without a solvent under micro-

**Scheme 9**

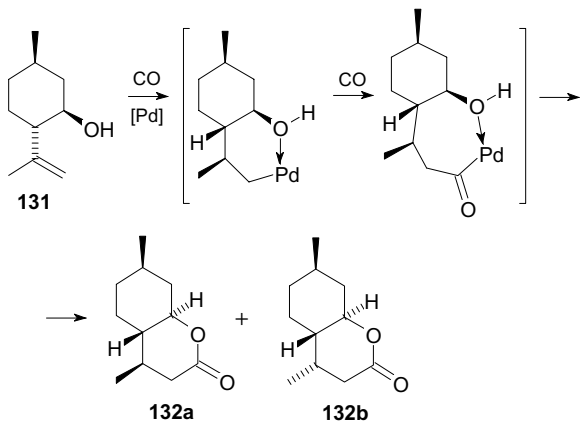
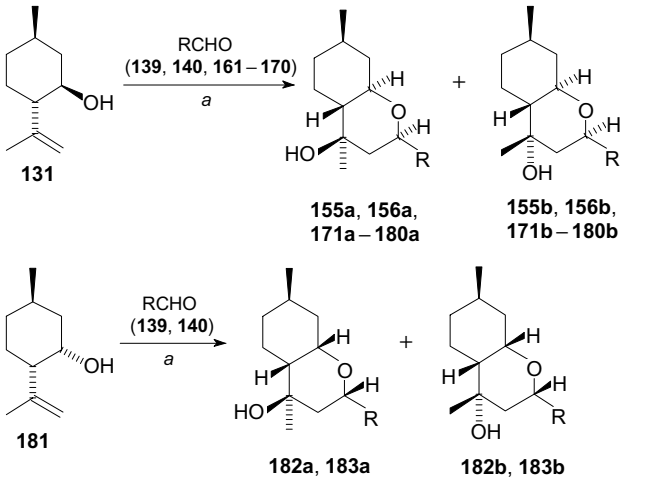



**Table 4**. Microwave-assisted synthesis of 4-hydroxyoctahydrochromenes from isopulegol (**131**) (see Scheme 10).[71]

| Aldehyde | R | Products | Yield (%) | Ratio **a** : **b** |
|---|---|---|---|---|
| **36** | Ph | **142a**,**b** | 76 | 9 : 1 |
| **42** | 2-Naph | **143a**,**b** | 80 | 10 : 1 |
| **66** | 4-$MeOC_6H_4$ | **144a**,**b** | 86 | 20 : 1 |
| **133** | 2-$MeOC_6H_4$ | **145a**,**b** | 76 | 13 : 2 |
| **47** | 4-$MeC_6H_4$ | **146a**,**b** | 82 | 25 : 1 |
| **37** | 4-$ClC_6H_4$ | **147a**,**b** | 78 | 5 : 1 |
| **134** | 2,4-$Cl_2C_6H_3$ | **148a**,**b** | 72 | 4 : 1 |
| **38** | 4-$BrC_6H_4$ | **149a**,**b** | 78 | 9 : 1 |
| **135** | 3-$BrC_6H_4$ | **150a**,**b** | 65 | 3 : 1 |
| **136** | 2-$BrC_6H_4$ | **151a**,**b** | 70 | 2 : 1 |
| **39** | 4-$FC_6H_4$ | **152a**,**b** | 64 | 3 : 1 |
| **137** | 2,4,5-$F_3C_6H_2$ | **153a**,**b** | 50 | 1 : 1 |
| **138** | 3-$O_2NC_6H_4$ | **154a**,**b** | 64 | 3 : 1 |
| **139** | 2-Fu | **155a**,**b** | 56 | 3 : 1 |
| **140** | 2-Th | **156a**,**b** | 50 | 2 : 1 |
| **21** | $Pr^n$ | **157a**,**b** | 70 | 5 : 1 |
| **141** | $Ph(CH_2)_3$ | **158a**,**b** | 76 | 4 : 1 |

**Note**. Fu is furyl, Th is thienyl.

**Scheme 11**




(*a*) K10 clay, 60 – 120 min;
R = 2-Fu (**139**; **182**, 41% yield), 2-Th (**140**; **183**, 75%)

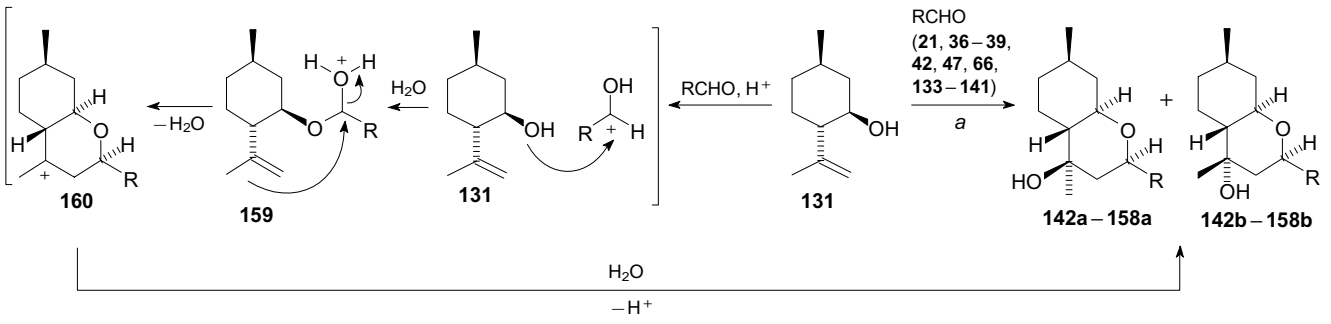
**Table 5**. Microwave-free synthesis of 4-hydroxyoctahydrochromene from (−)-isopulegol (**131**) (see Scheme 11).[72]

| Aldehyde | R | Products | Yield (%) | Ratio **a** : **b** |
|---|---|---|---|---|
| **139** | 2-Fu | **155a**,**b** | 86 | 3 : 1 |
| **140** | 2-Th | **156a**,**b** | 78 | 5 : 1 |
| **161** | 5-Methyl-2-furyl | **171a**,**b** | 65 | 7 : 2 |
| **162** | 5-Nitro-2-furyl | **172a**,**b** | 54 | 2 : 3 |
| **163** | 5-Methyl-2-thienyl | **173a**,**b** | 80 | 9 : 2 |
| **164** | 3-Methyl-2-thienyl | **174a**,**b** | 69 | 10 : 1 |
| **165** | 5-Bromo-2-thienyl | **175a**,**b** | 76 | 13 : 2 |
| **166** | 4-Bromo-2-thienyl | **176a**,**b** | 74 | 3 : 1 |
| **167** | 4,5-Dibromo-2-thienyl | **177a**,**b** | 37 | 4 : 1 |
| **168** | 5-Nitro-2-thienyl | **178a**,**b** | 50 | 1 : 1 |
| **169** | 3-Fu | **179a**,**b** | 61 | 8 : 1 |
| **170** | 3-Th | **180a**,**b** | 63 | 3 : 2 |

wave irradiation for 3 min giving rise to chromene type diastereomeric compounds **142a**,**b** – **158a**,**b** (Scheme 10, Table 4).[71]

This transformation may start with the interaction of the monoterpenoid **131** hydroxy group with the aldehyde to generate hemiacetal **159**. The carbocation **160**, which is formed upon the subsequent Prins type cyclization, reacts with water present in the reaction mixture to give diastereomeric octahydrochromenes.[71] Under these conditions, the nature of the substituent in the aldehyde aromatic ring does not affect significantly the product yields or diastereomer ratio. It can only be noted that the highest yield (86%) is attained in this case for 4-methoxybenzaldehyde (**66**) con-

**Scheme 10**




(*a*) K10 clay, MW (360 W), 3 min; MW is microwave irradiation

taining an electron-donating substituent in the *para*-position.

Later, it has been shown [72] that transformations of this type giving diastereomeric octahydrochromenes can also proceed without microwave assistance, although the reaction time increases in this case to 1 – 2 h (Scheme 11, Table 5). Moreover, in the reaction of (−)-isopulegol (**131**) with furfural (**139**) or 2-thiophenecarbaldehyde (**140**), switching to the microwave-free procedure increases the yields of products **155a**,**b** and **156a**,**b** from 56% and 50% (see Scheme 10) to 86% and 78% (see Scheme 11), respectively.

The reactions of monoterpenoid **131** with substituted heterocyclic aldehydes **161** – **170** proceed in a similar way to give products **171a**,**b** – **180a**,**b** (Scheme 11). The yields decreased in the case of nitro-substituted aldehydes **162** and **168** [72] or dibromo derivative **167**.[73]

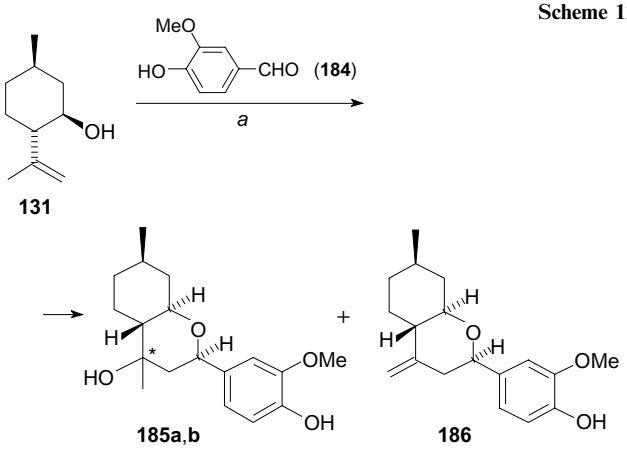
The reactions of (+)-neoisopulegol (**181**), which is isomeric to monoterpenoid **131** in the configuration of hydroxy group, with furfural (**139**) or 2-thiophenecarbaldehyde (**140**) also afforded heterocyclic products **182a**,**b** and **183a**,**b** (isomer ratios 3 : 2 and 1 : 1) with a chromene skeleton.[72] However, in the case of aldehyde **139**, the product yield considerably decreased in comparison with a similar reaction involving (−)-isopulegol (**131**).

An important task of modern pharmacology is to develop new efficient analgesic agents that would not produce adverse effects inherent in the currently used opioid analgesics and non-steroidal anti-inflammatory drugs.[74, 75] Monoterpenoids [76] and phytocannabinoids that combine monoterpene and aromatic moieties in the molecule [77] are promising sources of analgesics with a different mechanism of action. Indeed, study of the analgesic activity of compounds **155**, **156** and **171** – **180** as diastereomer mixtures prepared by the reactions of (−)-isopulegol (**131**) with heterocyclic aldehydes has shown [72] that most compounds exhibit an analgesic activity *in vivo* in the acetic acid-induced writhing test when used in a dose of 10 mg kg$^{-1}$ and compound **156** was also active in the hot plate test. Compound **156** remained active as the dose decreased to 1 mg kg$^{-1}$; its analgesic effect lasted for 24 h after single administration. Furthermore, it possesses low acute toxicity [half-lethal dose ($LD_{50}$) > 4500 mg kg$^{-1}$], which indicates good prospects for its further development as an analgesic agent.[72] Analogous derivative **183**, obtained from (+)-neoisopulegol (**181**), did not show analgesic activity.

Compounds **156a**,**b** and their bromo derivatives **175** – **177** have been assessed for the antiviral activity against the H1N1 influenza virus.[73] A crucial effect of the bromine position in the thiophene ring and the configuration of the carbon atom bearing the hydroxy group on the antiviral activity and cytotoxicity of these compounds was detected. The highest activity was found for compound **175a**, which had the selectivity index (the ratio of the mean toxic dose to the mean effective dose) of 25.

A number of acidic heterogeneous catalysts (metal- and H-modified zeolites and Ce-modified mesoporous silicate material MSM-41) have been tested in the reaction of isopulegol (**131**) with benzaldehyde (**36**), resulting in the formation of octahydrochromenes **142a**,**b**.[78, 79] The studies demonstrated the highest activity for Ce-MCM-41 possessing soft acidity: the selectivity to compound **142** was 83% to 93%, while complete conversion was attained in 1 – 2 h.

**Scheme 12**




(*a*) is acid-activated clay, PhMe, 35 °C

| HCl concentration /mol litre$^{-1}$ | Ratio | |
|---|---|---|
| | **185a** : **185b** | **185a**,**b** : **186** |
| 0.125 | 5.3 | 4.2 |
| 0.25 | 5.5 | 4.1 |
| 0.5 | 5.7 | 3.9 |
| 1.0 | 5.0 | 2.8 |
| 3.0 | 4.7 | 2.5 |

A thorough investigation was carried out for the effect of the structure and acidity of montmorillonite clays on the product ratio in the reaction of isopulegol (**131**) with vanillin (**184**) in toluene, which gives diastereomers **185a**,**b** and dehydration product **186** (Scheme 12).[80, 81] It was found that a higher concentration of HCl, which is used to activate the montmorillonite clay, leads to increasing number of Brønsted acid sites, which increases the contribution of the undesirable dehydration reaction. Also, it was found that the diastereoselectivity to product **185a** with the β-OH group decreases only when 1.0 M or more concentrated HCl is used. In the presence of kaolin clays as catalysts, the reaction rate increases linearly with increasing number of the Brønsted acid sites, so that a 90% selectivity to compounds **185a**,**b** with a diastereomer ratio of 6.8 – 7.0 can be attained.[82]

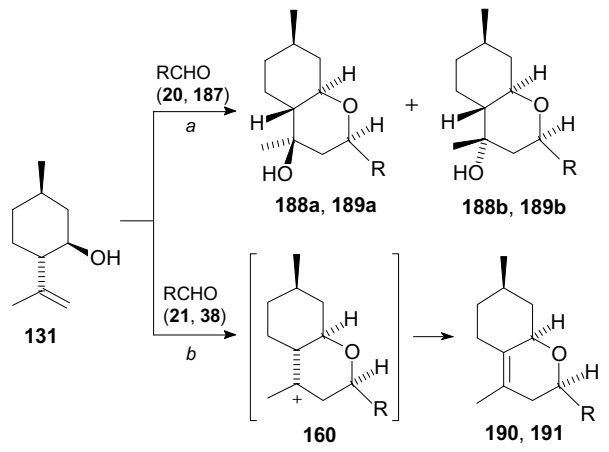
Silica gel-supported *p*-toluenesulfonic acid (TsOH) was used as a catalyst for the reactions of isopulegol (**131**) with aliphatic aldehydes — propanal (**20**) and isobutyraldehyde (**187**). The reactions afforded octahydrochromenes **188a**,**b** and **189a**,**b** in moderate yields and stereoisomer ratios of 4 : 1 and 7 : 1, respectively (Scheme 13).[83]

The reactions of monoterpenoid **131** with aldehydes **21** and **38** carried out in the presence of a Lewis acid ($BF_3 \cdot Et_2O$) at room temperature in benzene follow a different route. In this case, compounds **190** and **191** are formed, probably, as a result of proton elimination from carbocation **160** (see Scheme 13).[84]

The reaction of isopulegol (**131**) with *p*-methoxybenzaldehyde (**66**) in the presence of $I_2$ affords chromene products **144a**,**b** in 5 : 1 ratio (Scheme 14).[85]

In the researchers' opinion, the key step of the reaction is the addition of isopulegol (**131**) hydroxy groups to the aldehyde activated *via* the reaction with $I_2$ to give cation **192** (see Scheme 14). The subsequent transformations can fol-

**Scheme 13**

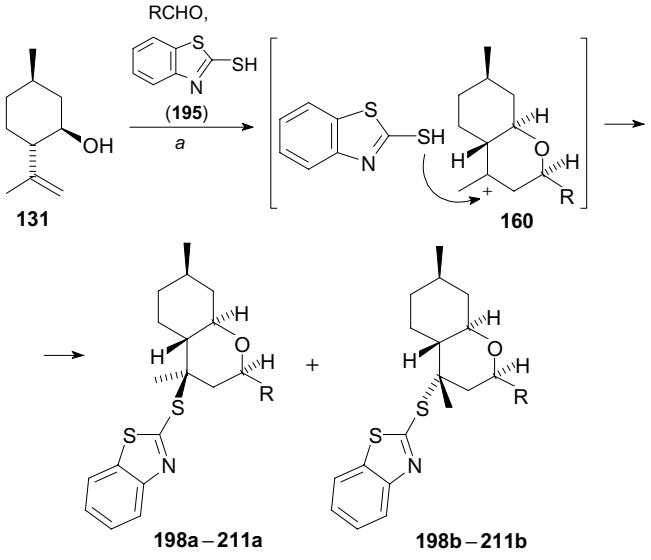



(*a*) $TsOH/SiO_2$; (*b*) $BF_3 \cdot Et_2O$, PhH, rt; R = Et (**20**; **188a**,**b**, 49% yield), $Pr^i$ (**187**; **189a**,**b**, 66%), $Pr^n$ (**21**; **190**, 64%), 4-$BrC_6H_4$ (**38**; **191**, 60%)

low the mechanism depicted in Scheme 10. The similar reaction with an aliphatic ketone [acetone (**193**)] requires somewhat more drastic conditions (refluxing in $CH_2Cl_2$) and stereoselectively gives product **194**.[86]

It has been assumed that the reactions of isopulegol (**131**) with aldehydes in the presence of various acid catalysts involve the formation of carbocation **160** (see Scheme 10). It is reasonable to predict that the introduction of additional nucleophiles into the reaction medium may give rise to octahydrochromenes containing some other heteroatomic substituents instead of the hydroxy group. Indeed, in the presence of a strong Brønsted acid ($HBF_4 \cdot Et_2O$) and S-nucleophile [2-sulfanylbenzothiazole (**195**)], reactions of isopulegol (**131**) with various aldehydes (compounds **6**, **21**, **22**, **36**–**38**, **42**, **43**, **47**, **66**, **139**, **140**, **196** and **197**) resulted in the synthesis of 4-benzothiazolylsulfanyl-substituted octahydrochromenes as mixtures of diastereoisomers (Scheme 15, Table 6).[87] The authors assume that the reaction involves the formation of the already mentioned carbocation **160**, which reacts with a nucleophile (thiol **195**) giving rise to sulfanyl-substituted octahydrochromenes **198a**,**b**–**211a**,**b**. The authors did not detect a significant influence of the nature of substituent in the

**Scheme 15**

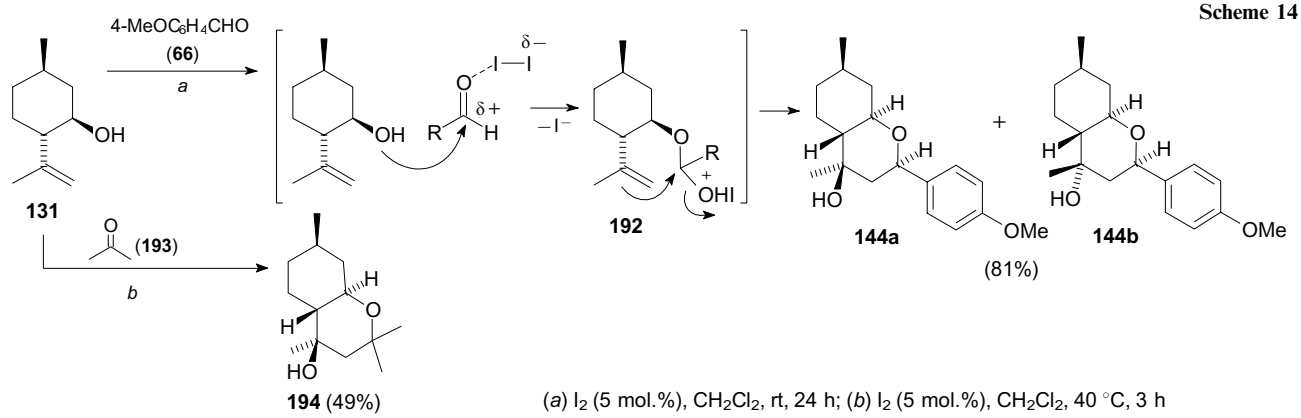



(*a*) $HBF_4 \cdot Et_2O$, $CH_2Cl_2$, 0 °C

**Table 6**. Synthesis of 4-[(benzothiazol-2-yl)sulfanyl]octahydrochromenes from isopulegol (**131**) in the presence of thiol **195** (see Scheme 15).[87]

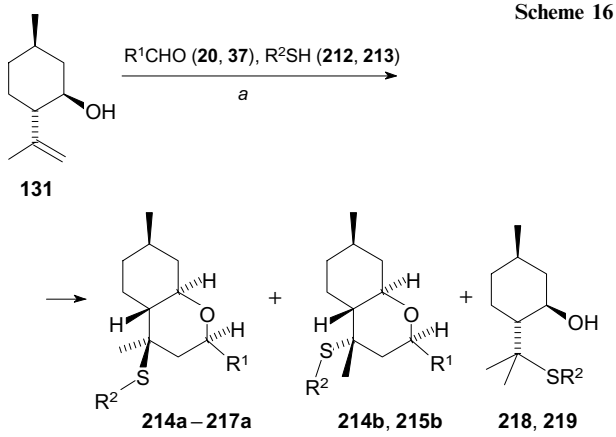
| Aldehyde | R | Products | Yield (%) | Ratio **a** : **b** |
|---|---|---|---|---|
| **6** | $Ph(CH_2)_2$ | **198a**,**b** | 69 | 9 : 1 |
| **21** | $Pr^n$ | **199a**,**b** | 61 | 5 : 1 |
| **22** | $Bu^i$ | **200a**,**b** | 68 | 1 : 1 |
| **36** | Ph | **201a**,**b** | 78 | 3 : 1 |
| **37** | 4-$ClC_6H_4$ | **202a**,**b** | 73 | 5 : 1 |
| **38** | 4-$BrC_6H_4$ | **203a**,**b** | 74 | 5 : 1 |
| **42** | 2-Naph | **204a**,**b** | 75 | 4 : 1 |
| **43** | PhCH=CH | **205a**,**b** | 62 | 5 : 1 |
| **47** | 4-$MeC_6H_4$ | **206a**,**b** | 78 | 6 : 1 |
| **66** | 4-$MeOC_6H_4$ | **207a**,**b** | 80 | 7 : 1 |
| **139** | 2-Fu | **208a**,**b** | 53 | 4 : 1 |
| **140** | 2-Th | **209a**,**b** | 58 | 1 : 1 |
| **196** | Anthracen-9-yl | **210a**,**b** | 70 | 3 : 1 |
| **197** | 3,4-$Cl_2C_6H_3$ | **211a**,**b** | 65 | 4 : 1 |

**Scheme 14**




(*a*) $I_2$ (5 mol.%), $CH_2Cl_2$, rt, 24 h; (*b*) $I_2$ (5 mol.%), $CH_2Cl_2$, 40 °C, 3 h

**Scheme 16**




(*a*) $HBF_4 \cdot Et_2O$ (20 mol.%), $CH_2Cl_2$, 0 °C;
$R^1$ = 4-$ClC_6H_4$ (**37**), Et (**20**); $R^2$ = 4-$ClC_6H_4$ (**212**), 4-$MeC_6H_4$ (**213**);
$R^1$ = 4-$ClC_6H_4$: $R^2$ = 4-$ClC_6H_4$ (**214a**,**b**, 60% yield), 4-$MeC_6H_4$ (**215a**,**b**, 66%); $R^1$ = Et: $R^2$ = 4-$ClC_6H_4$ (**216a**, 50%; **218**, 10%), 4-$MeC_6H_4$ (**217a**, 57%; **219**, 12%)

aldehyde aromatic ring on the reaction diastereoselectivity and product yields.

Apart from 2-sulfanylbenzothiazole (**195**), 4-chloro- (**212**) and 4-methylbenzenethiols (**213**) were used as S-nucleophiles in the reaction of isopulegol (**131**) with 4-chlorobenzaldehyde (**37**) or propanal (**20**).[87] The reaction of isopulegol (**131**) with aromatic aldehyde **37** or thiols **212** and **213** affords thio-substituted diastereomeric octahydrochromenes **214a**,**b** and **215a**,**b** (13 : 1 and 8 : 1 isomer ratios, respectively).[87] The reaction of monoterpenoid **131** with aliphatic aldehyde **20** proceeds stereoselectively giving only diastereomers **216a** and **217a**. However, under these conditions, compounds **218** and **219**, resulting from thiol addition to the double bond of isopulegol (**131**), were isolated as side products (Scheme 16).

In the presence of another strong Brønsted acid — trifluoromethanesulfonic acid (TfOH) — a similar three-component Prins – Ritter reaction takes place, involving isopulegol (**131**), aldehydes **6**, **36** – **38**, **42**, **47**, **48**, **66**, **82**, **138** – **140**, **187** and **197** and acetonitrile (Scheme 17, Table 7).[88]

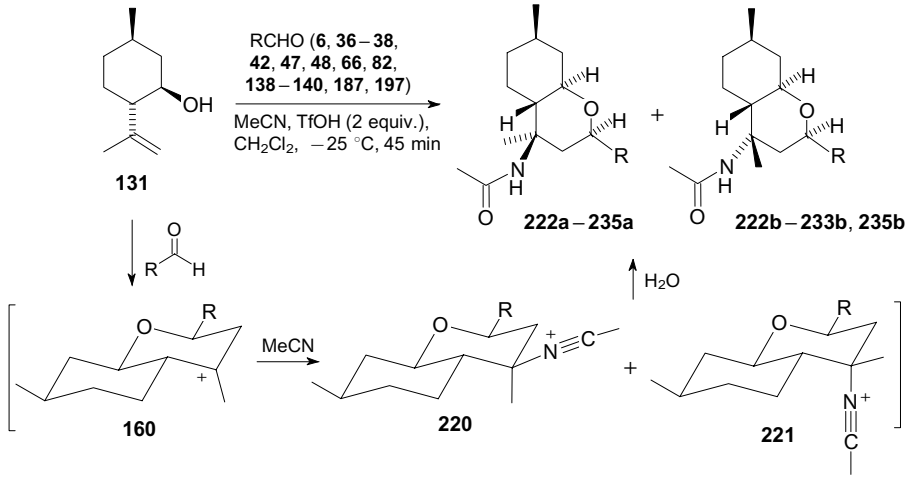
**Table 7**. Synthesis of 4-(acetamido)octahydrochromenes from isopulegol (**131**) in the presence of acetonitrile (see Scheme 17).[88]

| Aldehyde | R | Products | Yield (%) | Ratio **a** : **b** |
|---|---|---|---|---|
| **6** | $Ph(CH_2)_2$ | **222a**,**b** | 60 | 2 : 1 |
| **36** | Ph | **223a**,**b** | 62 | 5 : 1 |
| **37** | 4-$ClC_6H_4$ | **224a**,**b** | 70 | 5 : 1 |
| **38** | 4-$BrC_6H_4$ | **225a**,**b** | 62 | 4 : 1 |
| **42** | 2-Naph | **226a**,**b** | 68 | 4 : 1 |
| **66** | 4-$MeOC_6H_4$ | **227a**,**b** | 76 | 5 : 1 |
| **47** | 4-$MeC_6H_4$ | **228a**,**b** | 72 | 5 : 1 |
| **48** | cyclo-$C_6H_{11}$ | **229a**,**b** | 65 | 3 : 1 |
| **82** | 4-$Pr^iC_6H_4$ | **230a**,**b** | 76 | 4 : 1 |
| **138** | 3-$O_2NC_6H_4$ | **231a**,**b** | 64 | 7 : 2 |
| **139** | 2-Fu | **232a**,**b** | 67 | 3 : 1 |
| **140** | 2-Th | **233a**,**b** | 64 | 7 : 2 |
| **187** | $Pr^i$ | **234a** | 58 | |
| **197** | 3,4-$Cl_2C_6H_3$ | **235a**,**b** | 60 | 5 : 1 |

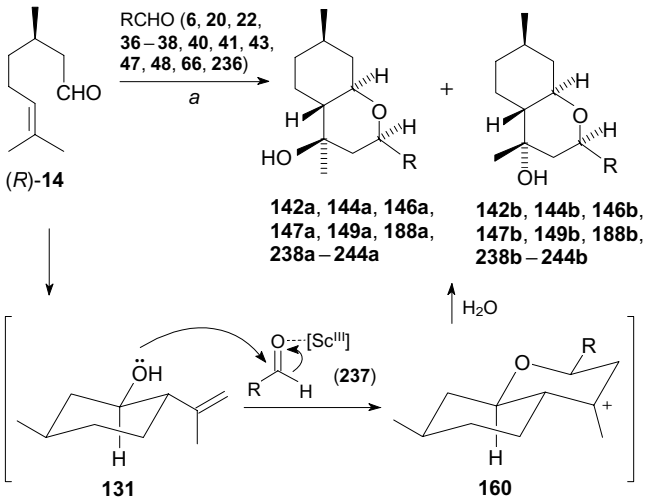
The reaction of carbocation **160** with acetonitrile resulted in the formation of intermediates **220** and **221**, which are hydrolyzed to give 4-(acetamido)octahydrochromenes **222a**,**b** – **233a**,**b**, **234a** and **235a**,**b**. This reaction can proceed for both aromatic aldehydes containing either electron-donating or electron-withdrawing substituents and heterocyclic or aliphatic aldehydes. No substantial effect of the electronic factors on the yields or diastereoselectivity of transformations was found; however, the reaction with isobutyraldehyde (**187**) was stereoselective and gave single 4-(acetamido)octahydrochromene **234a**.

Citronellal (**14**) is known to undergo intramolecular cyclization under acidic conditions to give a mixture of diastereomeric secondary alcohols with the *p*-menthane skeleton. The product ratio depends on the nature of the acid and reaction conditions, with isopulegol (**131**) being usually the major product.[24, 89] In the presence of aldehydes and catalytic amounts of $Sc(OTf)_3$ at −78 °C, (*R*)-citronellal [(*R*)-**14**] cyclizes to isopulegol (**131**), which subsequently reacts with aldehydes, including 1-naphthylcarbaldehyde (**236**). Aldehydes presumably react as complexes **237** to give good yields of the expected chromene type diastereomer mixtures **142a**,**b**, **144a**,**b**, **146a**,**b**, **147a**,**b**, **149a**,**b**, **188a**,**b** and **238a**,**b** – **244a**,**b** (Scheme 18, Table 8).[90] Com-

**Scheme 17**



**Scheme 18**




(*a*) $Sc(OTf)_3$ (5 mol.%), $CH_2Cl_2$, −78 °C → rt, 10 – 14 h

**Table 8**. Synthesis of 4-hydroxyoctahydrochromenes from (*R*)-citronellal [(*R*)-**14**] (see Scheme 18).[90]

| Aldehyde | R | Products | Yield (%) | Ratio **a** : **b** |
|---|---|---|---|---|
| **6** | $Ph(CH_2)_2$ | **238a**,**b** | 90 | 4 : 1 |
| **20** | Et | **188a**,**b** | 90 | 4 : 1 |
| **22** | $Bu^i$ | **239a**,**b** | 86 | 4 : 1 |
| **36** | Ph | **142a**,**b** | 88 | 9 : 1 |
| **37** | $4\text{-}ClC_6H_4$ | **147a**,**b** | 83 | 9 : 1 |
| **38** | $4\text{-}BrC_6H_4$ | **149a**,**b** | 82 | 9 : 1 |
| **40** | $4\text{-}O_2NC_6H_4$ | **240a**,**b** | 76 | 9 : 1 |
| **41** | $2\text{-}O_2NC_6H_4$ | **241a**,**b** | 70 | 9 : 1 |
| **43** | PhCH=CH | **242a**,**b** | 85 | 9 : 1 |
| **47** | $4\text{-}MeC_6H_4$ | **146a**,**b** | 78 | 9 : 1 |
| **48** | cyclo-$C_6H_{11}$ | **243a**,**b** | 88 | 4 : 1 |
| **66** | $4\text{-}MeOC_6H_4$ | **144a**,**b** | 78 | 9 : 1 |
| **236** | 1-Naph | **244a**,**b** | 86 | 9 : 1 |

pounds with the β-OH group were isolated as the major products in all cases; the diastereomer ratio was 4 : 1 to 9 : 1. The reaction time varied from 10 h for benzaldehyde (**36**) to 14 h for 2-nitrobenzaldehyde (**41**). It is noteworthy that the acid-sensitive *trans*-3-phenylprop-2-enal (**43**) can also undergo a similar reaction to give isomeric products **242a**,**b** in 9 : 1 ratio in 85% yield.[90] A possible mechanism of the process includes the cyclization of citronellal [(*R*)-**14**] to give isopulegol (**131**) and the reaction of the latter with the aldehyde to afford intermediate carbocation **160** (see Scheme 18).

A comparison of the yields of 4,7-dimethyloctahydro-2*H*-chromene type products obtained from the monoterpenoids citronellal (**14**) and isopulegol (**131**) using a variety of catalytic systems (Table 9) shows that the application of compound **14** in combination with $Sc(OTf)_3$ at −78 °C is, most often, preferred.

An exception is 4-methoxybenzaldehyde (**66**), which reacts with isopulegol (**131**) in the presence of the H-K10 clay to give octahydrochromenes **144a**,**b** in high yields and with high selectivity. However, it is worth mentioning that

**Table 9**. Comparison of the yields of products formed in the reactions of monoterpenoids **14** and **131** with aldehydes under various conditions.

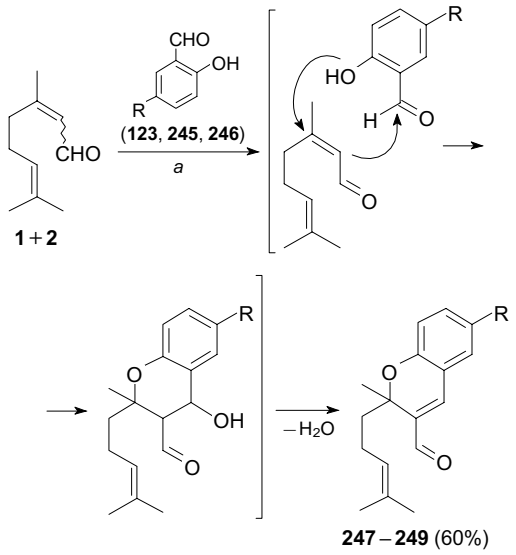
| Aldehyde | R | Products | From citronellal (**14**)[a] | | From isopulegol (**131**) | | |
|---|---|---|---|---|---|---|---|
| | | | yield (%) | **a** : **b** | see[b] | yield (%) | **a** : **b** |
| **20** | Et | **188a**,**b** | 90 | 4:1 | *a* | 49 | 4 : 1 |
| **36** | Ph | **142a**,**b** | 88 | 9:1 | *b* | 76 | 9 : 1 |
| **37** | $4\text{-}ClC_6H_4$ | **147a**,**b** | 83 | 9:1 | *b* | 78 | 5 : 1 |
| **38** | $4\text{-}BrC_6H_4$ | **148a**,**b** | 82 | 9:1 | *b* | 78 | 9 : 1 |
| **66** | $4\text{-}MeOC_6H_4$ | **144a**,**b** | 78 | 9:1 | *b* | 86 | 20 : 1 |
| | | | | | *c* | 81 | 5 : 1 |

[a] Reaction conditions: $Sc(OTf)_3$, $CH_2Cl_2$, −78 °C; [b] conditions: (*a*) $TsOH/SiO_2$, rt; (*b*) H-K10, MW; (*c*) $I_2$, $CH_2Cl_2$, rt.

$Sc(OTf)_3$ is incomparably more expensive than other catalysts.

Under basic conditions in the presence of $Na_2CO_3$, citral comprising a mixture of geranial (**1**) and neral (**2**) undergoes the oxa-Michael reaction with 2-hydroxybenzaldehyde (**123**), 5-chloro-2-hydroxybenzaldehyde (**245**) or 5-bromo-2-hydroxybenzaldehyde (**246**) to afford aromatic 2*H*-chromenes **247** – **249** (Scheme 19).[91,92] It is noteworthy that compounds **247** – **249** have been used to prepare polycyclic chromene derivatives possessing high cytotoxic activity.[92]

**Scheme 19**




(*a*) $Na_2CO_3$, dioxane, $H_2O$, 55 °C, 72 h;
R = H (**123**, **247**), Cl (**245**, **248**), Br (**246**, **249**)

As opposed to isopulegol (**131**), *p*-mentha-1,8-diene-5,6-diol (**250**) prepared by isomerization of verbenol epoxide (**251**) in the presence of various catalysts contains additionally a hydroxy group and a double bond. In the presence of K10 montmorillonite clay, monoterpenoid **250** reacts with aliphatic aldehydes **5**, **21**, **23**, **48**, **63**, **67**, **68**, **187** and **252** – **257**, giving rise to chromene type products **258a**,**b** – **271a**,**b** in moderate yields (Scheme 20,

**Scheme 20**

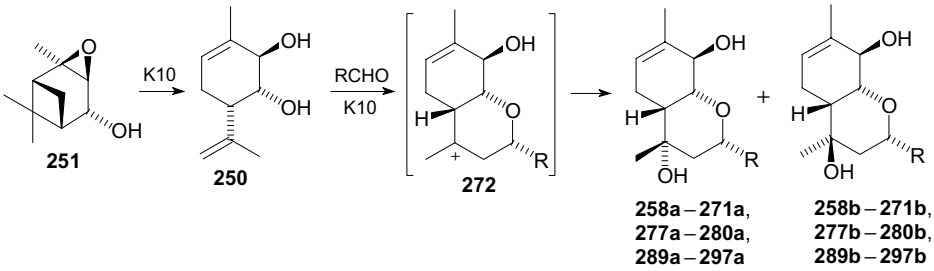



**Table 10**. Synthesis of hexahydrochromenes from diol **250** (see Scheme 20).

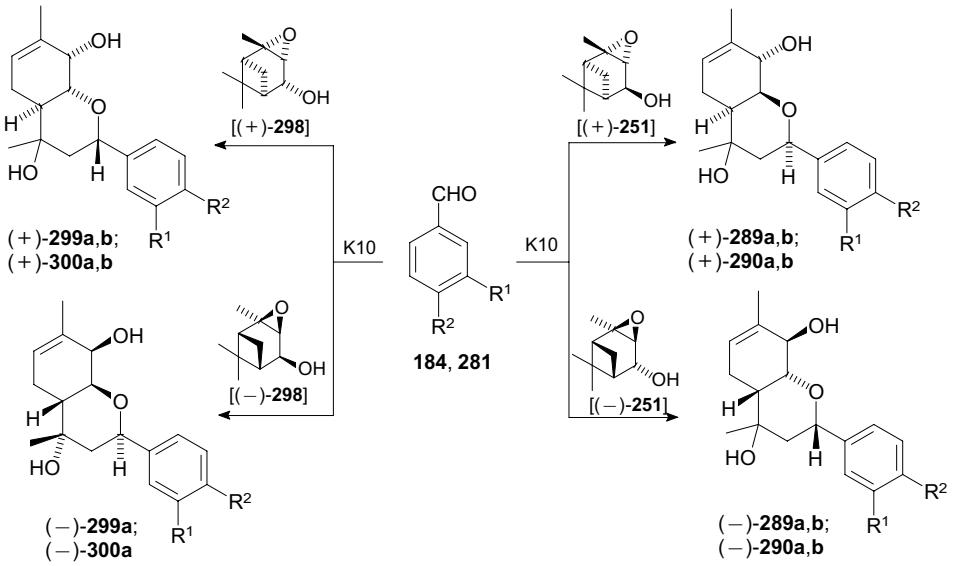
| Aldehyde | R | Products | Yield (%) | Ratio **a** : **b** | Ref. |
|---|---|---|---|---|---|
| **5** | n-$C_9H_{19}$ | **258a**,**b** | 60 | 1 : 1 | 94 |
| **21** | $Pr^n$ | **259a**,**b** | 45 | 1 : 1 | 94 |
| **23** | n-$C_6H_{13}$ | **260a**,**b** | 36 | 1 : 1 | 94 |
| **48** | cyclo-$C_6H_{11}$ | **261a**,**b** | 68 | 1 : 1 | 94 |
| **63** | All | **262a**,**b** | 70 | 2 : 1 | 94 |
| **67** | $CH_2$=CH | **263a**,**b** | 73 | 2 : 1 | 94 |
| **68** | $CH_2$=CMe | **264a**,**b** | 43 | 3 : 1 | 54 |
| **187** | $Pr^i$ | **265a**,**b** | 34 | 1.3 : 1 | 94 |
| **252** | EtCH=CH | **266a**,**b** | 80 | 2.3 : 1 | 94 |
| **253** | $Pr^n$CH=CH | **267a**,**b** | 78 | 2 : 1 | 94 |
| **254** | n-$C_5H_{11}$CH=CH | **268a**,**b** | 54 | 2.3 : 1 | 94 |
| **255** | n-$C_5H_{11}$CH=CHCH=CH | **269a**,**b** | 57 | 3 : 1 | 94 |
| **256** | n-$C_5H_{11}$ | **270a**,**b** | 59 | 1 : 1 | 94 |
| **257** | n-$C_7H_{15}$ | **271a**,**b** | 77 | 1 : 1 | 94 |
| **273** | 3,4,5-$(MeO)_3C_6H_2$ | **277a**,**b** | 39 | 3 : 2 | 95 |
| **274** | 2,3,4-$(MeO)_3C_6H_2$ | **278a**,**b** | 39 | 1 : 1 | 95 |
| **275** | 2,4,5-$(MeO)_3C_6H_2$ | **279a**,**b** | 39 | 2 : 1 | 95 |
| **276** | 2,4,6-$(MeO)_3C_6H_2$ | **280a**,**b** | 14 | 3 : 1 | 95 |
| **184** | 3-MeO-4-$HOC_6H_3$ | **289a**,**b** | 50 | 3 : 1 | 96 |
| **281** | 3-HO-4-$MeOC_6H_3$ | **290a**,**b** | 29 | 5 : 1 | 97 |
| **282** | 3,4-$(MeO)_2C_6H_3$ | **291a**,**b** | 42 | 3 : 1 | 96 |
| **283** | 3,4-$(HO)_2C_6H_3$ | **292a**,**b** | 43 | 5 : 2 | 96 |
| **284** | 2-HO-5-$MeOC_6H_3$ | **293a**,**b** | 38 | 3 : 1 | 96 |
| **285** | 3-MeO-4-$Bu^nOC_6H_3$ | **294a**,**b** | 56 | 2 : 1 | 96 |
| **286** | 3-MeO-4-(n-$C_6H_{13}O$)$C_6H_3$ | **295a**,**b** | 51 | 4 : 1 | 96 |
| **287** | 3,5-$(MeO)_2$-4-$HOC_6H_2$ | **296a**,**b** | 26 | 2 : 1 | 96 |
| **288** | 4-$MeSC_6H_4$ | **297a**,**b** | 32 | 1 : 1 | 96 |

Table 10).[54,93] Exceptions are reactions with saturated aldehydes such as heptanal (**23**) and isobutyraldehyde (**187**) in which the product yields are $<40\%$.[54,94] When α,β-unsaturated aldehydes are used, the isomer with the α-configured OH group is formed predominantly, whereas reactions with saturated aldehydes afford equal amounts of diastereomers. Most likely, the reaction involves the formation of carbocation **272** (see Scheme 20), which is similar to cation **160** generated from isopulegol (**131**) (see Scheme 10). An analgesic activity assay of these products *in vivo* in 10 mg $kg^{-1}$ dose revealed several compounds promising for further evaluation; the highest activity was found for **258a**,**b**, **262a**,**b** and **263a**,**b**, obtained by reactions of diol **250** with decanal (**5**), butenal **63** and propenal **67**, respectively.[94]

The reactions of diol **250** with trimethoxybenzaldehydes **273** – **276** have been investigated (see Scheme 20, Table 10).[95] As in the case of aliphatic aldehydes, chromenes **277a**,**b** – **280a**,**b** are formed as the major products in these reactions, their yields being ~40%; an exception is the spatially most hindered aldehyde **276**. (The structures of minor products of these reactions are discussed below.) As has already been noted, diol **250** is formed upon isomerization of (−)-*cis*-verbenol epoxide (**251**); therefore, compounds **277a**,**b** – **280a**,**b** can also be prepared from epoxide **251**, but in lower yields (11% – 25%), as a result of competing isomerization of the starting epoxide to cyclopentane-based products.[95] Compound **278a**,**b** (as a mixture of diastereomers) exhibited high analgesic activity in the acetic acid-induced writhing test in a dose of 10 mg $kg^{-1}$; the other representatives of this series were inactive.[95]

Clay-catalyzed reactions of *p*-mentha-1,8-diene-5,6-diol (**250**) with substituted aromatic aldehydes **184**, **281** – **288** containing various electron-donating substituents resulted

**Scheme 21**




$R^1$ = OMe, $R^2$ = OH (**184**, **289a**,**b**; **299a**,**b**); $R^1$ = OH, $R^2$ = OMe (**281**, **290a**,**b**; **300a**,**b**); for (+)-isomers: β-OH (**a**), α-OH (**b**); for (−)-isomers: α-OH (**a**), β-OH (**b**)

in the synthesis of a variety of hexahydrochromene derivatives — compounds **289a**,**b** – **297a**,**b** (see Scheme 20).[96, 97] Generally, the yields of the reaction products ranging from 26% to 56% were not affected significantly by the substituents in the aldehyde aromatic ring.

An analgesic activity assay by the acetic acid-induced writhing test and the hot plate test in animals has identified compounds **289a**,**b** and **290a**,**b**, containing hydroxy and methoxy groups in the aromatic moiety, as most efficient in both tests. Their efficiency was comparable with the efficiency of the reference agent (diclofenac), while their acute toxicity was markedly lower. A study of the mechanism of action of these compounds gave unexpected results: the mechanism of analgesic action was found to crucially depend on the mutual positions of the hydroxy and methoxy groups in the aromatic substituent of compounds **289a**,**b** and **290a**,**b**.[98] Actually, in the case of compound **289**, the analgesic effects involved the opioid and dopaminergic systems, whereas in compound **290**, the cannabinoid and adrenergic systems were significant.

In order to establish the influence of the relative and absolute configurations of compounds **289a**,**b** and **290a**,**b** on their analgesic activity, stereoisomers have been synthesized. Vanillin (**184**) and isovanillin (**281**) were reacted with isomeric verbenol epoxides (+)-**251** and (−)-**251**, (+)-**298** and (−)-**298**, obtained from (+)- and (−)-α-pinenes (**79**), respectively[99] (Scheme 21).[100]

According to analgesic activity assays of compounds **289a**,**b**, **290a**,**b**, **299a**,**b** and **300a**,**b** and single diastereomers **289a**, **289b**, **290a** and **290b**, both diastereomers make a contribution to the pain relieving effect in the case of **289**. For isovanillin derivatives **290a**,**b**, the effect is mainly caused by isomer **290a**. For other stereoisomers, the absolute configuration and either *cis*- or *trans*-positions of vicinal oxygen atoms in the hexahydrochromene skeleton had no influence on the analgesic activity.

The reactions of diol **250** with benzaldehyde (**36**) and 4-alkyl-substituted aromatic aldehydes **47**, **82** and **301** – **303** in the presence of the K10 clay have served for the preparation of a series of heterocyclic compounds **304a**,**b** – **309a**,**b** with the chromene skeleton (Scheme 22, Table 11).[101] It was found that the introduction of small alkyl groups into the aromatic ring of the aldehyde leads to increasing yield of hexahydrochromenes in comparison with that obtained for benzaldehyde (**36**). Meanwhile, in the presence of a branched isopropyl substituent or longer (butyl or octyl) carbon chains in the aldehyde, the yields of

**Scheme 22**

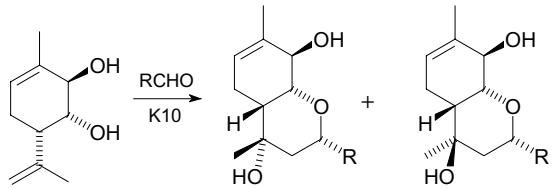



**Table 11**. Synthesis of hexahydrochromenes from diol **250** (see Scheme 22).

| Aldehyde | R | Products | Yield (%) | Ratio **a** : **b** | Ref. |
|---|---|---|---|---|---|
| **36** | Ph | **304a**,**b** | 43 | 1 : 1 | 101 |
| **47** | 4-$MeC_6H_4$ | **305a**,**b** | 70 | 1 : 1 | 101 |
| **82** | 4-$Pr^iC_6H_4$ | **306a**,**b** | 56 | 3 : 1 | 101 |
| **301** | 4-$EtC_6H_4$ | **307a**,**b** | 70 | 1 : 1 | 101 |
| **302** | 4-$Bu^nC_6H_4$ | **308a**,**b** | 52 | 2.5 : 1 | 101 |
| **303** | 4-(n-$C_8H_{17}$)$C_6H_4$ | **309a**,**b** | 42 | 2 : 1 | 101 |
| **140** | 2-Th | **310a**,**b** | 41 | 3.3 : 1 | 102 |
| **163** | 5-Methyl-2-thienyl | **311a**,**b** | 54 | 2.8 : 1 | 102 |
| **164** | 3-Methyl-2-thienyl | **312a**,**b** | 55 | 2.2 : 1 | 102 |
| **165** | 5-Bromo-2-thienyl | **313a**,**b** | 47 | 1.3 : 1 | 102 |
| **166** | 4-Bromo-2-thienyl | **314a**,**b** | 51 | 1 : 1 | 102 |
| **168** | 5-Nitro-2-thienyl | **315a**,**b** | 38 | 1.3 : 1 | 102 |

the target products decrease. The increase in the length of the alkyl chain promoted the predominant formation of the stereoisomer with the α-4-OH group. It is worth noting that in the presence of alkyl groups in position 4 of the aromatic ring, the analgesic activity, which has been observed for compound **304** obtained from benzaldehyde (**36**), disappears irrespective of the length and branching of the aliphatic group.

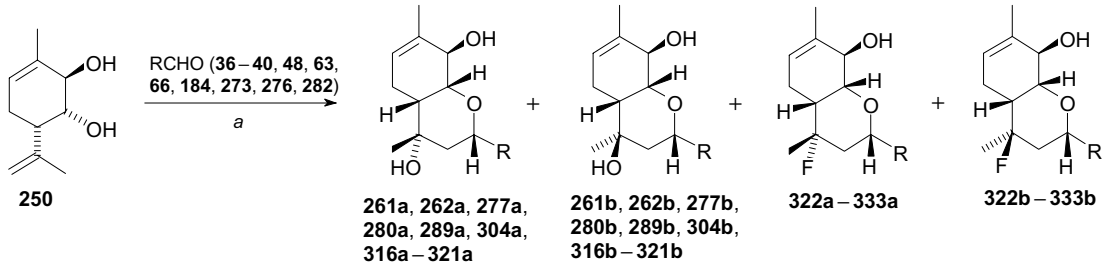
The reactions of monoterpenoid **250** with heteroaromatic aldehydes **140**, **163** – **166** and **168** catalyzed by the K10 montmorillonite clay give lower yields than analogous reactions of isopulegol (**131**) (see Scheme 11).[72] The reaction products **310a**,**b** – **315a**,**b** are formed in moderate yields (see Scheme 22 and Table 11).[102] Compound **310** containing an unsubstituted thiophene ring did not show analgesic activity, unlike compound **156** obtained from isopulegol (**131**).[72] Meanwhile, compounds **313** and **314** containing a bromine atom in the heteroaromatic moiety, when used in 10 mg $kg^{-1}$ doses, exhibited an analgesic effect in the hot plate test, but were inefficient in the acetic acid-induced writhing test.[102] Note that compound **315** containing a nitro group was, conversely, active in the acetic acid-induced writhing test, but showed no analgesic effect in the hot plate test. When the bromine atom in position 5 of the thiophene ring (compound **313**) was replaced by a methyl group (compound **311a**,**b**), hyperalgesia was observed instead of the analgesic effect.

A catalyst frequently used in the reactions of monoterpenoids with aldehydes is $BF_3 \cdot Et_2O$ (see Schemes 4, 6 and 13).[28, 44, 57, 84] It has been shown[103] that the $BF_3 \cdot Et_2O$ – $H_2O$ system employed in the reaction of diol **250** with aromatic and aliphatic aldehydes leads to the formation of not only hydroxyl-containing products **261a**,**b**, **262a**,**b**, **277a**,**b**, **280a**,**b**, **289a**,**b**, **304a**,**b** and **316a**,**b** – **321a**,**b**, but also fluorinated hexahydrochromenes **322a**,**b** – **333a**,**b** in 34% to 70% yields (Scheme 23, Table 12). Fluorination apparently proceeds as described for the reactions of isopulegol (**131**) with nucleophiles (see Schemes 15 – 17): in the first step, carbocation **272** is formed (see Scheme 20), which then reacts with the fluoride ion generated upon the reaction of $BF_3 \cdot Et_2O$ with water.[103]

The products are formed as mixtures of diastereomers, the 4*S* diastereomer with the α-OH group being the major component for hydroxyl-containing products and the 4*R* diastereomer predominating for fluorinated products.[103]

High virus virulence and ability to develop resistance to available drugs makes the search for antiviral agents of new structural types an important and relevant task.[104] Compounds exhibiting high antiviral activity were also detected among monoterpenoid derivatives.[5, 105, 106] A large range of hexahydrochromene type products containing a fluorine atom or a hydroxy group, which were prepared by reactions of diol **250** with aromatic aldehydes, were tested for the influenza antiviral activity against H1N1.[107] Indeed, some of these compounds showed a high antiviral activity. Note that the nature of the introduced substituent (fluorine atom or hydroxy group) had a considerable influence on the antiviral effect. Indeed, compound **316a**,**b** containing a chlorine atom in the aromatic ring proved to be most active among hydroxyl-containing products, while compound **332a**,**b** with three methoxy groups proved to be most active among products with a fluorine atom. Combination of high activity and low cytotoxicity of compound **332a**,**b** resulted in a high selectivity index of 55.

**Scheme 23**




(*a*) $BF_3 \cdot Et_2O$, $H_2O$, $CH_2Cl_2$, 2 °C, 8 – 72 h

**Table 12**. Synthesis of 4-substituted hexahydrochromenes from diol **250** (see Scheme 23).[103]

| Aldehyde | R | Diols | Yield (%) | Ratio **a** : **b** | Fluorides | Yield (%) | Ratio **a** : **b** |
|---|---|---|---|---|---|---|---|
| **36** | Ph | **304a**,**b** | 24 | 3 : 1 | **322a**,**b** | 55 | 1 : 7 |
| **37** | 4-$ClC_6H_4$ | **316a**,**b** | 17 | 3 : 1 | **323a**,**b** | 58 | 1 : 6 |
| **38** | 4-$BrC_6H_4$ | **317a**,**b** | 13 | 2 : 1 | **324a**,**b** | 60 | 1 : 10 |
| **39** | 4-$FC_6H_4$ | **318a**,**b** | 17 | 2 : 1 | **325a**,**b** | 47 | 1 : 6 |
| **40** | 4-$O_2NC_6H_4$ | **319a**,**b** | 17 | 1 : 1 | **326a**,**b** | 53 | 1 : 12 |
| **48** | cyclo-$C_6H_{11}$ | **261a**,**b** | 27 | 3 : 1 | **327a**,**b** | 61 | 1 : 3 |
| **63** | All | **262a**,**b** | 20 | 2 : 1 | **328a**,**b** | 57 | 1 : 3 |
| **66** | 4-$MeOC_6H_4$ | **320a**,**b** | 24 | 4 : 1 | **329a**,**b** | 34 | 1 : 4 |
| **184** | 4-HO-3-$MeOC_6H_3$ | **289a**,**b** | 35 | 3 : 1 | **330a**,**b** | 60 | 1 : 1 |
| **273** | 3,4,5-$(MeO)_3C_6H_2$ | **277a**,**b** | 7 | 3 : 2 | **331a**,**b** | 70 | 1 : 4 |
| **276** | 2,4,6-$(MeO)_3C_6H_2$ | **280a**,**b** | 35 | 1 : 1 | **332a**,**b** | 42 | 1 : 10 |
| **282** | 3,4-$(MeO)_2C_6H_3$ | **321a**,**b** | 20 | 5 : 1 | **333a**,**b** | 35 | 1 : 3 |

Thus, compounds with the polyhydro-2*H*-chromene skeleton are obtained, most often, from (−)-isopulegol (**131**) or from monoterpenoids with a similar structure, which contain an exocyclic double bond and a hydroxy group in the homoallylic position. Under acid catalysis, these monoterpenoids can react with the aldehyde carbonyl group owing to the presence of the hydroxy group. The subsequent carbocyclization and formation of a six-membered heterocycle are enabled by the presence of the double bond in position 3 to the hydroxy group (see Scheme 10). The addition of a nucleophile to the reaction mixture can be used to introduce the acetamide or thioester group or a fluorine atom into the product.

### 3.3. Compounds with the benzodioxine skeleton

(−)-*cis*-Verbenol epoxide (**251**) reacts with butenal (**63**) and aromatic aldehydes **36** – **40**, **66**, **123**, **197** and **334** – **336** in the presence of montmorillonite clay to afford heterocyclic products **337** – **348** with the benzodioxine skeleton (Scheme 24, Table 13).[54, 108] When a substituent was present in the *meta*-position of the aromatic ring of the aldehyde (compounds **197**, **335** and **336**) and when butenal (**63**) or 4-(trifluoromethyl)benzaldehyde (**334**) was used, products **262a**,**b**, **349a**,**b** – **352a**,**b** with the hexahydro-2*H*-chromene skeleton were also isolated from the reaction mixture.[54, 109] The main cause for the low yield of benzodioxines is the formation of epoxide **251** isomerization products — hydroxy ketone **353** and diol **250**, which may subsequently react with aldehydes to give chromenes.

A possible mechanism of formation of benzodioxines **337** – **348** includes protonation and opening of the epoxide ring in monoterpenoid **251** to give cation **354**, which then rearranges to cation **355** with the *p*-menthane skeleton. The reaction of this cation with the aldehyde and the subsequent heterocyclization of intermediate **356** afford benzodioxine products (see Scheme 24).[54]

The analgesic activity assay of obtained compounds demonstrated that most of derivatives with the benzodioxine skeleton used in a 10 mg $kg^{-1}$ dose exhibit high analgesic activity.[109] Among the tested compounds, benzodioxines **338** and **341** containing a chlorine atom or a nitro group in the aromatic ring *para*-position are most promising.

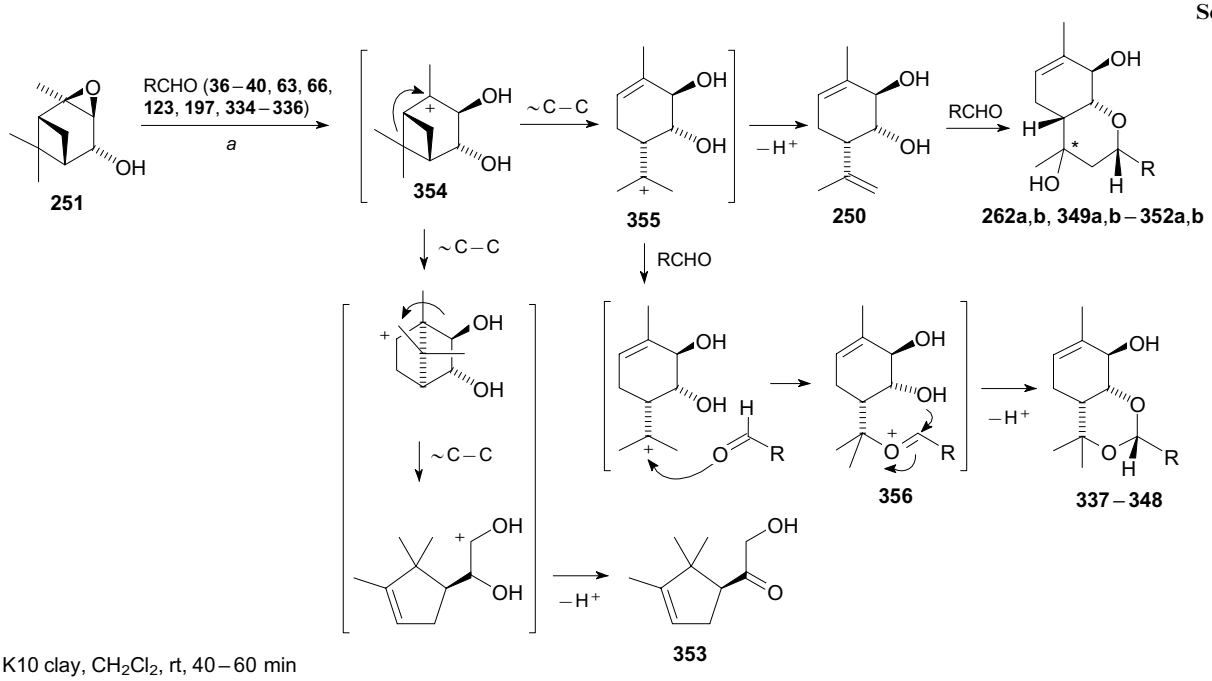
**Table 13**. Products of reactions of (−)-*cis*-verbenol epoxide (**251**) with aldehydes in the presence of clay (see Scheme 24).[54, 109]

| Aldehyde | R | Products [yield (%)] |
|---|---|---|
| **36** | Ph | **337** (46) |
| **37** | 4-$ClC_6H_4$ | **338** (8) |
| **38** | 4-$BrC_6H_4$ | **339** (6) |
| **39** | 4-$FC_6H_4$ | **340** (15) |
| **40** | 4-$O_2NC_6H_4$ | **341** (5) |
| **63** | All | **342** (16) + **262a**,**b** (14) |
| **66** | 4-$MeOC_6H_4$ | **343** (13) |
| **123** | 2-$HOC_6H_4$ | **344** (4) |
| **197** | 3,4-$Cl_2C_6H_3$ | **345** (29) + **349a**,**b** (37) |
| **334** | 4-$F_3CC_6H_4$ | **346** (21) + **350a**,**b** (18) |
| **335** | 3-$ClC_6H_4$ | **347** (11) + **351a**,**b** (37) |
| **336** | 3-$FC_6H_4$ | **348** (10) + **352a**,**b** (28) |

A study of the effects of various modified β-zeolites on the yield of benzodioxine **337** (see Scheme 24) in the reaction of (−)-*cis*-verbenol epoxide (**251**) with benzaldehyde (**36** ) has shown the possibility to increase the yield of this product by modification of the heterogeneous acid catalyst.[110] The zeolite Fe-H-β-150 as the catalyst and a fivefold excess of benzaldehyde (**36**) in toluene at 70 °C were found to be the reaction conditions of choice. The selectivity to product **337** was 46 mol.% for complete conversion of monoterpenoid **251**. The authors attributed the increase in the selectivity to increase in the number of Lewis acid sites on going from the zeolite H-β-150 to the iron analogue Fe-H-β-150.[110]

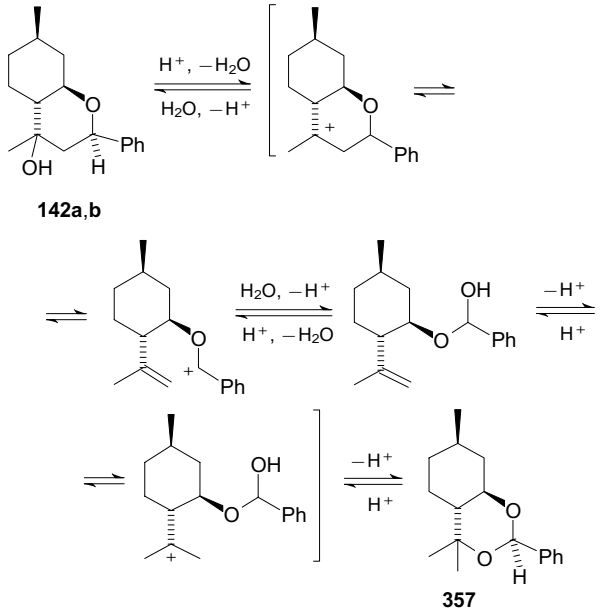
It has been shown that octahydrochromenes **142a**,**b** formed in the reaction of isopulegol (**131**) with benzaldehyde (**36**) can be converted to compound **357** with the benzodioxine skeleton (Scheme 25).[79] The rearrangement is catalyzed by the mesoporous silicate material

**Scheme 24**




(*a*) K10 clay, $CH_2Cl_2$, rt, 40 – 60 min

**Scheme 25**




Ce-MCM-41; the highest selectivity to compound **357** was 36% for the reaction time of 30 min.

### 3.4. Formation of compounds with the isobenzofuran skeleton

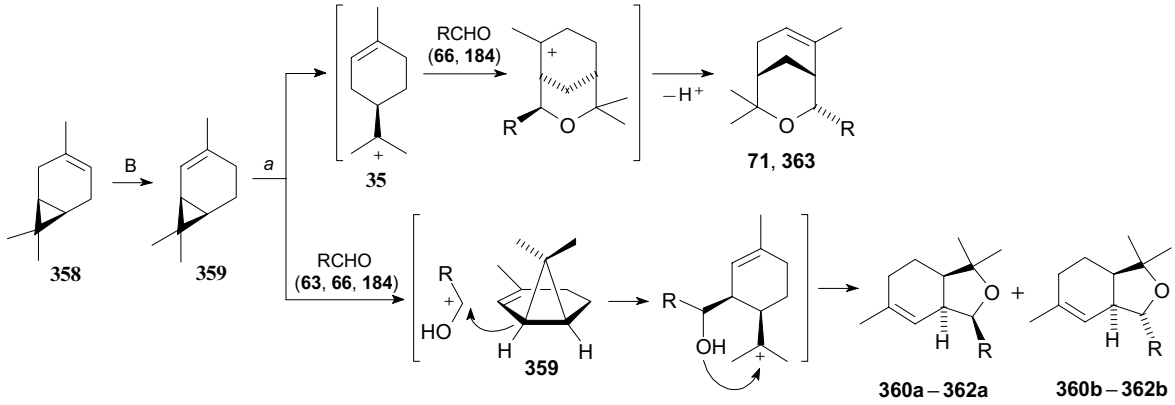
(+)-3-Carene (**358**) (Scheme 26) is abundant in turpentine from pine trees and is highly optically pure.[46] Although the isomeric (+)-2-carene (**359**) is also frequently encountered in nature, its content in essential oils is usually very low[111] and isolation of (+)-2-carene (**359**) from the oils is a challenge. (+)-2-Carene (**359**) can be obtained by keeping (+)-3-carene (**358**) with strong bases (B) at high temperature (under these conditions, an equilibrium mixture of 2- and 3-carenes in ~2 : 3 ratio is formed)[112] or by treating (+)-3-carene (**358**) with acid-activated illite clay.[113] Further isolation of single 2-carene (**359**) is performed in a distillation column.

(+)-2-Carene (**359**) reacts with butenal (**63**) in the presence of the K10 clay for 3 days to give products **360a**,**b** with the isobenzofuran skeleton and with 1 : 1 diastereomer ratio (see Scheme 26).[114] The possible mechanism of formation of compounds **360a**,**b** includes the attack by the protonated aldehyde on the cyclopropane moiety of compound **359** and subsequent intramolecular heterocyclization. Note that the reaction with an aldehyde under these conditions gives the product of attack by the protonated aldehyde only on the cyclopropane moiety, but not on the C=C double bond of monoterpene **359**. The *cis*-fusion of the rings in compounds **360a**,**b** was also unexpected. According to Il'ina *et al.*,[114] a possible explanation to this fact is adsorption of 2-carene (**359**) and aldehyde on closely located catalytic sites, for example, in the interlayer space of clay, which precludes the attack that would lead to the product with *trans*-fused rings.

The reaction of 2-carene (**359**) with 4-methoxybenzaldehyde (**66**) or vanillin (**184**) in the presence of the K10 clay gives isobenzofurans **361a**,**b** and **362a**,**b** and 3-oxabicyclo[3.3.1]nonane type compounds **71** and **363** as the minor products (see Scheme 26).[114] Products **71** and **363** are evidently formed *via* the same *p*-menthane type intermediate cation **35** as the products of reactions of other monoterpenoids (see Scheme 4). It is noteworthy that the use of 2- and 3-carenes in 2 : 3 ratio (instead of single 2-carene) in the clay-catalyzed reactions with aldehydes **66** and **184** leads to increasing yields of isobenzofuran products to 88% and 52%, respectively.[114] A study of the physiological activity of these isobenzofurans has shown that compound **362** obtained by the reaction of 2-carene (**359**) with 4-hydroxy-3-methoxybenzaldehyde (**184**) shows a considerable neuroprotective activity *in vivo* on the MPTP neurotoxin induced Parkinson's disease model.[115]

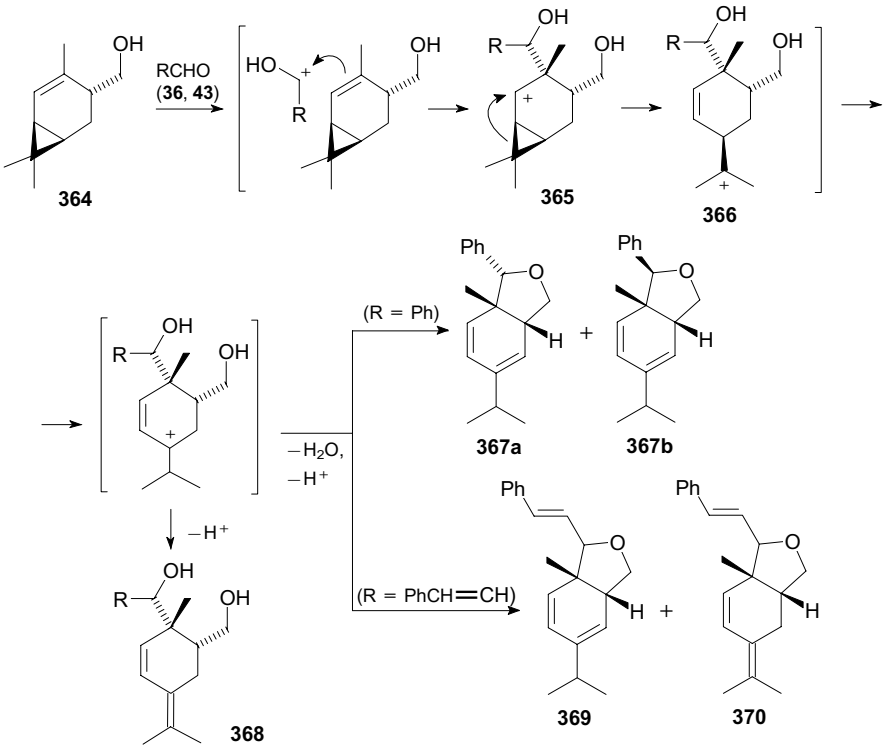
*trans*-4-Hydroxymethyl-2-carene (**364**), which has been synthesized from (+)-3-carene (**358**) and formaldehyde,[116] also reacts with benzaldehyde (**36**) to give isobenzofuran type products, but with different positions of substituents. The reaction evidently starts with the attack by the protonated aldehyde on the double bond of monoterpenoid, by analogy with the Prins reaction (Scheme 27).[38] Carane type carbocation **365** formed in the first step is first isomerized, and the subsequent heterocyclization of *p*-menthane type cation **366** yields isobenzofurans **367a**,**b**. Also, alcohol **368** was isolated from the reaction mixture, which confirmed the proposed mechanism. The double bond insertion between the aldehyde group and the phenyl substituent in the 3-phenylpropenal (**43**) molecule furnished only isobenzofuran products **369** and **370**.[117]

**Scheme 26**




(*a*) K10 clay, $CH_2Cl_2$, rt, 3 days; R = All (**63**; **360a**,**b**, 23% yield), 4-$MeOC_6H_4$ (**66**; **361a**,**b**, 31%; **71**, 5%), 4-HO-3-$MeOC_6H_3$ (**184**; **362a**,**b**, 33%; **363**, 5%)

**Scheme 27**



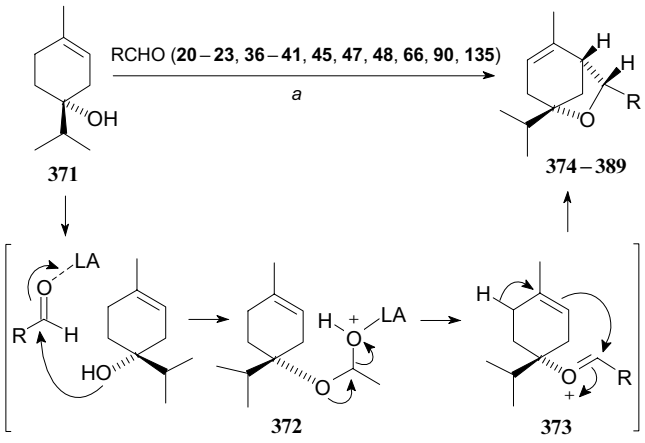

(*a*) Clay, $CH_2Cl_2$, rt, 30 – 50 min; R = Ph (**36**; **367a**, 8% yield; **367b**, 6%; **368**, 34%), PhCH═CH (**43**; **369**, 57%; **370**, 15%)

### 3.5. Compounds with the 6-oxabicyclo[3.2.1]oct-2-ene skeleton

4-Terpineol (**371**) is less abundant in nature than isomeric α-terpineol (**77**); it is present in the essential oils of the plants *Alpina zerumbet*, *Tanacetum cadmeum* and *Melaleuca alternifolia*.[118] The reactions of monoterpenoid **371** with aldehydes **20** – **23**, **36** – **41**, **45**, **47**, **48**, **66**, **90** and **135** are catalyzed by Lewis acids (Scheme 28).[119] Among the catalysts used [$BF_3 \cdot Et_2O$, $Sc(OTf)_3$, $In(OTf)_3$, $Bi(OTf)_3$, $InCl_3$], the best results were obtained for $In(OTf)_3$ and dichloromethane proved to be the best solvent.

It has been assumed[119] that aldehyde reacts initially with the Lewis acid, which facilitates the nucleophilic attack by the hydroxy group to give hemiacetal **372**, which is then converted to oxonium ion **373** (see Scheme 28, Table 14). Then the intermediate oxonium ion undergoes cyclization to give 6-oxabicyclo[3.2.1]octene products **374** – **389**. The yield of heterocyclic products in the reactions of compound **371** with aliphatic aldehydes was noticeably higher than that for aromatic aldehydes. Electron-withdrawing substituents in the aromatic ring lead to decreasing yields. The observed trends are attributable to stabilization of the oxonium ion **373** caused by the electron-donating effect of aliphatic groups or substituents in the aromatic ring.

**Scheme 28**

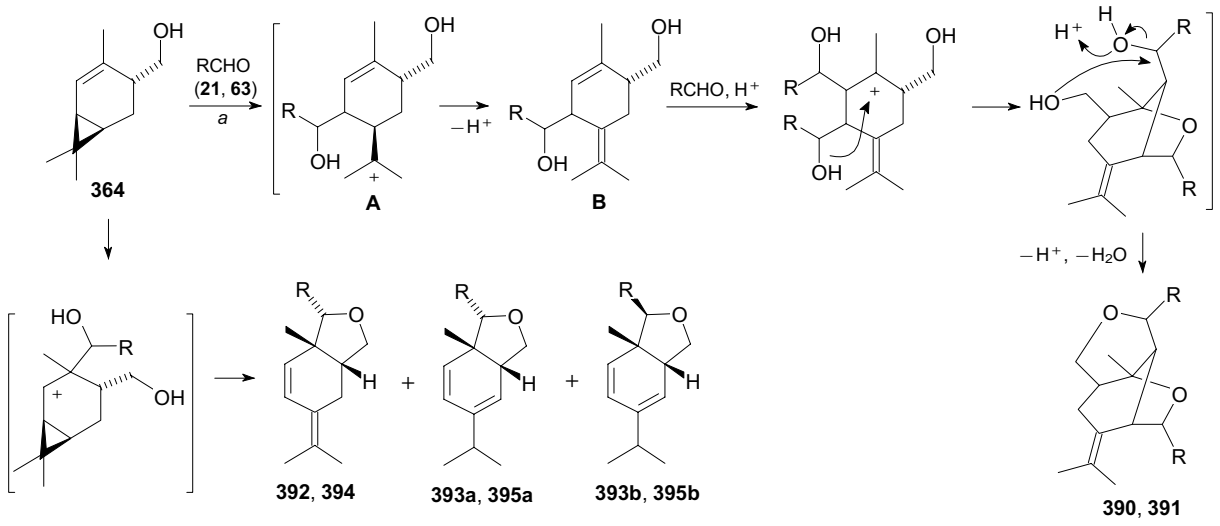



(*a*) $In(OTf)_3$, $CH_2Cl_2$, 0 °C → rt, 5 – 8 h; LA is Lewis acid

**Table 14**. Synthesis of 6-oxabicyclo[3.2.1]oct-2-ene type compounds from 4-terpineol (**371**) (see Scheme 28).[119]

| Aldehyde | R | Product | Yield (%) |
|---|---|---|---|
| **20** | Et | **374** | 94 |
| **21** | $Pr^n$ | **375** | 92 |
| **22** | $Bu^i$ | **376** | 88 |
| **23** | n-$C_6H_{13}$ | **377** | 85 |
| **36** | Ph | **378** | 75 |
| **37** | 4-$ClC_6H_4$ | **379** | 68 |
| **38** | 4-$BrC_6H_4$ | **380** | 65 |
| **39** | 4-$FC_6H_4$ | **381** | 66 |
| **40** | 4-$O_2NC_6H_4$ | **382** | 62 |
| **41** | 2-$O_2NC_6H_4$ | **383** | 64 |
| **45** | 4-$MeO_2CC_6H_4$ | **384** | 60 |
| **47** | 4-$MeC_6H_4$ | **385** | 82 |
| **48** | cyclo-$C_6H_{11}$ | **386** | 84 |
| **66** | 4-$MeOC_6H_4$ | **387** | 80 |
| **90** | Bn | **388** | 82 |
| **135** | 3-$BrC_6H_4$ | **389** | 64 |

**Scheme 29**



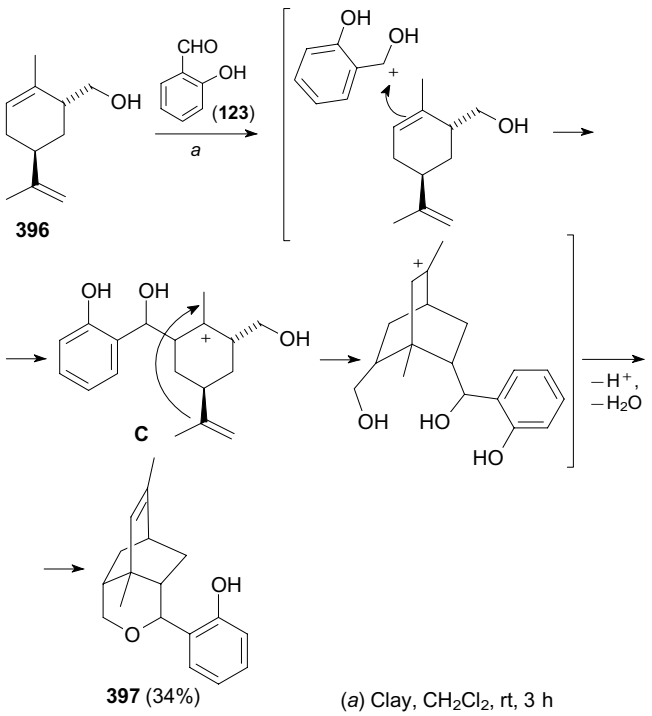

(*a*) Clay, $CH_2Cl_2$, rt, 30 min; R = $Pr^n$ (**21**; **390**, 51% yield; **392**, 23%; **393a**, 9%; **393b**, 9%), All (**63**; **391**, 16%; **394**, 30%; **395a**, 8%; **395b**, 4%)

## 4. Tricyclic products of reactions of monoterpenoids with carbonyl compounds

The reactions of *trans*-4-hydroxymethyl-2-carene (**364**) with aliphatic aldehydes — butanal (**21**) and butenal (**63**) — in the presence of montmorillonite clay afford tricyclic compounds **390** and **391** in 51% and 16% yields, respectively (Scheme 29).[38] The reaction is accompanied by the formation of isobenzofuran products **392** – **395**; the possible reaction mechanism is shown in Scheme 27. Presumably, the reaction starts with the attack by the protonated aldehyde on the cyclopropane moiety of monoterpenoid **364** [as in the reaction of 2-carene (**359**) with aldehydes (see Scheme 26)] rather than on the double bond, as occurs in the synthesis of isobenzofuran type compounds. Cation **A** formed in this step eliminates a proton being converted to *p*-menthane type diol **B**, which is attacked by a second aldehyde molecule on the carbon atom of the endocyclic double bond; the subsequent intramolecular cyclization leads to products **390** and **391** as single stereoisomers. However, the absolute configuration of the product is not indicated in the publication [38] (see Scheme 29).

The reaction of 6-(hydroxymethyl)limonene (**396**) with salicylaldehyde (**123**) in the presence of montmorillonite clay gives tricyclic product **397** in 34% yield (Scheme 30).[38] The key step of the presumptive mechanism of formation of compound **397** is intramolecular carbocyclization of cation **C**.

**Scheme 30**




A broad range of reactions of monoterpenoid diol **250** with aromatic aldehydes **66**, **184**, **273**, **274**, **281**, **282** and **287** in the presence of the K10 clay [95 – 97, 120, 121] give not only the hexahydrochromene type products (**277a**,**b**, **278a**,**b**, **289a**,**b** – **291a**,**b**, **296a**,**b** and **320a**,**b**) (the mechanism is depicted in Scheme 20), but also tricyclic compounds **398** – **404** with the 4,6-(epoxymethano)chromene skeleton as the minor products (Scheme 31, Table 15). The yields of these products are low, but the compounds have a unique structure, appear as single stereoisomers and cannot be synthesized by other methods. In products **398** – **404**, the arrangement of the aromatic substituent in position 2 of the skeleton (see Scheme 31) differs from the substituent position in the hexahydrochromene type products; hence, these products are formed *via* different pathways. Presumably, the acid-activated aldehyde molecule first reacts with the endocyclic double bond of diol **250**.[120] Then, after proton elimination and tautomerization, the reaction with a second aldehyde molecule may take place to give carbocation **D**. The subsequent heterocyclization and proton elimination lead to tricyclic products with the 4,6-(epoxymethano)chromene skeleton. An assessment of the cytotoxic activity of compounds **398** – **404** in human tumour cell lines revealed a moderate cytotoxicity: $CTD_{50}$ (50% cytotoxic dose) was more than 64 μmol $litre^{-1}$ (Ref. 121).

**Scheme 31**

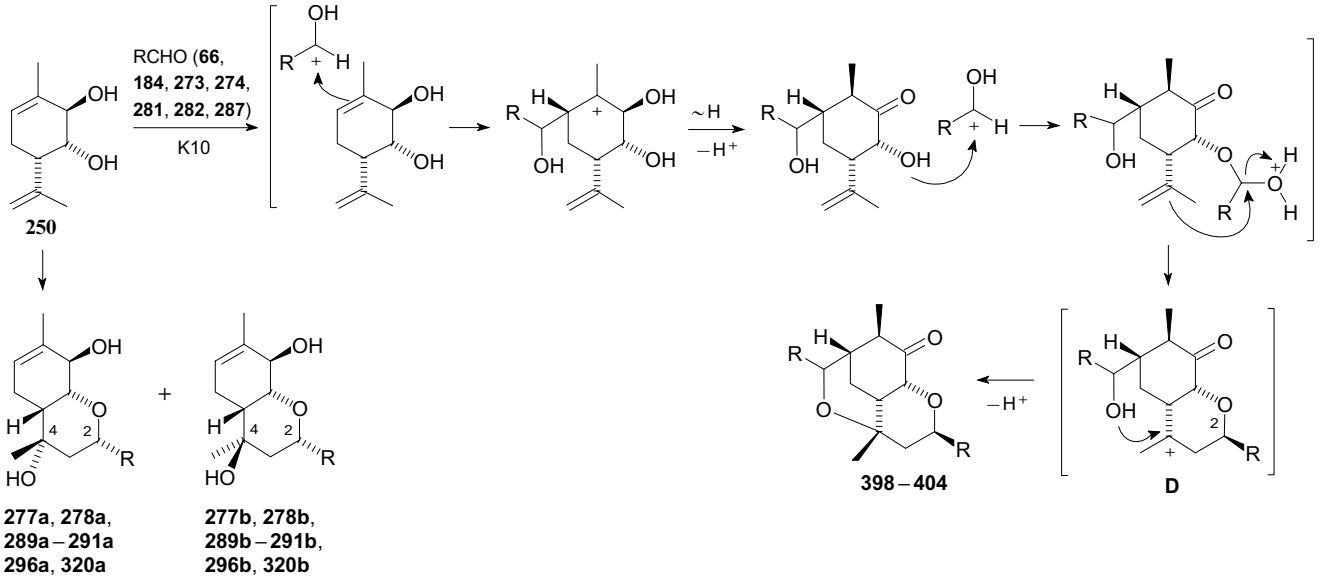


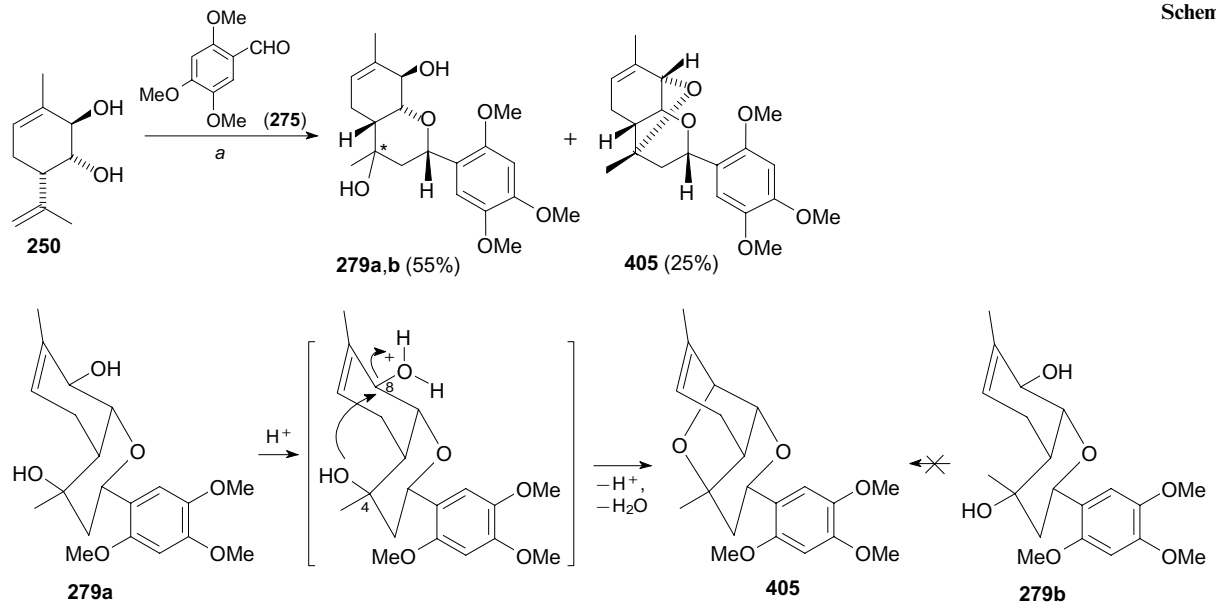

**Table 15**. Products of reactions of diol **250** with aldehydes in the presence of clay (see Scheme 31).

| Aldehyde | R | Products [yield (%)] | Ref. |
|---|---|---|---|
| **66** | 4-$MeOC_6H_4$ | **398** (11) + **320a**,**b** (43) | 96 |
| **274** | 2,3,4-$(MeO)_3C_6H_2$ | **399** (9) + **278a**,**b** (39) | 95 |
| **184** | 3-MeO-4-$HOC_6H_3$ | **400** (11) + **289a**,**b** (50) | 121 |
| **273** | 3,4,5-$(MeO)_3C_6H_2$ | **401** (9) + **277a**,**b** (39) | 97 |
| **281** | 3-HO-4-$MeOC_6H_3$ | **402** (8) + **290a**,**b** (29) | 97 |
| **282** | 3,4-$(MeO)_2C_6H_3$ | **403** (10) + **291a**,**b** (42) | 120 |
| **287** | 3,5-$(MeO)_2$-4-$HOC_6H_2$ | **404** (8) + **296a**,**b** (26) | 96 |

In the reactions of monoterpenoid **250** with 2,4,5-trimethoxybenzaldehyde (**275**) carried out in the presence of montmorillonite clay[95] or the $BF_3 \cdot Et_2O - H_2O$ system,[103] minor tricyclic product **405** of a different (4,8-epoxychromene) type, was also isolated (Scheme 32). Obviously, this product results from intramolecular heterocyclization of chromene **279**, which starts with the protonation of the hydroxy group in position 8 followed by nucleophilic attack by the hydroxy group in position 4; for steric reasons, the intramolecular heterocyclization occurs only in *S*-isomer **279a**, but not in *R*-isomer **279b**.[120]

Biological activity assays for compound **405** have revealed high analgesic activity *in vivo* in combination with low toxicity, which attests to good prospects of using this

**Scheme 32**




(*a*) K10 clay, rt, 7 days; 4-OH group configuration: α (**a**), β (**b**)

compound for drug development.[95] A systematic study of the effect of the number and positions of methoxy groups in the aromatic aldehyde on the possibility of formation of 4,8-epoxychromene type derivatives in the K10 clay-catalyzed reactions with diol **250** has shown that for this reaction to proceed, alkoxy groups should be present in positions 2 and 4 of the aldehyde aromatic ring.[120]

## 5. Tetracyclic products of reactions of monoterpenoids with carbonyl compounds

Tetracyclic compounds are often formed in the reactions of monoterpenoids with salicylaldehyde (**123**), because the presence of the phenolic group in the *ortho*-position to the aldehyde function opens up the way for additional cyclization in the intermediate carbocation. The reaction of geraniol (**18**) with aromatic aldehydes in the presence of $BF_3 \cdot Et_2O$ affords 3-oxabicyclo[3.3.1]nonene type bicyclic products (see Scheme 4). However, a similar reaction of monoterpenoid **18** with salicylaldehyde (**123**) yields tetracyclic product **406** of an absolutely different type (Scheme 33). In carbocation **407** generated in the reaction, the position of the hydroxy group is favourable for cyclization; therefore, closure of an additional ring takes place in the final step instead of proton elimination from this carbocation giving 3-oxabicyclo[3.3.1]nonene type derivatives.[28]

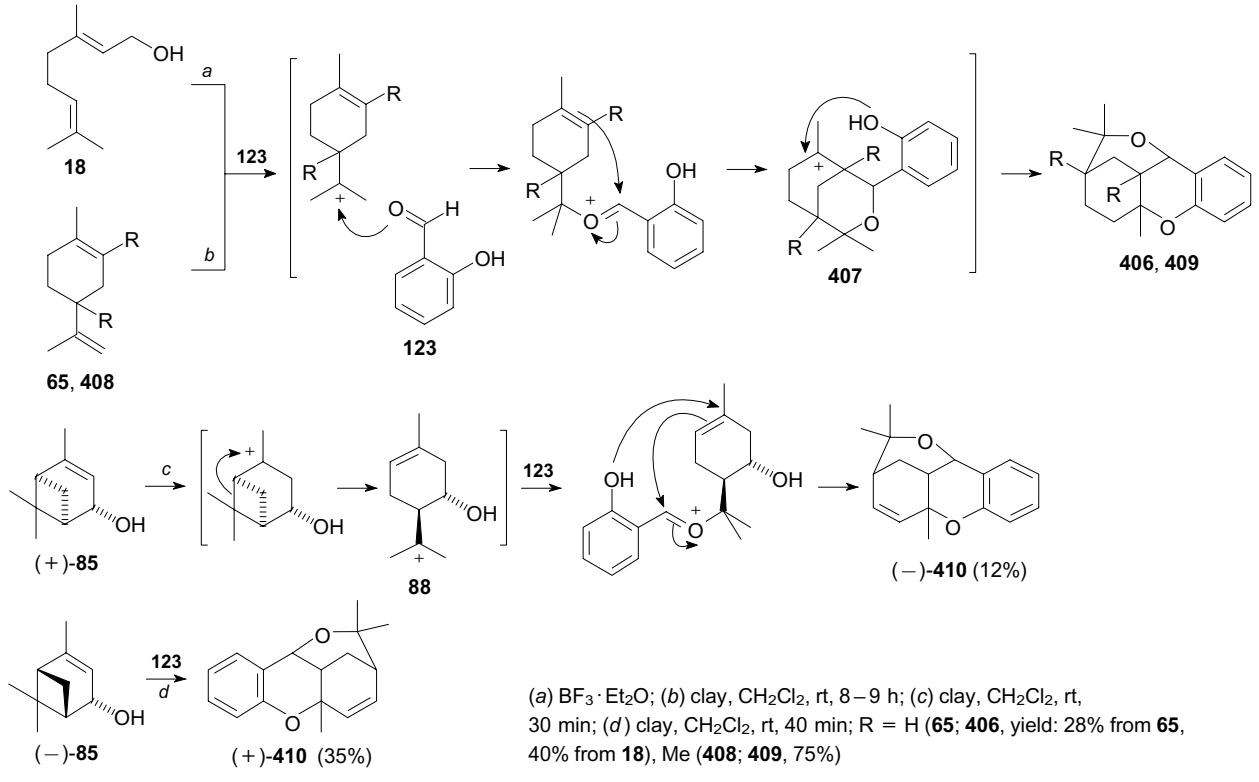
(*R*)-Limonene (**65**) and its structural analogue, 4-isopropenyl-1,2,4-trimethylcyclohexene (**408**), also react with salicylaldehyde (**123**) in the presence of clay to afford tetracyclic compounds **406** and **409**, respectively (see Scheme 33).[37, 122] Like in the transformations involving geraniol (**18**), the reaction does not stop after the formation of a bicyclic compound; instead, the cationic centre interacts with the hydroxy group giving rise to products **406** and **409** comprising fused xanthene and tetrahydropyran moieties. When limonene (**65**) is reacted with aldehyde **123** in dichloromethane, the yield of tetracyclic product **406** is only 28%.[37] Meanwhile, by depositing on clay of, first, aldehyde **123** in dichloromethane followed by solvent evaporation and then monoterpene **65** in dichloromethane followed by one more solvent evaporation, one can reduce the reaction time from 8 to 0.5 h, and the yield of compound **406** increases simultaneously to 73%.[123]

The use of bicyclic (+)-*trans*-verbenol [(+)-**85**] as the starting monoterpenoid to react with aldehyde **123** leads to similar tetracyclic product (−)-**410** (see Scheme 33).[54] The presence of a hydroxy group in monoterpenoid (+)-**85** and, hence, in the intermediate *p*-menthane carbocation **88** formed upon isomerization accounts for the generation of one more double bond in product (−)-**410** *via* dehydration. The reaction of salicylaldehyde (**123**) with a stereoisomer of (+)-**85** — (−)-*cis*-verbenol [(−)-**85**] — affords enantiomeric product (+)-**410**.[54]

Compounds **411** and **412** with a different type of skeleton are formed in the reaction between clay-supported *trans*-4-hydroxymethyl-2-carene (**364**) and 2-hydroxybenzaldehyde (**123**) or 2,4-dihydroxybenzaldehyde (**413**) (Scheme 34).[38, 124] A possible mechanism of this reaction includes the attack by the protonated aldehyde on the double bond of substrate **364**, formation of cation **414** and the subsequent heterocyclizations resulting in compounds with a xanthene skeleton fused with a tetrahydrofuran ring.[38] Although compounds **411** and **412** are obtained as single stereoisomers, their configuration is not indicated in the paper.

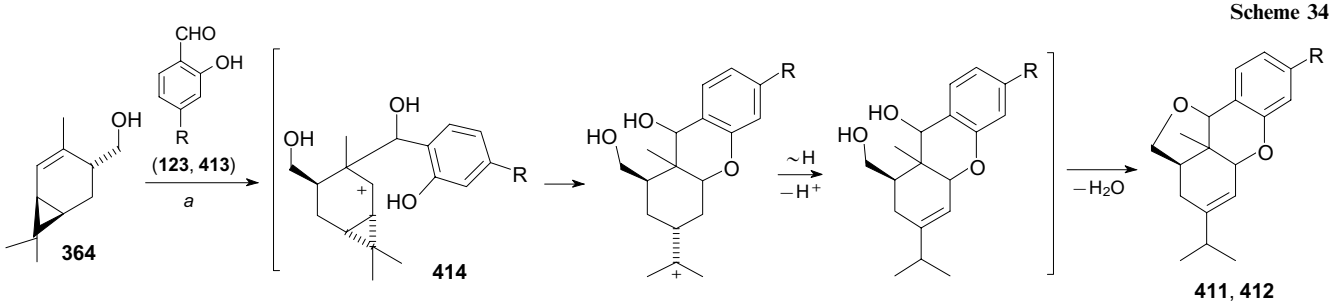
When several electron-donating hydroxy and/or methoxy groups are present in the aromatic ring of aldehydes, the K10 clay-catalyzed reaction with monoterpenoid **364** may involve cyclization to give tetracyclic products even when the aldehyde molecule has no *ortho*-phenolic group.

**Scheme 33**

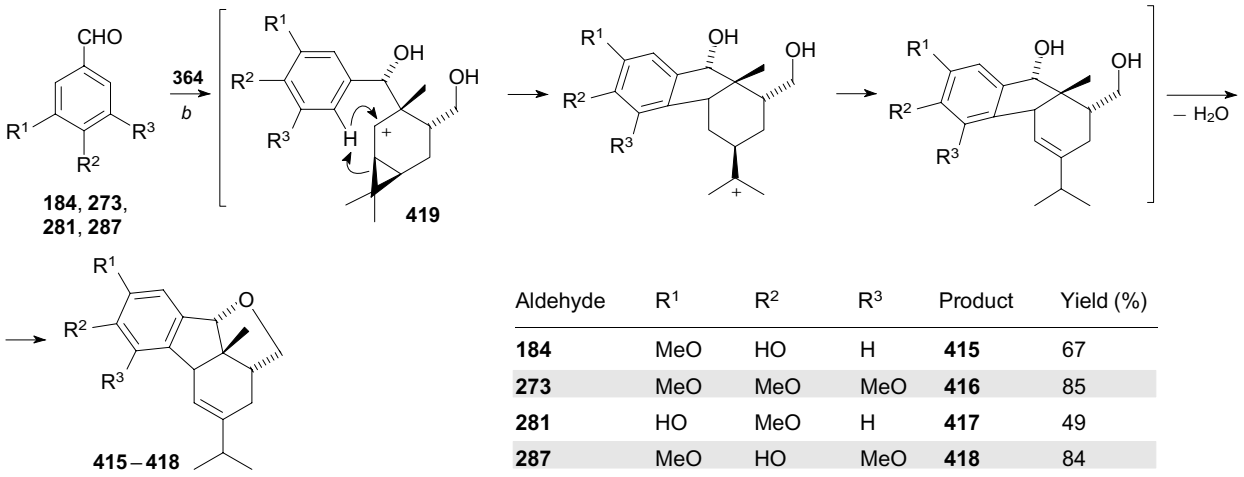



(*a*) $BF_3 \cdot Et_2O$; (*b*) clay, $CH_2Cl_2$, rt, 8 – 9 h; (*c*) clay, $CH_2Cl_2$, rt, 30 min; (*d*) clay, $CH_2Cl_2$, rt, 40 min; R = H (**65**; **406**, yield: 28% from **65**, 40% from **18**), Me (**408**; **409**, 75%)

**Scheme 34**




(*a*) Clay, $CH_2Cl_2$, rt, 30 min; R = H (**123**; **411**, 62% yield), HO (**413**; **412**, 29%)

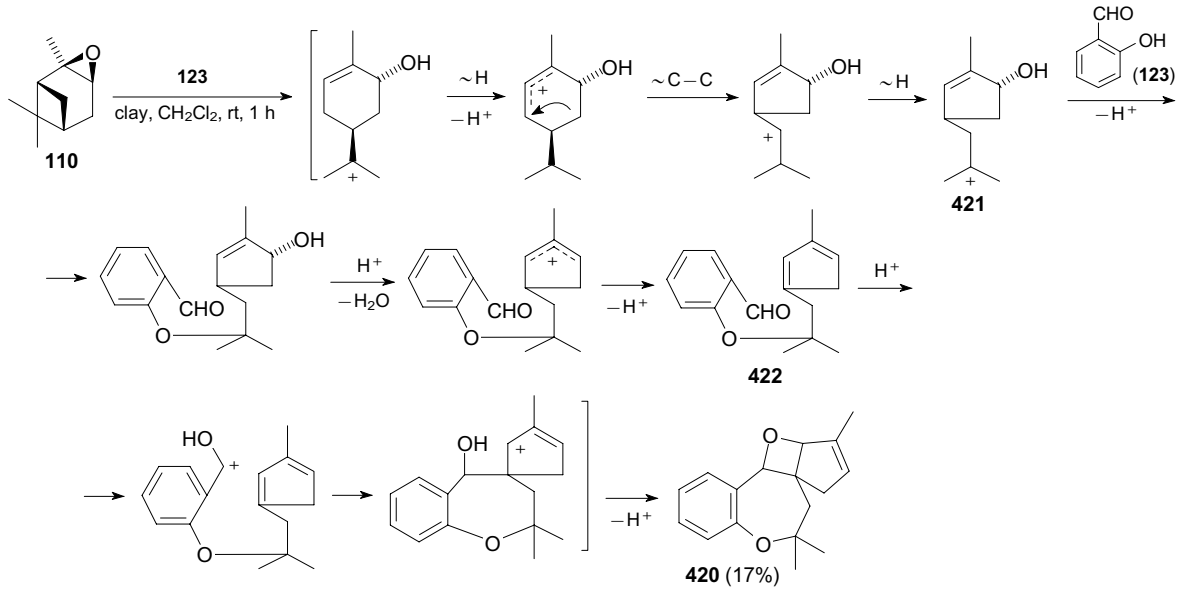



| Aldehyde | $R^1$ | $R^2$ | $R^3$ | Product | Yield (%) |
|---|---|---|---|---|---|
| **184** | MeO | HO | H | **415** | 67 |
| **273** | MeO | MeO | MeO | **416** | 85 |
| **281** | HO | MeO | H | **417** | 49 |
| **287** | MeO | HO | MeO | **418** | 84 |

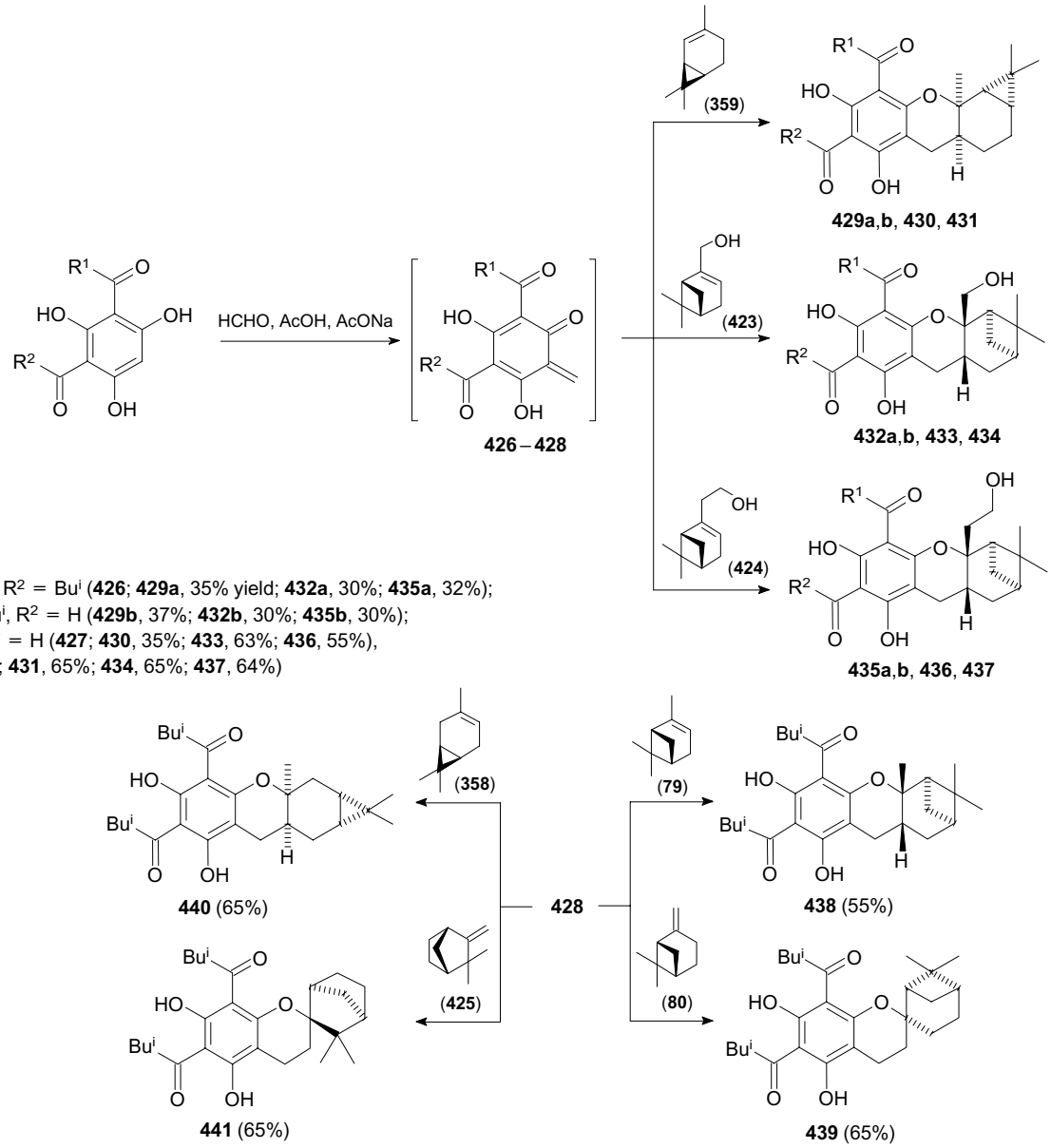
(*b*) K10 clay, $CH_2Cl_2$, rt, 3 h

Indeed, the K10 clay-catalyzed reactions of *trans*-4-hydroxymethyl-2-carene (**364**) with aldehydes **184**, **273**, **281** and **287** containing electron-donating substituents result in the formation of products **415** – **418** with the hexahydrofluoreno[9,1-*bc*]furan skeleton (see Scheme 34).[124] Presumably, in the presence of electron-donating substituents, the attack by the cationic centre of carbocation **419** on the *ortho*-position of the aromatic ring becomes more favourable than opening of the three-membered ring, which is observed when benzaldehyde (**36**) is employed as the carbonyl component (see Scheme 27). An assessment of the cytotoxic activity of compounds **415** – **418** has shown that compound **417**, resulting from the reaction of *trans*-4-hydroxymethyl-2-carene (**364**) with 3-hydroxy-4-methoxybenzaldehyde (**281**), possesses high activity against the

**Scheme 35**



**Scheme 36**




lymphoblastoid cell line MT-4, being superior over doxorubicin used as the reference agent.[124]

The reaction of α-pinene epoxide (**110**) with salicylaldehyde (**123**) in the presence of montmorillonite clay is accompanied by extensive rearrangement of the pinane skeleton, resulting in very unusual compound **420** containing fused seven-, six-, five- and four-membered rings (Scheme 35).[53] The key intermediates assumed for this reaction are cyclopentane type cation **421** and aldehyde **422**. Despite the fact that all asymmetric centres present in the initial molecule **110** are involved in the process, the transformations are stereospecific and give single isomers, the absolute configurations of which are not indicated in the publication.

Analogues of natural phloroglucinol – terpene adducts have been synthesized using bicyclic monoterpenoids — α-pinene (**79**), (−)-β-pinene (**80**), (+)-3-carene (**358**), (+)-2-carene (**359**), (−)-myrtenol (**423**), (−)-nopol (**424**) and camphene (**425**).[125] The reactions proceed in acetic acid in the presence of sodium acetate at 60 °C for 2 h. The first step comprises the Knoevenagel condensation of formaldehyde with diacylated phloroglucinol and gives *o*-quinone methides **426** – **428**, which then undergo the [2 + 4]-cycloaddition to monoterpenoids to form target adducts **429** – **441** (Scheme 36). When unsymmetrical phloroglucinol is used as the starting compound, both regioisomers are formed in comparable amounts. It should be noted that the cited paper[125] contains quite a few misprints in depicting the absolute configurations of the starting monoterpenes and their fragments incorporated in the products; here we present the configurations of compounds based on the structures of the monoterpene enantiomers used.

Biological activity assays for the products have revealed high antiparasitic and antibacterial activities for compounds **429a**, **429b** and **435a**.[125]

## 6. Conclusion

The principal approach to the synthesis of oxygen-containing heterocyclic compounds based on monoterpenoids is their reactions with carbonyl compounds, mainly, aldehydes. These reactions result in the formation of compounds with different types of skeletons including mono-, bi-, tri- and tetracyclic systems. Almost all of the transformations are acid-catalyzed; the catalysts used most often are Lewis acids, montmorillonite clays and modified zeolites.

Owing to the ability of monoterpenoids of various structural types to rearrange to *p*-menthane type carbocations upon protonation, one and the same heterocyclic products can be obtained using different starting terpenoids. However, many polycyclic compounds are formed only from monoterpenoids of a particular structure with a specified arrangement of functional groups.

Despite the fact that many and, in some cases, all asymmetric centres present in the terpenoid molecule are involved in the transformations, the reactions are usually stereoselective. Since many monoterpenoids are available in the enantiomerically pure state, optically active heterocyclic compounds can be obtained in one preparative step, and often it is possible to isolate both enantiomers. In most cases, structural details of aldehydes do not have a crucial effect on the reaction pathway, but affect substantially only the product yields. Meanwhile, in the reactions of salicylaldehyde, tandem heterocyclizations involving also the phenolic hydroxy group often take place.

Generally, the most complex multistep transformations occur when oxygen-containing pinane and carane monoterpenoids are reacted with aldehydes in the presence of clays, especially when the starting aldehydes contain one or several oxygen-containing substituents. Although in some cases, the product yields in these reactions are moderate, the reactions can be used to prepare unique polyheterocyclic compounds, difficult to obtain by other methods, in one preparative step. It is noteworthy that these reactions usually bear a high potential for increasing the yields of target products, mainly by varying the catalyst type or by modifying the catalysts.

Although the biological activities of oxygen-containing heterocyclic compounds prepared from monoterpenoids have started to receive considerable attention only in the last several years, compounds exhibiting high analgesic, neuroprotective, antiviral and antitumour activities have already been found among the products.

A poorly studied, but quite promising trend for further research in this area is to carry out the described reactions for various ketones and to perform multicomponent reactions, which would provide products with a variety of functional substituents.

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