ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 1, pp. 1–23. © Pleiades Publishing, Ltd., 2008.
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REVIEW

Dedicated to Full Member of the Russian Academy of Sciences G.A. Tolstikov on his 75th anniversary

Acid-Catalyzed Transformations of Pinane Terpenoids. New Prospects

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Received June 11, 2007

Abstract—The review discusses recent advances in the field of acid-catalyzed intra- and intermolecular transformations of pinane terpenoids and their oxygen-containing derivatives.

DOI: 10.1134/S1070428008010016

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Field of scientific interest: chemistry of natural compounds.

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Fields of scientific interest: chemistry of natural compounds, asymmetric synthesis.

1. INTRODUCTION

Interest of researchers in the chemistry of terpenes belonging to the pinane series, i.e., those possessing a 2,6,6-trimethyl[3.1.1]heptane skeleton, and their oxygen-containing derivatives originates mainly from the accessibility of these compounds, their chemical lability, and often high optical purity. Pinene derivatives are used as starting compounds in asymmetric syntheses

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Fields of scientific interest: chemistry of natural and biologically active compounds.

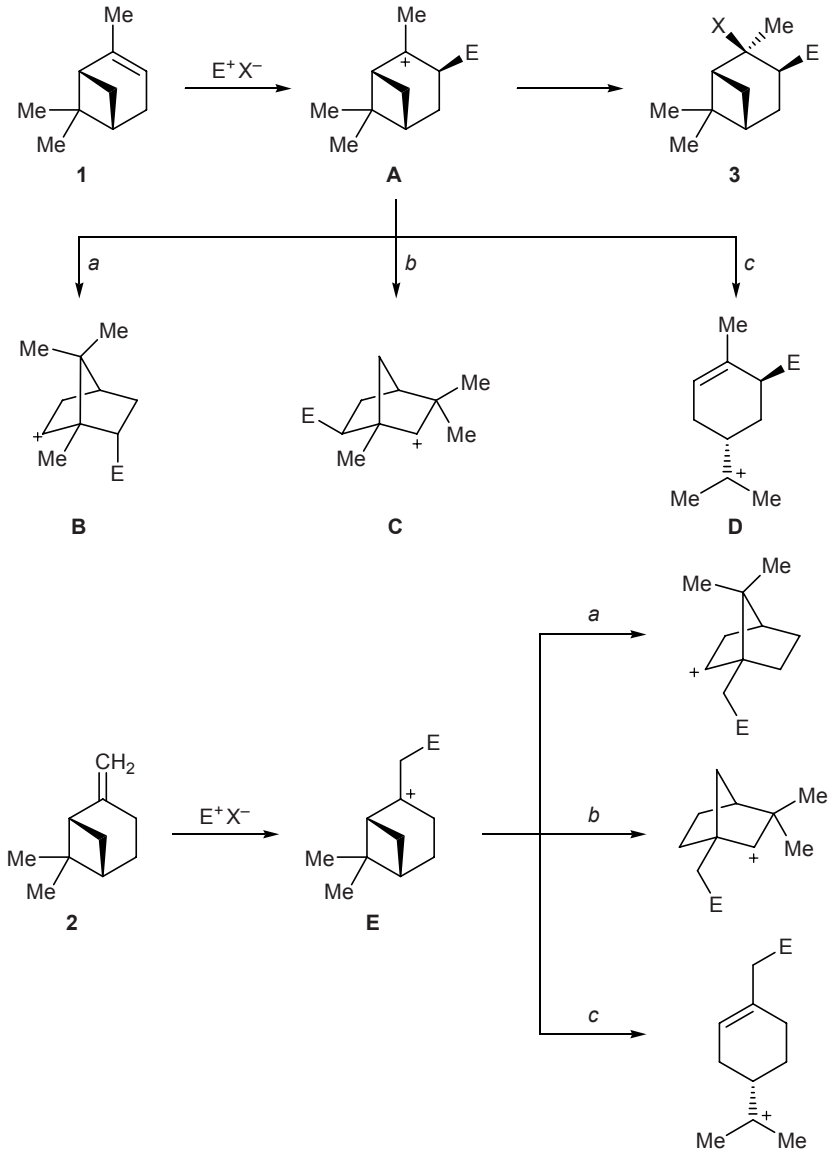
[1–5] and are valuable sources of biologically active substances [6, 7]. Pinane terpenoids in acid medium are generally involved in numerous transformations leading to complex mixtures of products; this is one of the main factors that restrict wide application of these compounds in fine organic synthesis. On the other hand, essential dependence of the ratio of the transformation products on the acid catalyst nature in some cases makes it possible to find conditions favoring formation of one or another product [8], which stimulates search for new catalytic systems and reaction conditions.

Undoubtedly, the most comprehensive review on transformations of α- and β-pinenes and their derivatives was published in [9]; it covers the data reported until 1985. More recent reviews were concerned mainly with a single type of catalyst or initial terpenoid [10–12]. In the present review we summarized data on acid-catalyzed transformations of pinane terpenoids, which were reported mainly in the past decade.

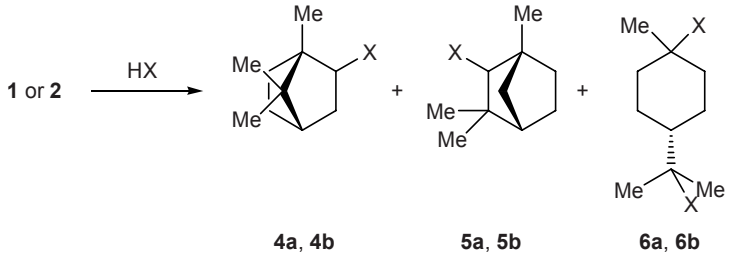
2. TRANSFORMATIONS OF α- AND β-PINENES IN THE PRESENCE OF ACID CATALYSTS

α-Pinene (**1**) and β-pinene (**2**) (Scheme 1) have found wide applications as solvents for paints and varnishes, as well as starting materials for the manufacture of camphor, insecticides, fragrant substances, drugs, and compounds used in fine organic synthesis. Isomeric pinenes are highly labile under acidic conditions,

Scheme 1.



Scheme 2.



4a, **4b** **5a**, **5b** **6a**, **6b**

X = Cl (**a**), Br (**b**).

and the corresponding transformations have been studied in sufficient detail [9]. Acid-catalyzed reactions of α- and β-pinenes give rise mainly to compounds of the *p*-menthane, fenchane, or bornane series, and the product ratio depends upon both catalyst nature and reaction conditions.

Electrophilic reagents E^+ attack the endocyclic double bond in α-pinene (**1**) preferentially at the less sterically hindered side with formation of cation **A**. Further transformations of the latter are determined by both catalyst nature and reaction conditions. Addition of nucleophile X^- to cation **A** at the side opposite to the geminal methyl groups to give compounds like **3** is a very rare case. As a rule, carbocation **A** undergoes rearrangement along one of the following pathways: (*a*) migration of the C^1–C^6 bond to form cation **B**; (*b*) migration of the C^1–C^7 bond leading to cation **C**; and (*c*) cleavage of the C^1–C^6 bond with formation of cation **D** (Scheme 1) [13].

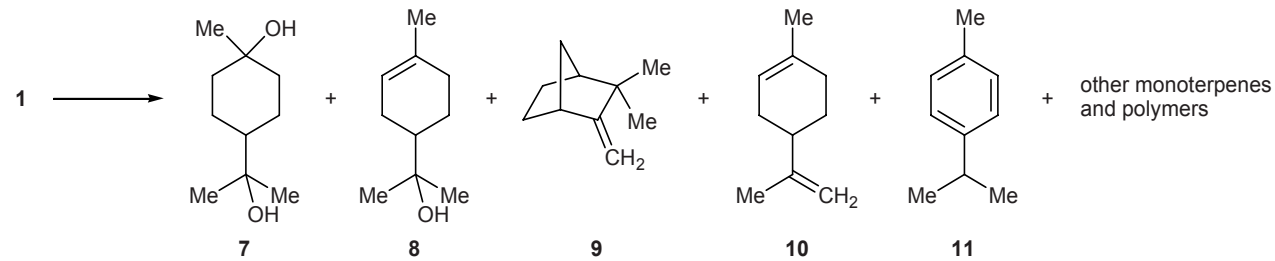
As a rule, path *a* requires anhydrous conditions, and the products are compounds of the bornane or isobornane series. Reactions along pathway *b* usually accompany pathway *a*, leading to α-substituted fenchanes. Reactions *a* and *b* occur preferentially in the presence of strong acids as catalysts or strong nucleophiles at low temperature. Aqueous medium and elevated temperature favor pathway *c* yielding *p*-menthane derivatives [5]. It was presumed [14, 15] that cation **A** in anhydrous systems is less stable than in aqueous systems and that its skeletal rearrangements are faster than ring opening. In aqueous or other strongly polar media, C–C bond cleavage in solvation-stabilized ions gives cation **D**. The nonclassical ion theory is not generally accepted for pinane terpenoids, although it is used fairly frequently. In many cases, ion pair formation is assumed to rationalize the nature of cationic species involved in electrophilic reactions [9].

Initial attack by electrophilic reagent E^+ at the double bond of β-pinene (**2**) gives 10-substituted cation **E** whose transformations also include skeletal rearrangements of the pinane skeleton, which follow pathways similar to those described above for α-pinene (**1**) (Scheme 1).

Addition of HCl [16] and HBr [17, 18] to α- and β-pinenes under anhydrous conditions (Scheme 2) leads to the corresponding bornyl halides **4a** and **4b** as the major products; also, minor amounts of fenchyl halides **5a** and **5b** and dihydrolimonene dihalides **6a** and **6b** were formed. When α- or β-pinene was saturated with hydrogen chloride under anhydrous conditions, the yield of compound **6a** did not exceed 10–15%, while in the presence of water the yield of bornyl chloride **4a** sharply decreased due to preferential formation of limonene dihydrochloride **6a** [19].

Treatment of α- and β-pinenes with dilute aqueous solutions of organic and inorganic acids gives rise mainly to compounds having a *p*-menthane skeleton, the major product being terpine hydrate (**7**) and α-terpineol (**8**) (Scheme 3) which are widely used in perfumery [20]. Camphene (**9**), dipentene (**10**), *p*-cy-

Scheme 3.



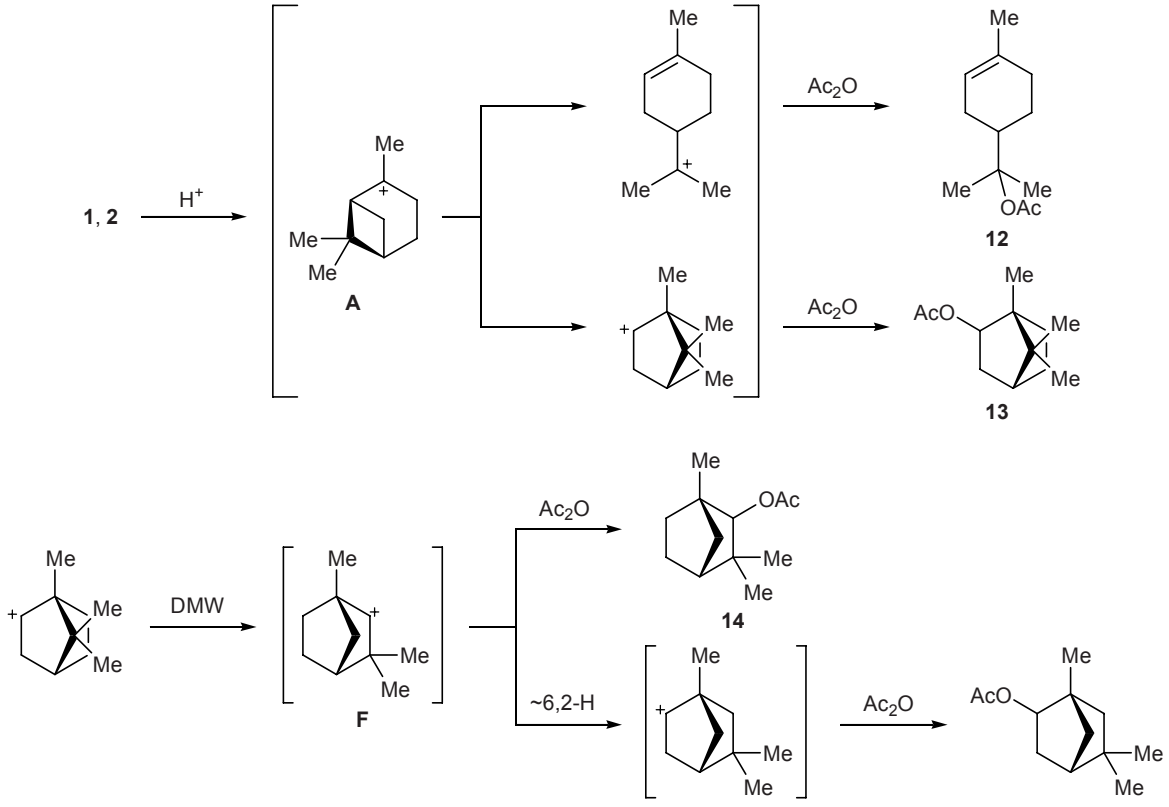
7 **8** **9** **10** **11**

mene (**11**), and some other compounds are formed as by-products. For instance, diol **7** was obtained in 85–90% yield by keeping α-pinene (**1**) in a 26.5% aqueous solution of perchloric acid [21], while the major transformation product of α- and β-pinenes **1** and **2** in acetone–sulfuric acid was α-terpineol (**8**) [22]; however, a large amount of by-products was also formed. Using chloroacetic acid as catalyst, Roman-Agurri et al. [23] succeeded in obtaining α-terpineol (**8**) with a selectivity of 70%, the conversion of initial α-pinene (**1**) being almost complete. Studies on a series of heterogeneous catalysts showed that the highest selectivity for compounds **7** and **8** was achieved using the composite catalyst $Cs_{2.5}H_{0.5}PW_{12}O_{40}$–$SiO_2$ in the presence of water and an organic solvent [20]; depending on the latter, either α-terpineol (**8**) or terpine hydrate (**7**) was formed as the major product.

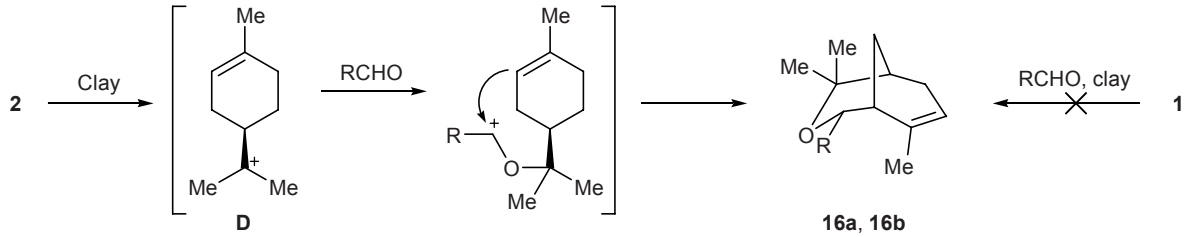
Catalytic isomerization of α-pinene (**1**) into camphene (**9**) and *dl*-limonene (**10**, dipentene) over solid heterogeneous catalysts was studied most thoroughly; this reaction is used in large-scale syntheses. The first data on the use of heterogeneous catalysts in the isomerization of α-pinene (**1**) were reported as early as 1915 [24]. Subsequently, numerous acid catalysts were proposed and tested in this reaction [11, 12, 25]. Apart from camphene (**9**) and dipentene (**10**), other mono- and bicyclic terpenes, dimers, and polymers were formed. Therefore, numerous acid catalysts were tested with a view to raise the yield of camphene (**9**) and minimize polymerization processes. Clays were tried as catalysts in many studies. For example, camphene (**9**) was formed in 50–55% yield in the isomerization of α- and β-pinenes over activated clay at 160–170°C [26]. On the other hand, clays as catalysts for the transformation of pinenes into camphene are not free from essential disadvantages, such as moderate selectivity for camphene **9** (~60%), formation of a considerable amount of fenchanes that are difficult to separate, high catalytic activity (which complicates control over the process), and a large contribution of polymerization. Therefore, metatitanic acid was subsequently used to catalyze isomerization of pinenes into camphene; as a result, the above listed disadvantages were mainly eliminated, and camphene was synthesized in up to 85% yield [12].

Reactions of pinenes with acetic anhydride over K-10 clay lead to the formation of compounds **12** and **13** as a result of isomerization of the pinane skeleton into *p*-menthane and bornane, respectively; in addition, norbornane derivative **14** is formed via more profound

Scheme 4.



Scheme 5.



R = MeCH=CH (**a**, 56%), Pr (**b**, 27%).

rearrangement of the pinane framework (double Wagner–Meerwein rearrangement, DWM) [27]. Although protonation of both isomeric pinenes should give the same cation **A**, the product composition depends on the initial pinene: in the reaction with α-pinene (**1**) the ratio **12**:**13**:**14** was 2.5:3:1, while in the reaction with β-pinene (**2**), 4:2:1 [27]. The reaction catalyzed by wide-pore H-β-zeolite instead of K-10 gave both compounds **12**–**14** and a considerable amount of **15**; the latter is likely to result from 6,2-H shift in cation **F** (Scheme 4). In both cases (i.e., in the presence of both K-10 and H-β-zeolite) the reaction mixture contained *p*-cymene and dipentene.

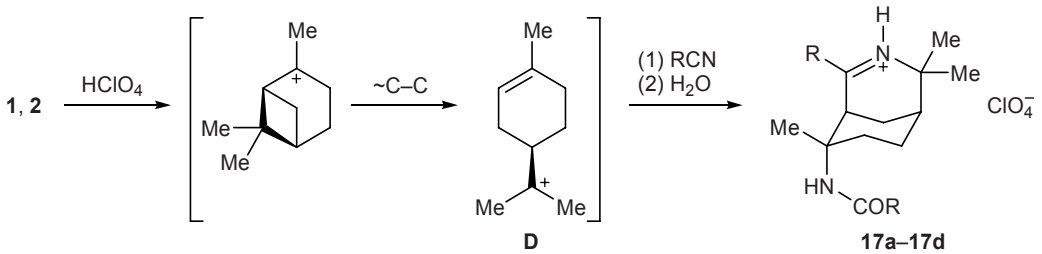
β-Pinene (**2**) reacted with crotonaldehyde and butyraldehyde over askanite–bentonite clay to give bicyclic ethers **16a** and **16b** (Scheme 5) [28]. A probable mechanism includes formation of cation **D** and its subsequent reaction with the aldehyde molecule, followed by intramolecular carbocyclization and elimination of proton. Compounds **16a** and **16b** were synthesized previously by reaction of dipentene with the corresponding aldehydes in the presence of clay, but their yields were appreciably smaller [29]. Bicyclic ethers like **16** have recently attracted interest due to their selectivity for estrogen receptor α- and β-agonists [30]. Unlike β-pinene (**2**), α-pinene (**1**) failed to react with aldehydes: only considerable tarring was observed [28].

The Ritter reaction provides a very convenient tool for studying skeletal rearrangements. On the one hand, the presence in the reaction mixture of a weak nucleophile (nitrile) ensures chemical stabilization of intermediate carbocations. On the other hand, the lifetime of the most labile cations is too short to react with a weak nucleophile (unlike, e.g., acid-catalyzed rearrangements of terpenoids in methanolic solution); as a result, relatively simple mixtures of products or (in some cases) individual compounds can be obtained. Reactions of α- and β-pinenes with nitriles in the presence of perchloric acid gave products **17a**–**17d** having a 3-azabicyclo[3.1.1]nonane skeleton. Obviously, the reaction involves intermediate formation of *p*-menthane carbocation **D** which reacts with nitriles to produce **17a**–**17d** in 80–90% yield (Scheme 6) [31].

The main products of the reaction of phenol with α-pinene (**1**) in the presence of boron trifluoride–ether complex were phenyl ether **18** and isocamphylphenol **19** (Scheme 7) [32]. An analogous reaction catalyzed by Amberlite 118 gave bis-phenols **20** and **21** [33]. β-Pinene (**2**) reacted with phenols over H-β-zeolite to afford optically active tricyclic ethers **22** and **23** [34].

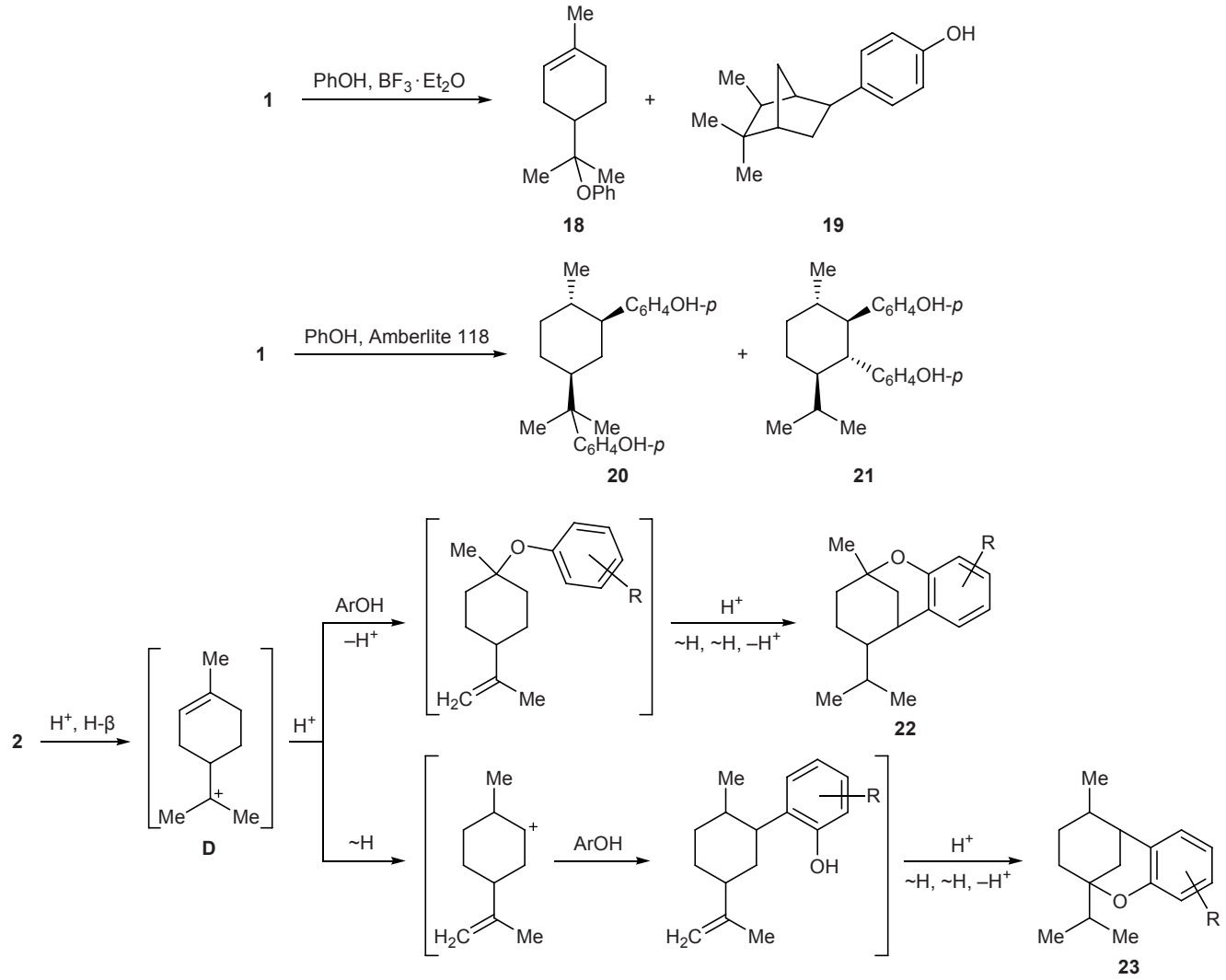
The reaction of β-pinene (**2**) with *N*-(2-sulfanylpropionyl)glycine in the presence of $ZnCl_2$ is likely to involve intermediate formation of *p*-menthyl cation **D** which adds at the sulfanyl group; the subsequent esterification of the carboxy group with ethanol used as solvent results in the formation of amino acid ester **24** (Scheme 8) [35]. Unlike the above reactions, treatment of β-pinene **2** with paraformaldehyde (Prins reaction) in the presence of montmorillonite impregnated with $ZnCl_2$ gave 75% of nopol (**25**) [36].

Scheme 6.

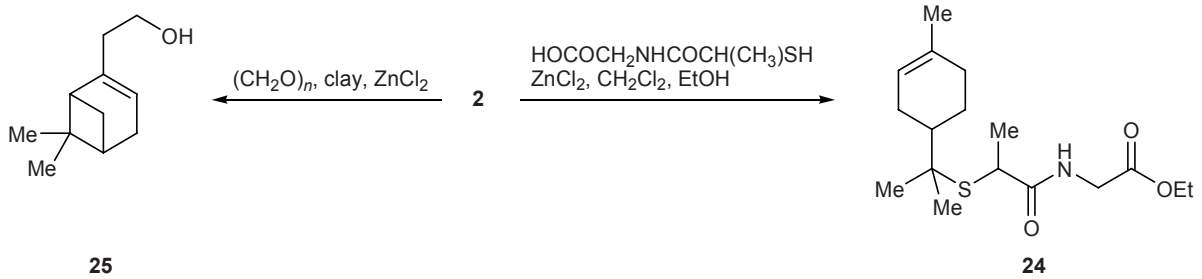


R = Me, Ph, 2-ClC_6H_4, 4-$MeOC_6H_4$.

Scheme 7.



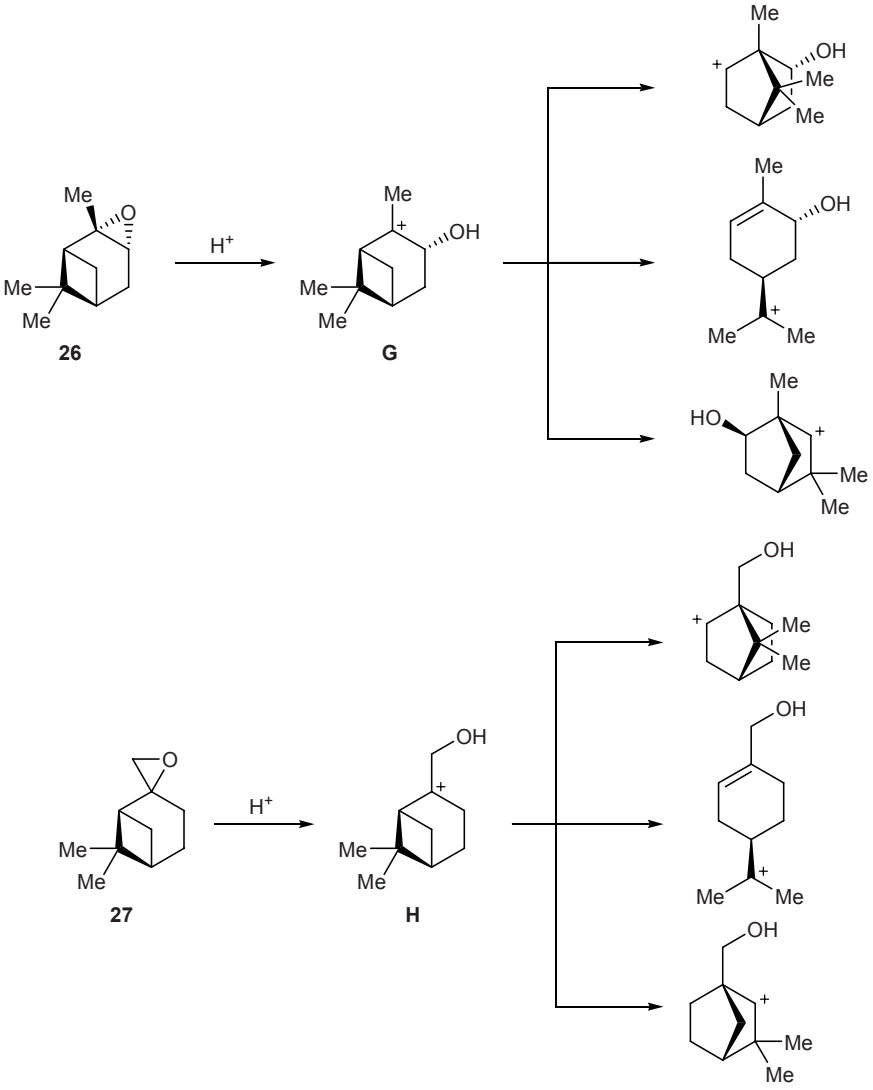
Scheme 8.



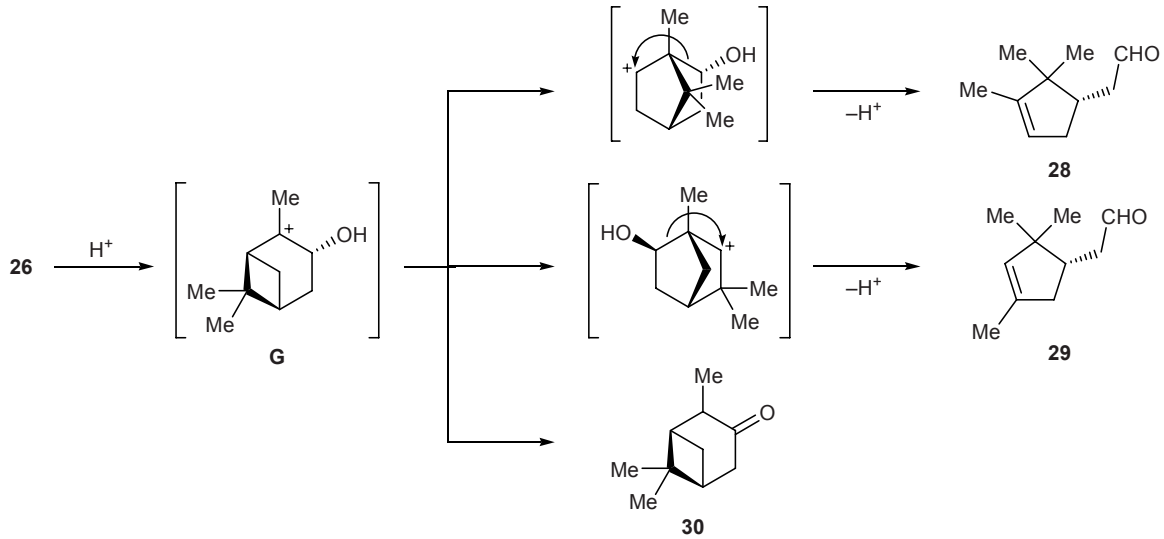
3. TRANSFORMATIONS OF α- AND β-PINENE EPOXIDES

Opening of an epoxide ring in acid medium takes a path involving formation of the most stable carbocations. Protonation and opening of the oxirane ring in epoxy derivatives of α- and β-pinenes **26** and **27** gives carbocations **G** and **H** whose further transformations follow three pathways (Scheme 9) that are similar to the transformations of protonated α- and β-pinenes. The resulting carbocations are capable of undergoing various transformations, including skeletal rearrangements, giving rise to a variety of products. For example, isomerization and polymerization processes

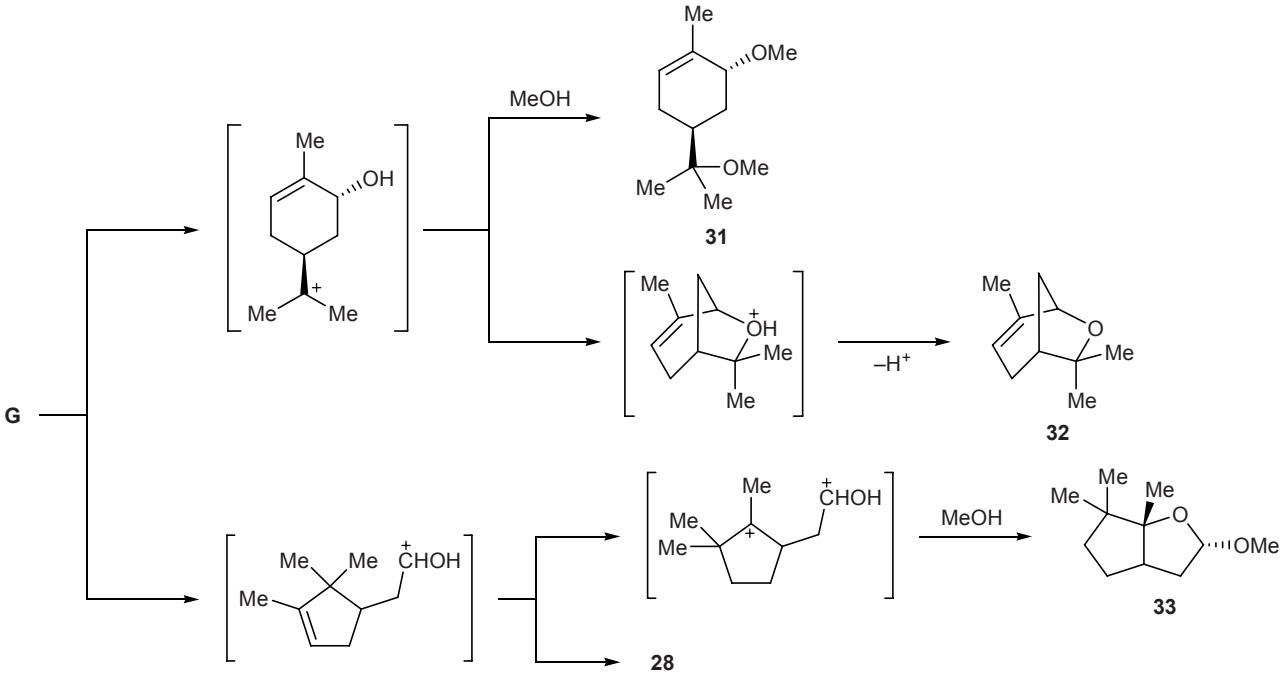
Scheme 9.



Scheme 10.



Scheme 11.

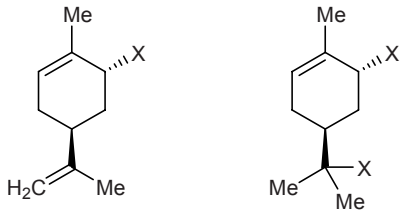


occurring with epoxy derivative **26** in acid medium could produce up to 200 different compounds [8].

Treatment of compound **26** with Lewis acids (BF_3, $ZnBr_2$) gives campholenaldehyde (**28**) as the major product; aldehyde **26** is the key compound in the synthesis of a number of substances possessing a sandalwood odor [37]; aldehyde **29** is often formed as minor product in these transformations (Scheme 10) [38]. In the presence of $InCl_3$, 85% of aldehyde **28** is selectively formed [39]. Treatment of α-pinene epoxide **26** with *p*-toluenesulfonic acid provides aldehyde **28** [40]. The yield of **28** in the isomerization of **26** over SiO_2–Al_2O_3 (Si/Al 70) or SiO_2–ZrO_2 under mild conditions (5 min at room temperature) attained 72%, though some by-products were also formed [41]; among the latter, pinocamphone (**30**) and aldehyde **29** were identified. Acid Ti-β-zeolites whose catalytic activity originates from the presence of Lewis acid centers ensured preparation of campholenaldehyde (**28**) in 93% yield via gas-phase isomerization of compound **26**, the substrate conversion being quantitative [42].

The behavior of α-pinene epoxide (**26**) in the superacidic system HSO_3F–SO_2FCl at –120°C (followed by quenching with methanol) was studied in [43]. In addition to the expected products having *p*-menthane (compound **31**) and campholene skeletons (**28**), bicyclic ethers **32** and **33** were formed (Scheme 11).

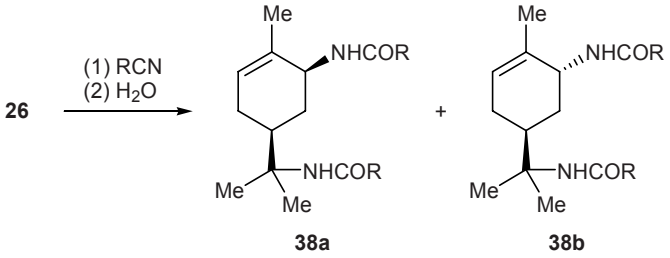
trans-Carveol (**34**) was obtained by isomerization of epoxypinane **26** using specially synthesized molecularly imprinted polymers (MIPs) as catalysts [44] (MIPs contain sockets possessing a high affinity for definite molecules). The reaction of epoxide **26** with water saturated with carbon dioxide gave sobrerol **35** in quantitative yield [45]. Epoxide **26** reacted with acetic anhydride at 140°C to produce aldehyde **28** (20%) and sobrerol diacetate **36** (26%) as the major products [46]; in the presence of K-10 montmorillonite, aldehyde **28** (19%), the corresponding acylal, compound **36** (22%), and *trans*-carvyl acetate **37** (2%) were obtained [47].



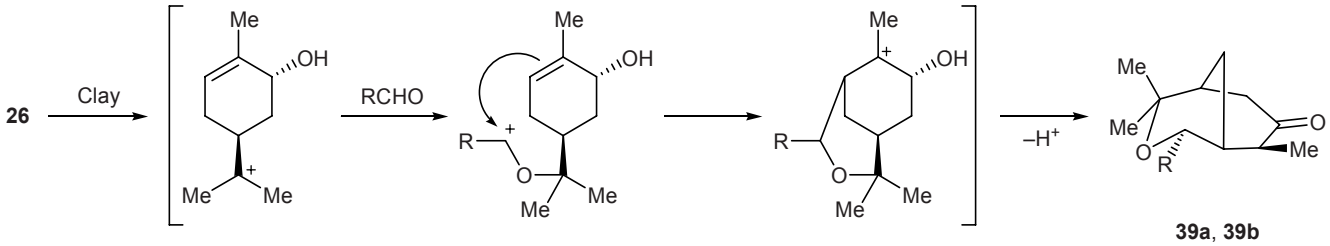
34, **35**, X = HO; **36**, **37**, X = AcO.

cis and *trans* Isomers **38a** and **38b** at a ratio of ~1 : 4 were formed in the Ritter reaction of **26** with nitriles in the presence of sulfuric acid [48] (Scheme 12). The reactions of epoxide **26** with crotonaldehyde and α-methylacrolein over askanite–bentonite clay gave bicyclic compounds **39a** (22%) and **39b** (15%), respectively [49] (Scheme 13). α-Pinene (**1**) did not react with aldehyde in the presence of clay.

Scheme 12.

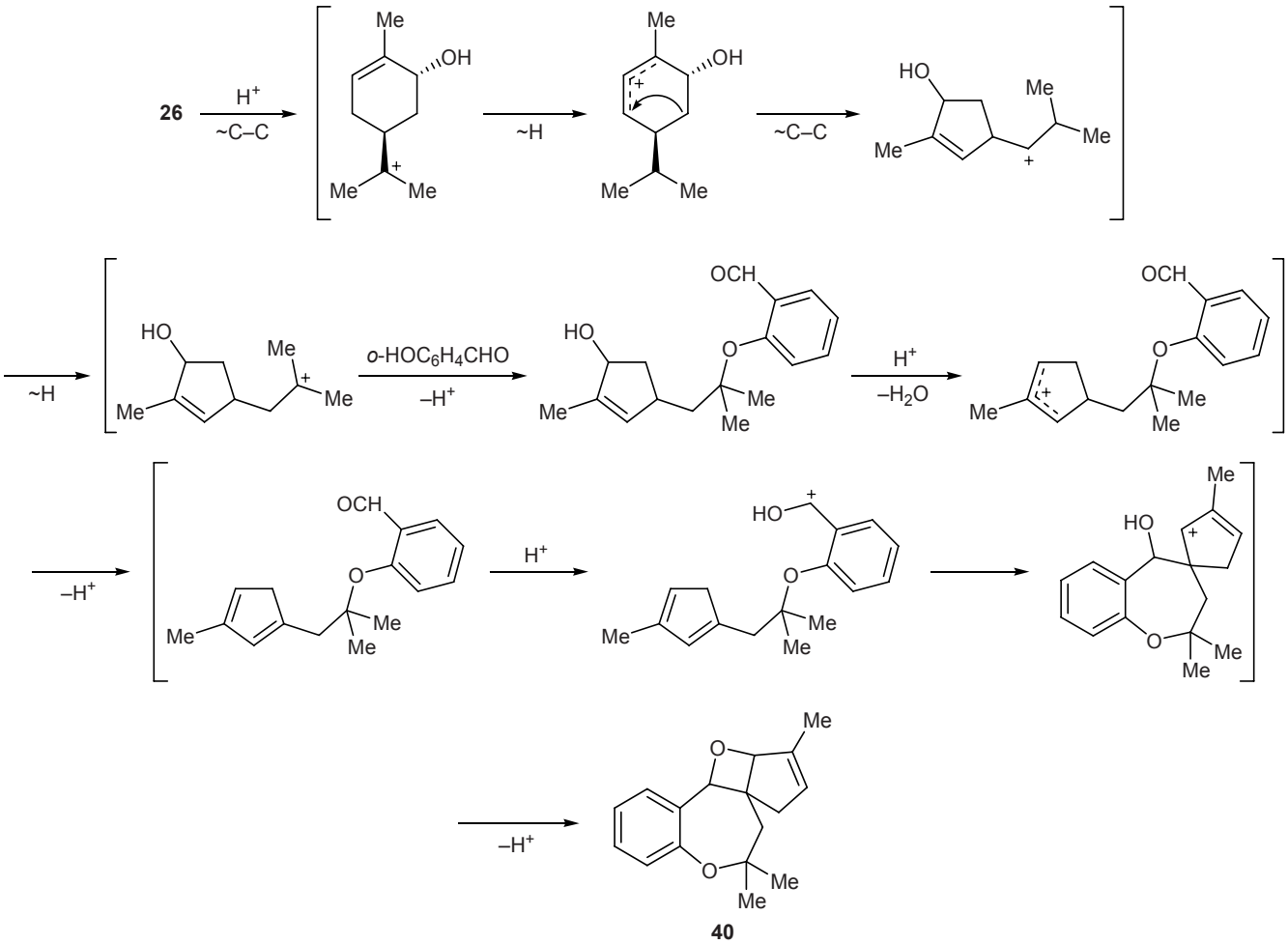


Scheme 13.

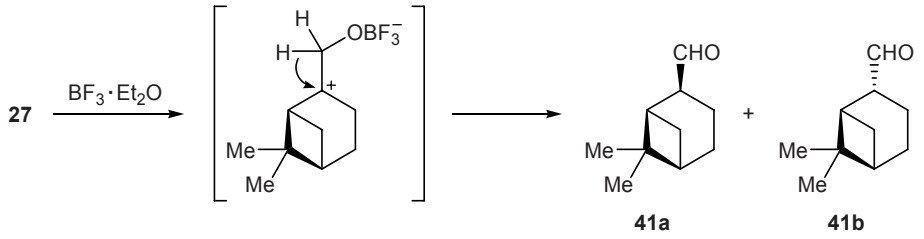


R = MeCH=CH (**a**), CH_2=C(Me) (**b**).

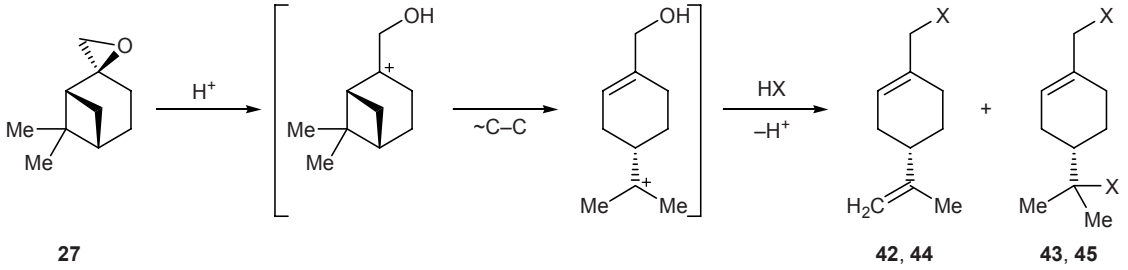
Scheme 14.



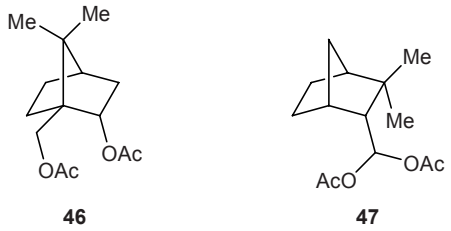
Scheme 15.



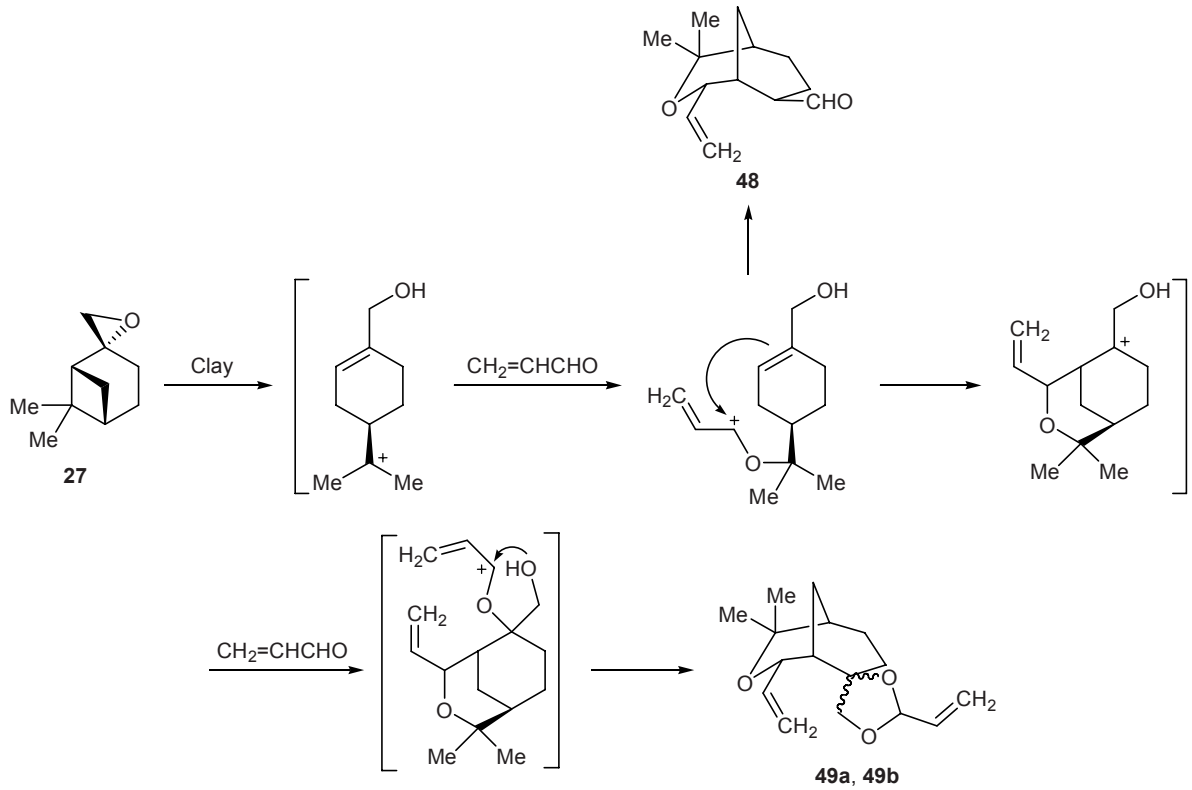
Scheme 16.



42, **43**, X = OH; **44**, **45**, X = OAc.



Scheme 17.



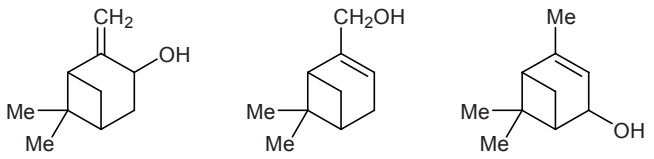
Compound **26** reacted with salicylaldehyde over askanite–bentonite clay quite differently than with α-methylacrolein and crotonaldehyde; the reaction was accompanied by profound rearrangement of the pinane skeleton, yielding tetracyclic diether **40** (17%). The reaction mechanism was interpreted assuming a scheme including more than 10 steps [50] (Scheme 14). In all cases, apart from intermolecular reaction products, the transformations of α-pinene epoxide **26** with aldehydes were accompanied by formation of intramolecular rearrangement products, aldehyde **28** and *p*-cymene (**11**). In the reaction of epoxide **26** with salicylaldehyde catalyzed by trifluoroacetic acid, only isomerization products were formed [49].

A considerably lesser number of studies were concerned with acid-catalyzed transformations of β-pinene epoxide **27**. Treatment of a mixture of *cis*- and *trans*-epoxides **27** with boron trifluoride–ether complex resulted in the formation of a mixture of *cis*- and *trans*-myrtanals **41a** and **41b** with the same isomer ratio (~2:3) [50] (Scheme 15). Like epoxide **26**, compound **27** in acid aqueous solution undergoes opening of the four-membered ring with formation of *p*-menthyl cation. Deprotonation of the latter gives perillic alcohol **42**, while addition of water leads to diol **43** (Scheme 16) [51]. Addition of solid carbon dioxide to a suspension of **27** in water resulted in the formation of 90% of diol **43**. The reaction of β-pinene epoxide **27** with acetic anhydride over K-10 clay afforded acetates **44** and **45** together with bicyclic compounds having camphane (**46**) and isocamphane skeletons (**47**) (Scheme 16) [47].

Bicyclic aldehyde **48** (6%) and tricyclic spiro compounds **49a** and **49b** (9%) were isolated in the reaction of **27** with acrolein over askanite–bentonite and K-10 montmorillonite clays. Compounds **49a** and **49b** were formed as a result of addition of two acrolein molecules to epoxide **27** [49] (Scheme 17). No isomerization products of β-pinene epoxide **27** were detected. When the reaction was carried out using acidic H-β-zeolite as catalyst, no intermolecular transformation products were formed, but strong tarring of the initial epoxide was observed.

4. TRANSFORMATIONS OF ALCOHOLS OF THE PINANE SERIES

Pinocarveols **50a** and **50b**, myrtenol (**51**), and verbenol (**52**) are allylic alcohols having a pinane skeleton and differing by the positions of the double bond and the hydroxy group. Addition of hydrogen bromide to *trans*-pinocarveol (**50a**) or the corresponding acetate yields mainly fenchene derivatives **53** (R = H, Ac) [52, 53] (Scheme 18).



50a, **50b** **51** **52**

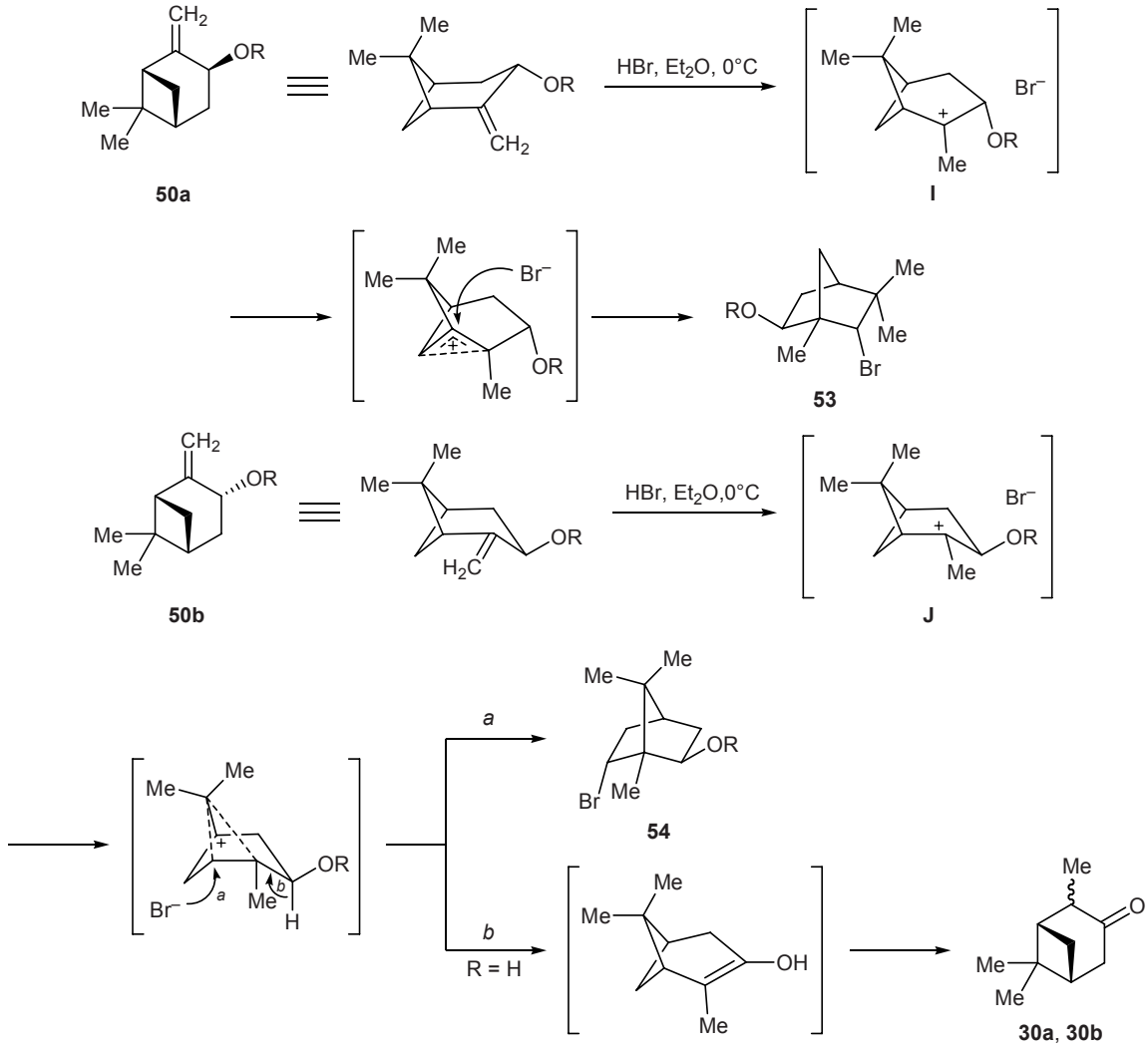
Quite different products were obtained under analogous conditions from *cis*-pinocarveol (**50b**) and its acetate: the alcohol gave rise to a mixture of *endo*-6-bromoisoborneol (**54**, R = H) and epimeric pinocamphones **30a** and **30b**, while only compound **54** was formed from the acetate (R = Ac). The different reactivities of compounds **50a** and **50b** were ascribed to their different preferential conformations [52, 53]. Proton addition at the less sterically hindered side of molecules **50a** and **50b** leads to formation of intermediate cations **I** and **J**, each undergoing stereospecific rearrangements to produce the corresponding fenchyl or bornane derivatives.

After keeping of (+)-*trans*-pinocarveol (**50a**) over askanite–bentonite clay, initial alcohol **50a** (conversion 75%), (–)-myrtenol (**51**, 33%), and condensation product **55** (11%) were isolated from the reaction mixture [54] (Scheme 19). Presumably, compound **55** was formed via reaction of carbocation **K** with *trans*-pinocarveol (**50a**). Although the reaction mixture contained alcohols **50a** and **50b** in comparable amounts and both these were capable of adding to cation **K** at two positions, only compound **55** was formed in an appreciable amount.

(–)-Myrtenol (**51**) in the presence of askanite–bentonite underwent transformation into (+)-*trans*-pinocarveol (**50a**, 9%), perillic alcohol **42** (12%), and *p*-cymene derivative **56** (6%), the conversion of **51** being 44% [54] (Scheme 20). The presence among the products of a compound having a *p*-menthane skeleton suggests that the isomerization of **51** over clay involves not only formation of carbocation **K** from allylic alcohol **51** protonated at the hydroxy group but also protonation of the double-bonded carbon atom, followed by skeletal rearrangement of carbocation **L** into *p*-menthyl cation (Scheme 20).

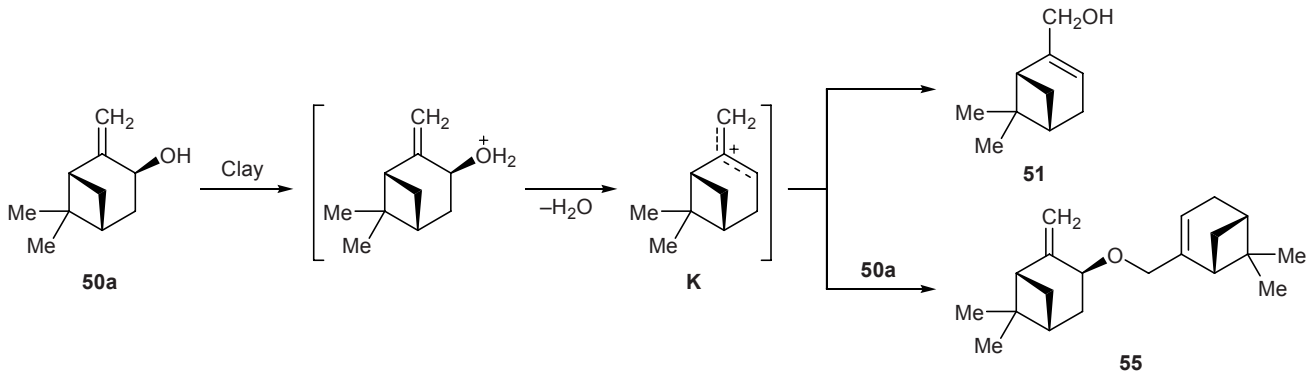
Thus interconversion of *trans*-pinocarveol (**50a**) and (–)-myrtenol (**51**) is one of the main transformation pathways of these compounds over askanite–bentonite. As a result, in both cases the reaction mixture

Scheme 18.



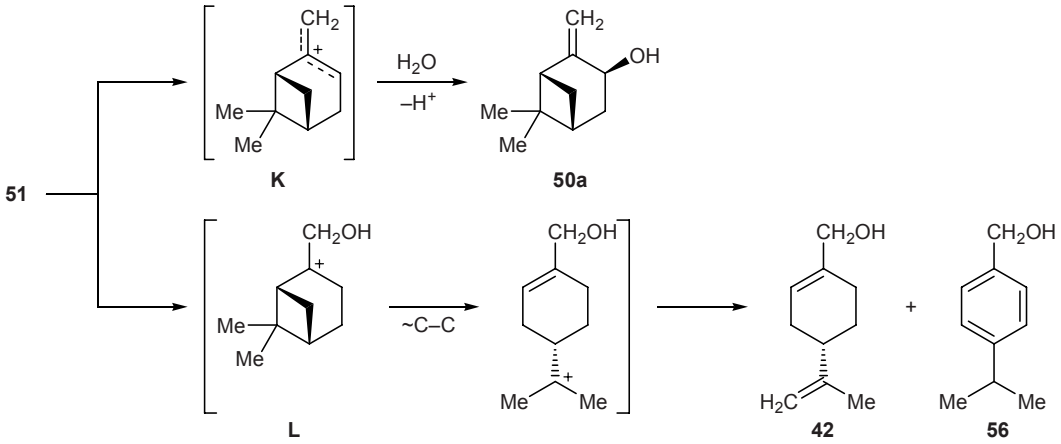
R = H, Ac.

Scheme 19.

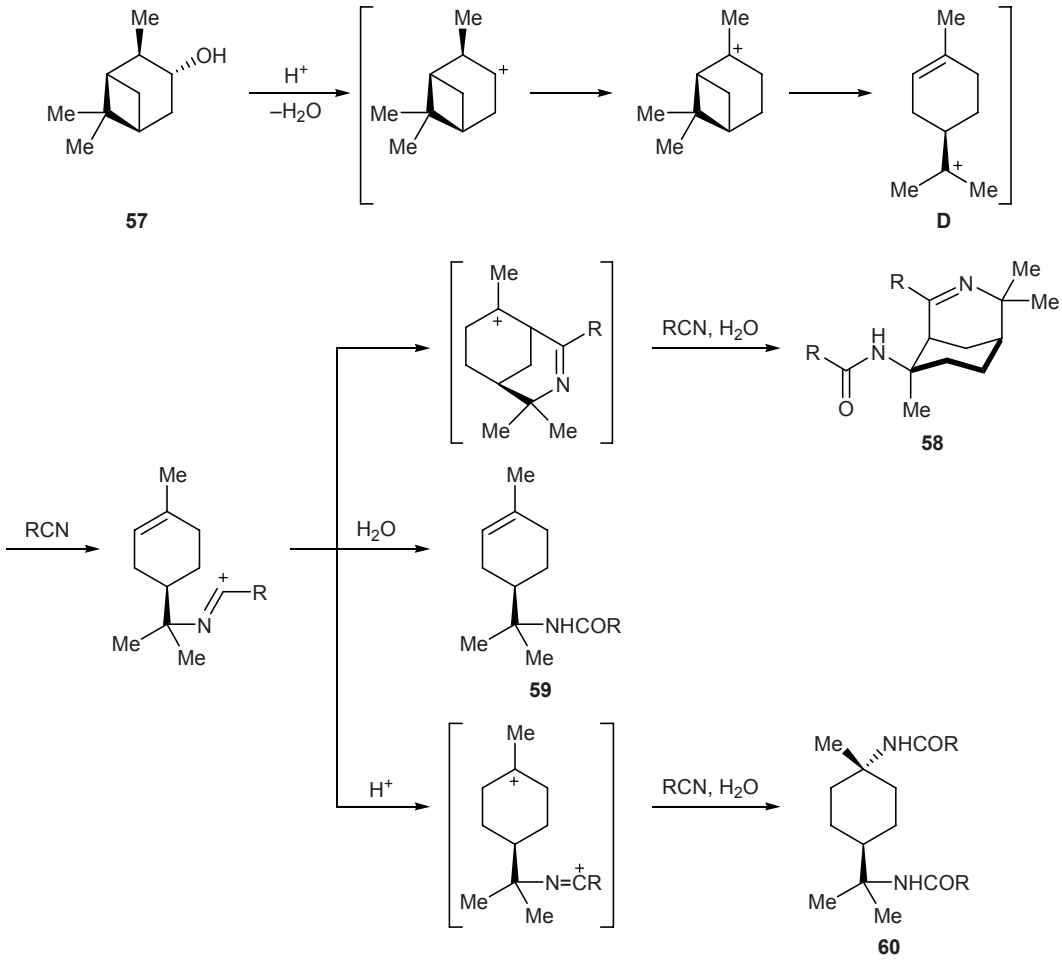


contains compounds **50a** and **51**. On the other hand, some specific isomerization products are formed in each case. This is quite surprising, for it seems that the clay is capable of distinguishing the same compound taken as starting material and formed during the process. Compounds **58**–**60** were the main products obtained in the reaction of pinan-3-ol (**57**) with nitriles in the presence of sulfuric acid [55] (Scheme 21). The

Scheme 20.



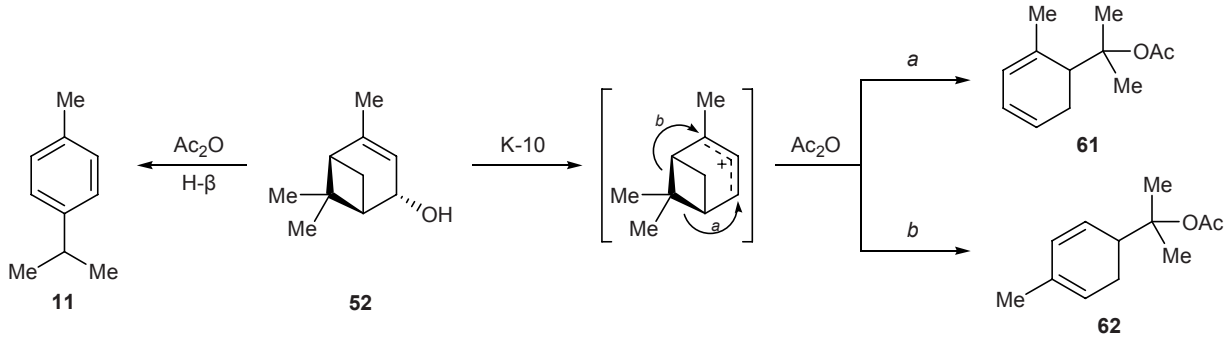
Scheme 21.



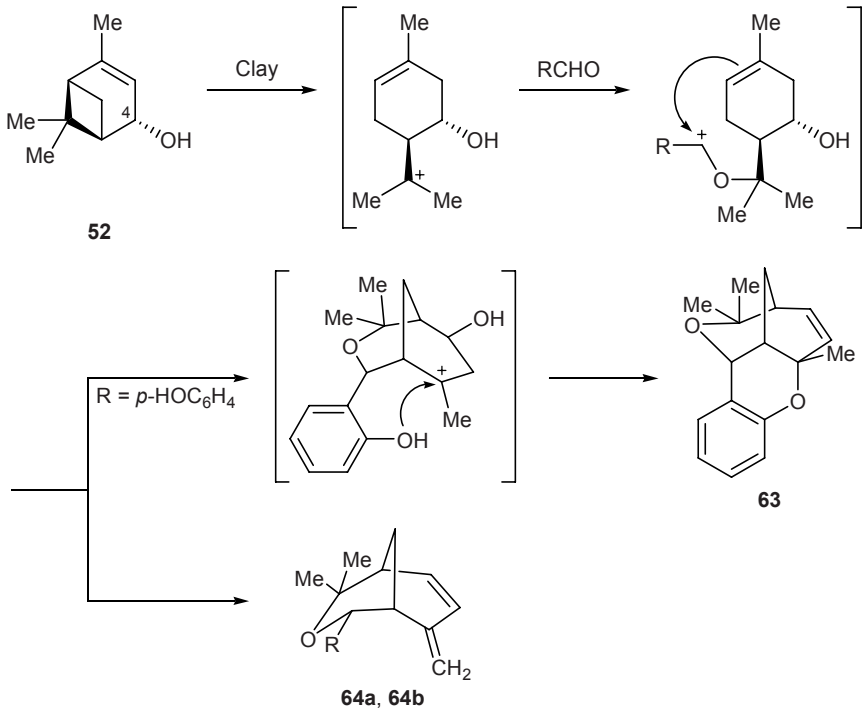
R = Me (70%), Et (67%), *i*-Pr (63%).

results were rationalized on the basis of a mechanism involving initial acid-catalyzed elimination of the hydroxy group to give secondary carbocation which is converted into more stable tertiary cation via hydride shift. Next follows rearrangement of the pinane skeleton into *p*-menthane (cation **D**). Cation **D** takes up nucleophile (nitrile) with formation of intermediate which is transformed along three pathways leading to

Scheme 22.



Scheme 23.



R = MeCH=CH (**a**), CH_2=C(Me) (**b**).

compounds **58**, **59**, and **60** at a ratio of 3 : 1 : 1. The proposed mechanism is supported by the facts that the Ritter reaction of α- and β-pinenes gives compounds **17a**–**17d** (Scheme 6) which are structurally related to bicyclic product **58** and that compound **57** in methanol does not change in the presence of sulfuric acid.

trans-Verbenol (**52**) reacted with acetic anhydride over H-β-zeolite to give *p*-cymene (**11**). In the presence of synthetic K-10 montmorillonite, compound **52** gave rise to *o*- and *p*-menthyl acetates **61** and **62** [27] (Scheme 22). In the reaction of *trans*-verbenol (**52**) with salicylaldehyde over askanite–bentonite, *p*-cymene (**11**, 33%) and tetracyclic compound **63** (12%) were formed [54] (Scheme 23). A product with the same skeleton as in **63** was obtained previously by reaction of salicylaldehyde with limonene (**10**) in the presence of clay [56].

Clay-catalyzed reactions of *trans*-verbenol (**52**) with aliphatic aldehydes are characterized by increased yield of intermolecular products and reduced fraction of *p*-cymene (**11**) [54]. For example, 26% of **64a** and 8% of **11** were formed in the reaction of **52** with crotonaldehyde, while the reaction of **52** with α-methylacrolein gave 10% of **11** and 25% of **64b** (major product).

Analogous transformations of *cis*-verbenol and aldehydes over clay resulted in the formation of compounds that are epimeric to **64a** and **64b** obtained from

(+)-*trans*-verbenol (**52**) [54]. This means that orientation of the hydroxy group in verbenol does not affect the direction of intermolecular reactions. Moreover, *trans*-verbenol methyl ether reacted similarly. On the other hand, the presence of a hydroxy (or methoxy) group in the 4-position is very important. Neither verbenone (4-oxo derivative) nor myrtenol (**51**, 10-hydroxy derivative) nor α-pinene (**1**, no oxygen-containing groups) reacted with aldehydes in the presence of clay [54].

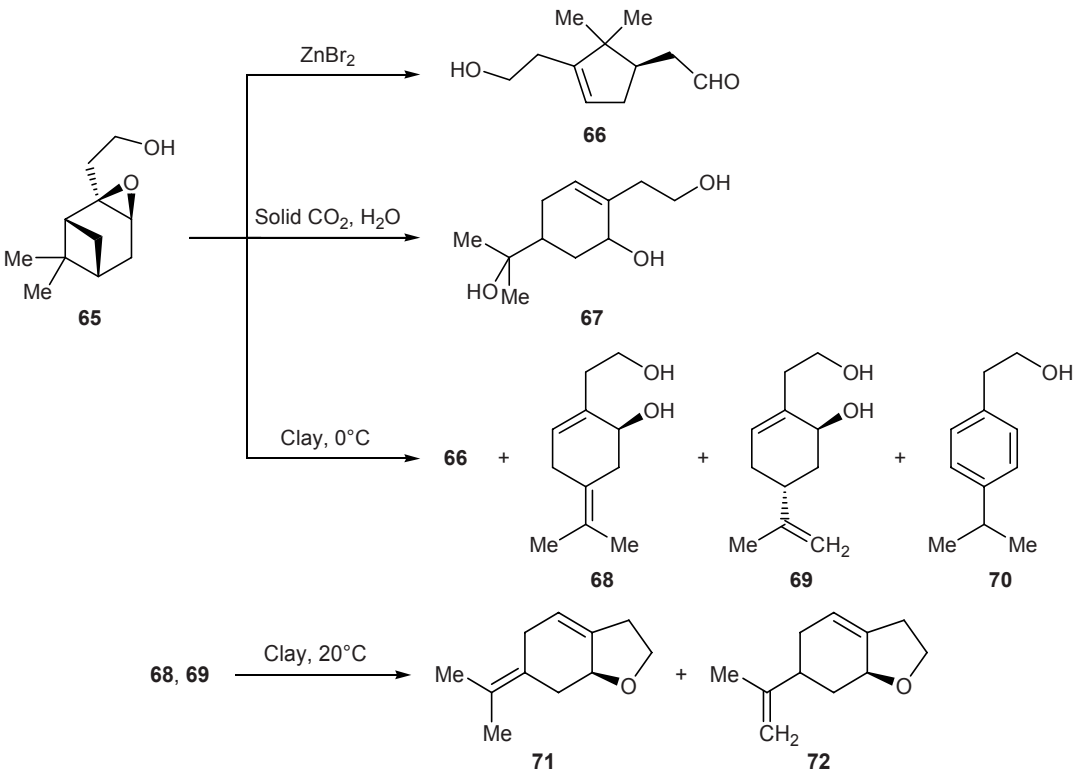
5. TRANSFORMATIONS OF EPOXY ALCOHOLS OF THE PINANE SERIES

Nopol epoxide **65** in boiling toluene in the presence of $ZnBr_2$ was converted into aldehyde **66** (yield 61%) [57]; addition of solid carbon dioxide to a mixture of **65** with water quantitatively afforded triol **67** [58] (Scheme 24). The main transformation products of epoxide **65** over askanite–bentonite at –25°C were aldehyde **66** (20%) and *p*-menthanediols **68** and **69** at a ratio of ~1:3 (overall yield 35%) [59]. Raising the temperature to 0°C slightly reduced the yield of diols **68** and **69** (overall yield 30%, ratio 1:1) and aldehyde **66** (16%); in addition, a small amount of alcohol **70** (6%) was isolated from the reaction mixture (Scheme 24). Further rise in temperature (to 20°C) resulted in considerable change of the composition of the reaction mixture. Apart from compounds **66** and **70**, a mixture of bicyclic products **71** and **72** was isolated; compounds **71** and **72** were formed via cyclization of diols **68** and **69** [59].

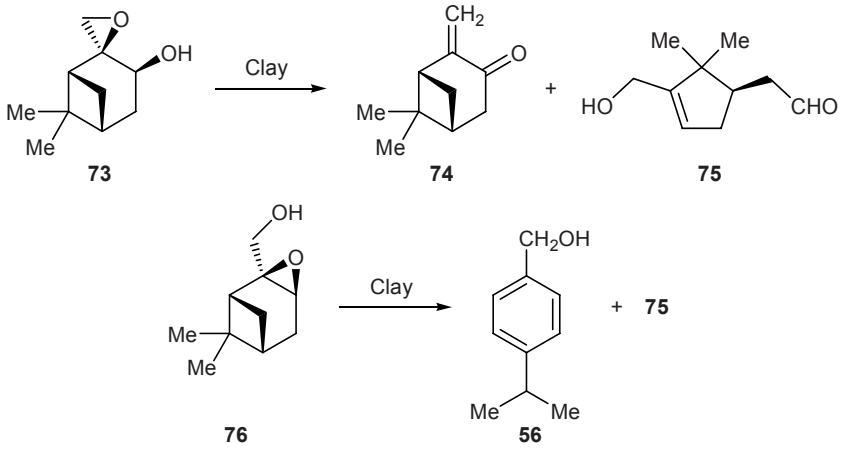
Epoxy derivative of *trans*-pinocarveol (compound **73**) in the presence of clay gave rise to a complex mixture of products, from which pinocarvone **74** (6%) and compound **75** (campholenaldehyde analog, 19%) were isolated. Myrtenol epoxide **76** was transformed into 16% of aromatic *p*-isopropylphenylmethanol (**56**) and 27% of hydroxy aldehyde **75** [54] (Scheme 25).

The reaction of verbenol epoxide **77** in the presence of $ZnBr_2$ afforded compound **78** [60] (Scheme 26), while the major product of its transformation over askanite–bentonite was *trans*-diol **79** with a *p*-menthane skeleton (47%); in addition, a small amount of hydroxy ketone **78** (5%) was formed [54]. Epoxide **77** reacted with aromatic aldehydes in the presence of clay (Scheme 27) to give isomerization products **78** and **79** together with bicyclic diethers **80a** and **80b** [54]. A probable mechanism of formation of these compounds includes formation of carbocation having a *p*-menthane skeleton and its subsequent reaction with aldehyde molecule. In the final step, the most favorable is heterocyclization of intermediate carbocation **M**

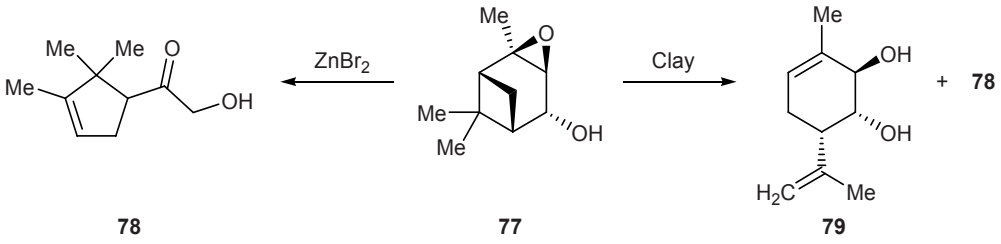
Scheme 24.



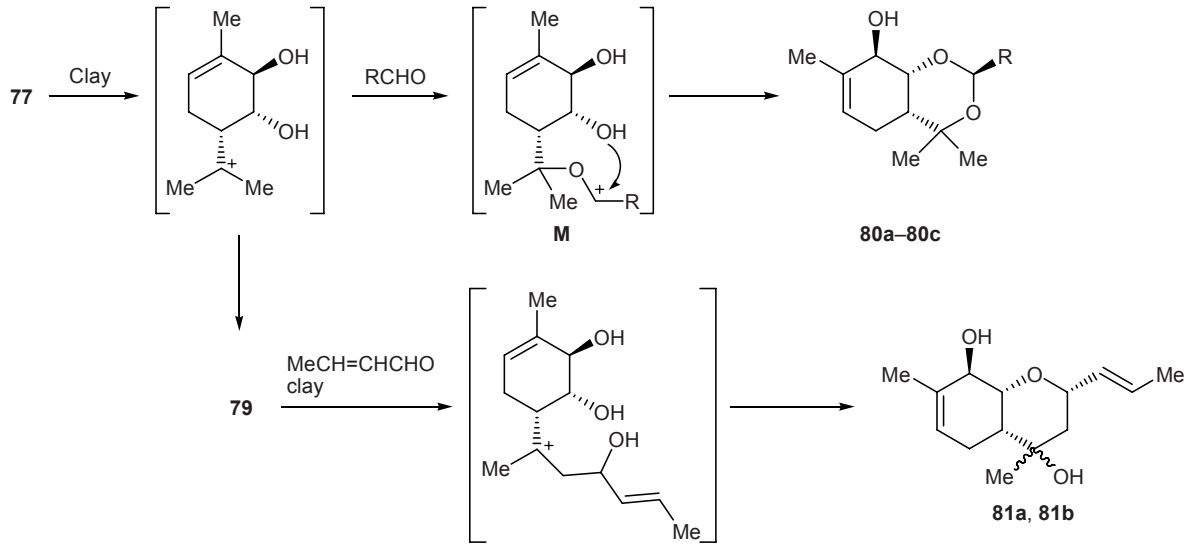
Scheme 25.



Scheme 26.



Scheme 27.



R = *p*-$MeOC_6H_4$ (**a**), *o*-HOC_6H_4 (**b**), MeCH=CH (**c**).

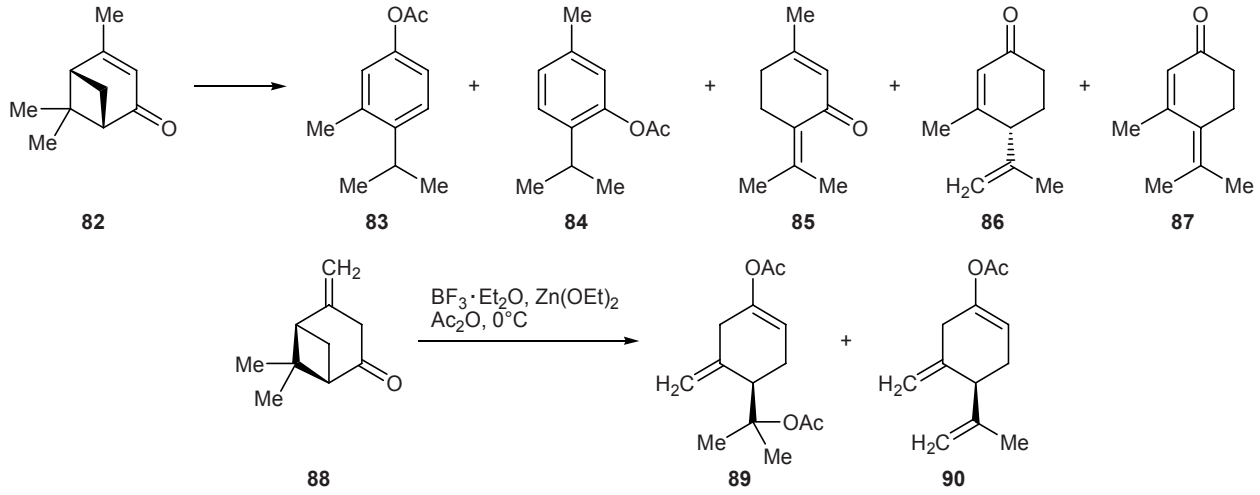
rather than carbocyclization, as in reactions of other oxygen-containing pinane derivatives (see Schemes 5, 13, 17, and 23). In going from aromatic aldehydes to crotonaldehyde, a new reaction path appears: apart from compound **80c** and isomerization products, diastereoisomeric diols **81a** and **81b** were isolated from the reaction mixture.

6. TRANSFORMATIONS OF CARBONYL COMPOUNDS OF THE PINANE SERIES

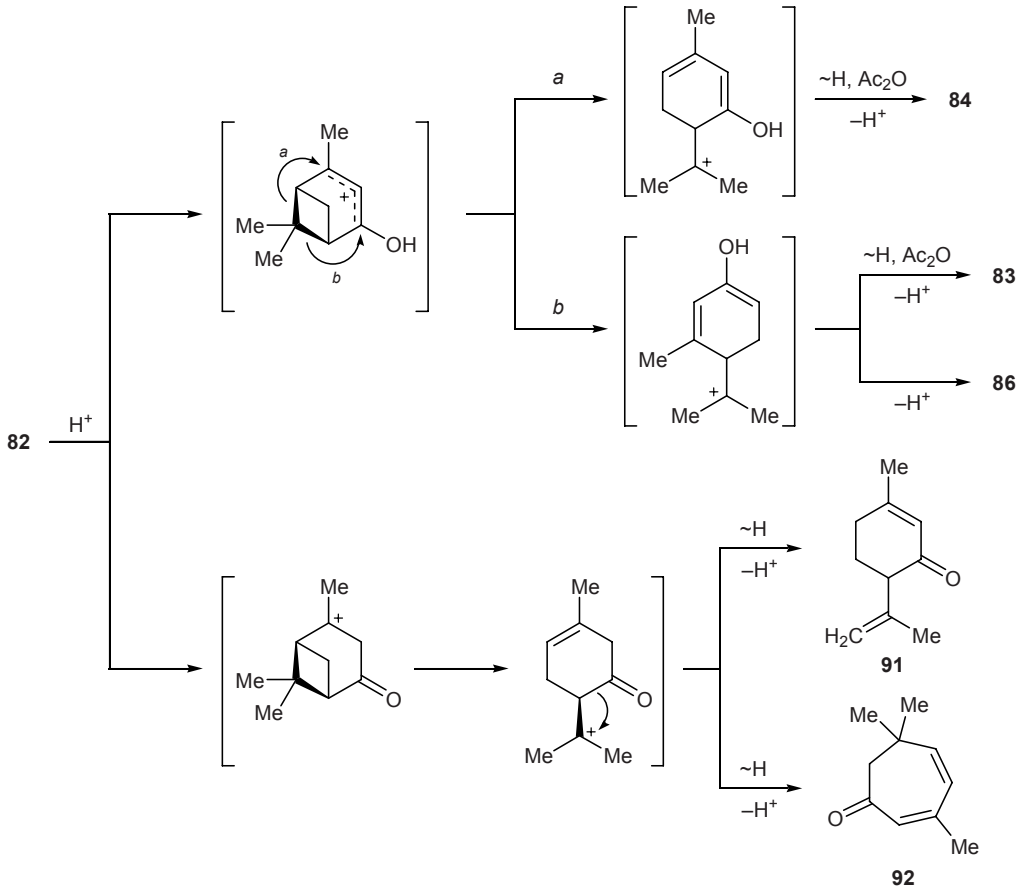
Heating of verbenone (**82**) in a mixture of acetic acid and acetic anhydride in the presence of *p*-toluenesulfonic acid resulted in the formation of aromatic phenyl acetates **83** and **84** as the major products (over-

all yield 45%) and smaller amounts of compounds **85**–**87** [61] (Scheme 28). In the presence of the catalytic system $BF_3 \cdot OEt_2/Zn(OAc)_2/Ac_2O$ the conversion of **82** was 96%, and compound **84** was isolated as the major product (yield 21%) [62]. Under analogous conditions, unconjugated enone **88** readily undergoes isomerization even at 0°C to give only *o*-menthane derivatives, diacetate **89** and monoacetate **90** in 64 and 6% yield, respectively [62]. Verbenone (**82**) in acetic anhydride in the presence of K-10 clay was converted mainly into enones **86**, **91**, and **92** (~44%), while acetates **83** and **90** were formed in smaller amounts (11 and 9%, re-

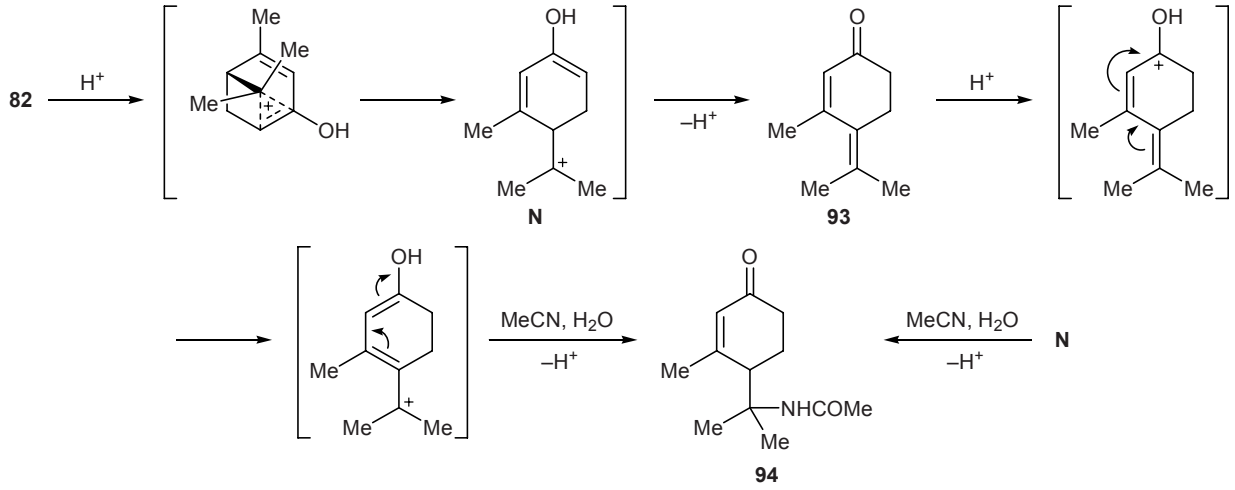
Scheme 28.



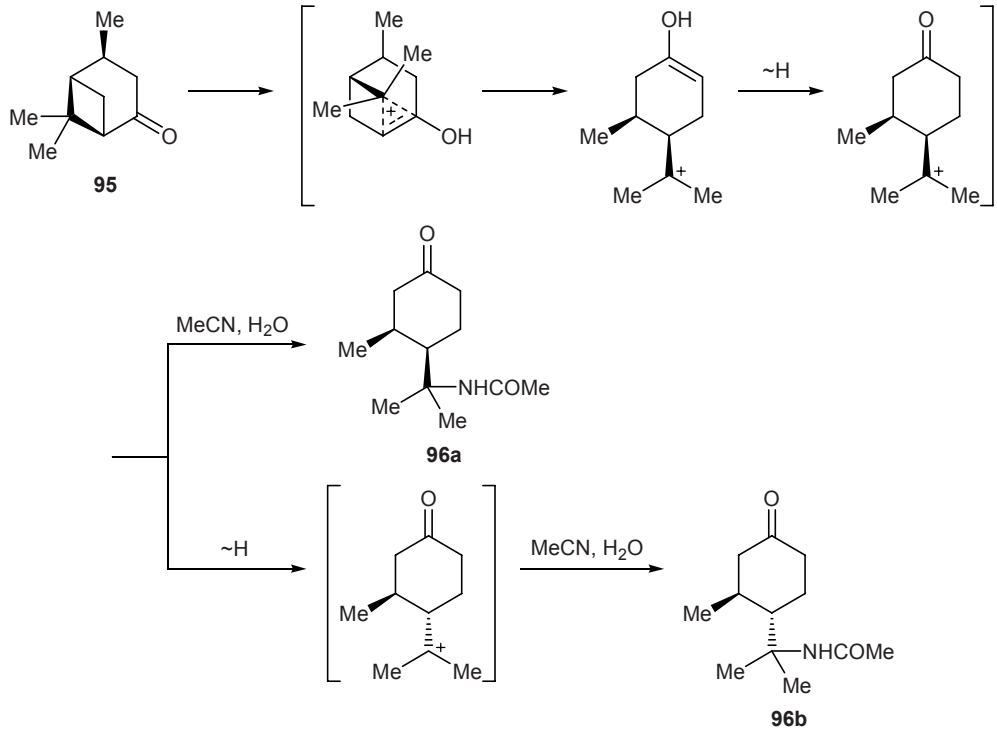
Scheme 29.



Scheme 30.



Scheme 31.



spectively; Scheme 29) [27]. The structure of products **91** and **92** suggests that in the first step the substrate is protonated at the double carbon–carbon bond and that *o*-menthane derivatives **83** and **86** are formed via protonation of the carbonyl group in **82** [27]. It should be noted that only tars were obtained when ketone **82** was kept over K-10 clay in the absence of acetic anhydride, other conditions being similar.

The Ritter reaction of verbenone (**82**) selectively produced *o*-menthane derivatives [63] (Scheme 30). In the presence of 4 equiv of sulfuric acid, the major product was dienone **93**, and the minor, keto amide **94**; larger amount of sulfuric acid (8 equiv) favored formation of amide **94**, while dienone **93** became the minor product. Under these conditions, compound **93** was selectively converted into amide **94**. These data may be rationalized as follows. In moderately acidic medium, the most thermodynamically favorable is stabilization of intermediate carbocation **N** via elimination of proton, leading to dienone **93** with a conjugated 6π-electron system. Higher concentration of sulfuric acid hinders deprotonation process for kinetic reasons,

and intermediate cation **N** is stabilized via nucleophilic addition of acetonitrile molecule; the subsequent hydrolysis yields keto amide **94** [63] (Scheme 30).

Study on the Ritter reaction of a saturated carbonyl compound of the pinane series, verbanone (**95**), with acetonitrile showed [64] that the ratio of stereoisomeric products **96a** and **96b** of the *o*-menthane series depends on the conditions and acid catalyst nature (Scheme 31). In the presence of sulfuric acid at 15°C, a mixture of **96a** and **96b** was formed at a ratio of 1:1; lower temperature favored increased fraction of *cis* isomer **96a** (2:1 to 3:1), but the reaction considerably slowed down. A mixture of stereoisomers **96a** and **96b** at a ratio of 3:1 was also obtained in the reaction catalyzed by boron trifluoride–ether complex at 15°C. The reduced fraction of isomer **96b** with *trans* arrangement of the substituents at lower temperature may be explained by the fact that the rate of hydride shifts is more sensitive to temperature than the rate of nucleophile addition. Higher selectivity in the reaction catalyzed by $BF_3 \cdot Et_2O$ is likely to result from formation of less conformationally labile intermediates.

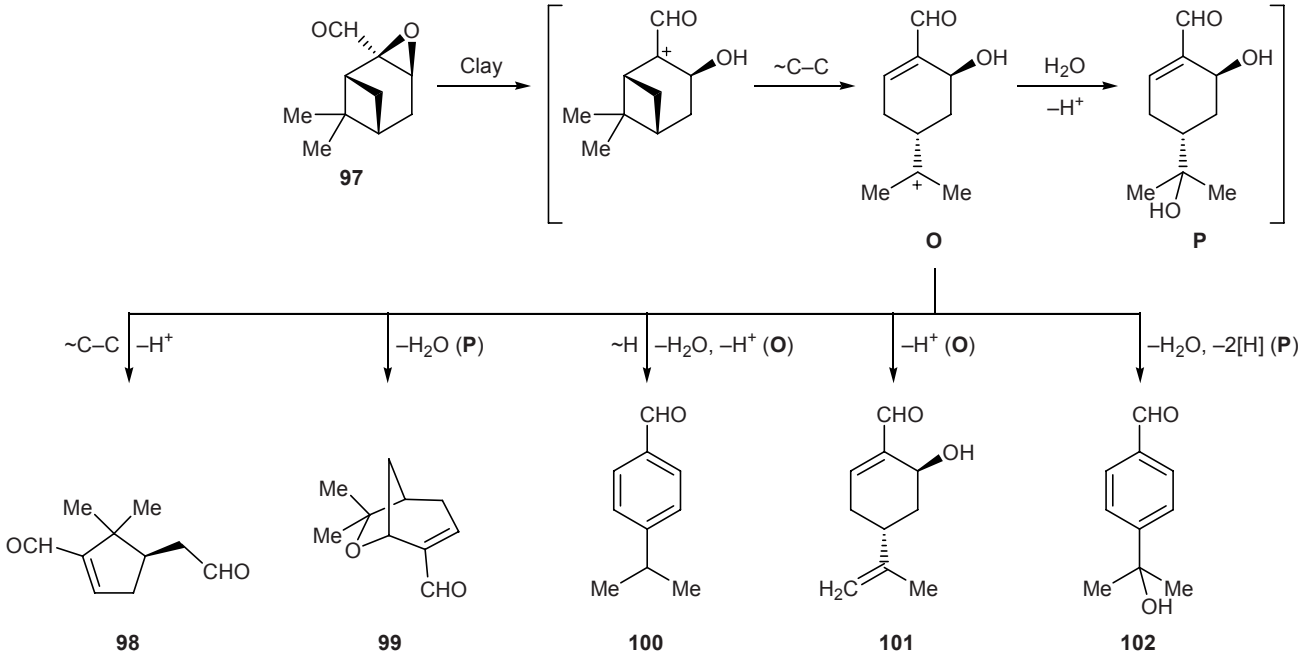
7. TRANSFORMATIONS OF EPOXY CARBONYL PINANE DERIVATIVES

A set of aldehydes was obtained from myrtenal epoxide **97** over askanite–bentonite; the product mixture contained dialdehyde **98** (21%), bicyclic aldehyde **99** (7%), and aldehydes **100**–**102** having a *p*-menthane skeleton (14, 5, and 2%, respectively), the conversion of the initial epoxide being 85% [65] (Scheme 32). As might expected, the major product was campholenaldehyde analog **98**, while the formation of bicyclic aldehyde **99** turned out to be surprising. In fact, only two examples of the transformation of α-pinene epoxide **26** and its derivatives into compounds having a 6-oxabicyclo[3.2.1]octane skeleton have been reported. Motherwell et al. [44] isolated pinol **32** as minor product in the isomerization of epoxide **26** over molecularly imprinted polymers. The same product was obtained by transformation of **26** in superacidic medium at –120°C (Scheme 11) [43]. Therefore, the formation of **99** in the presence of common askanite–bentonite at room temperature (without using special conditions or catalysts ensuring conformational control over isomerization of epoxide **97**) is quite unusual.

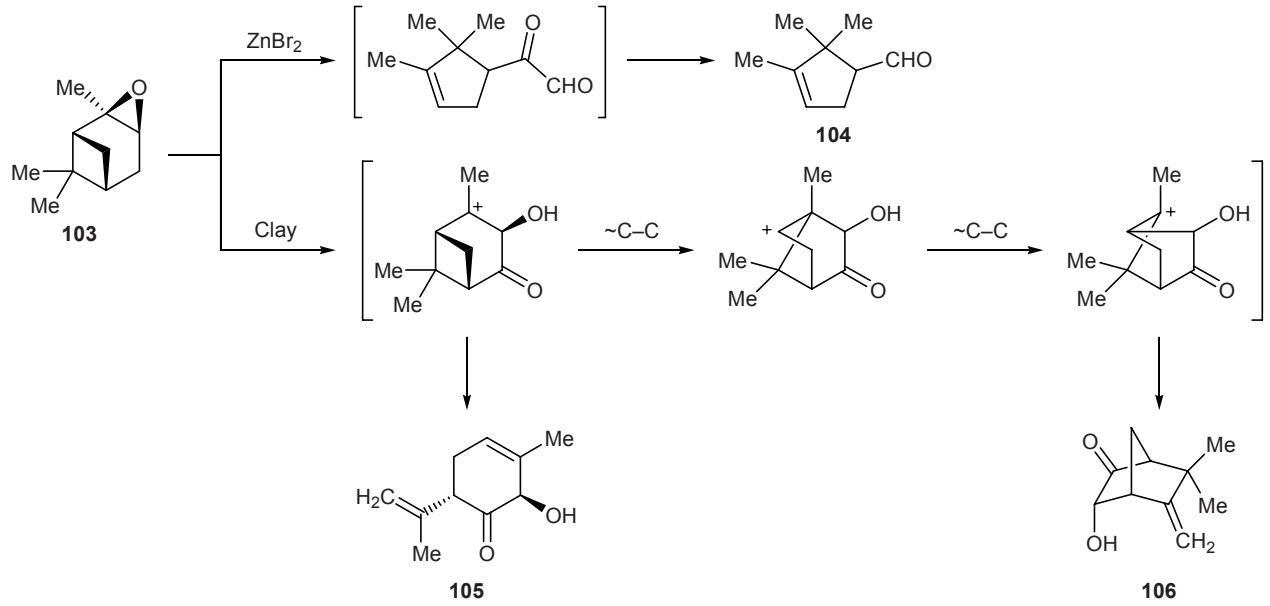
Taking into account *trans* arrangement of the hydroxy and isopropenyl groups, bicyclic aldehyde **97** could not be formed by direct cyclization of cation **O** (Scheme 32). It is most probable that compound **97** arises from intramolecular cyclization of intermediate species **P**. Here, an important factor is likely to be adsorption on the catalyst surface, which fixes a certain conformation of myrtenal epoxide **97** or intermediates derived therefrom.

In the presence of $ZnBr_2$, verbenone epoxide **103** was converted into aldehyde **104** (30%) [66], presumably as a result of expulsion of carbon(II) oxide mole-

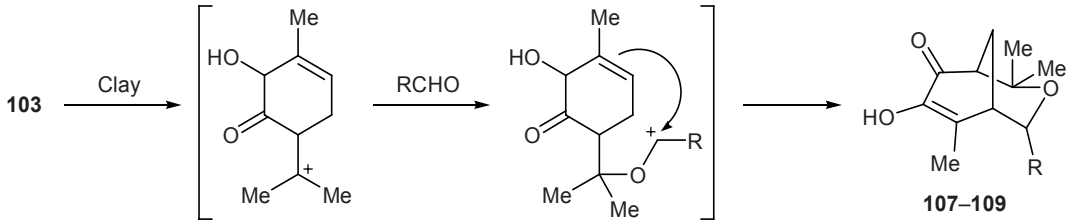
Scheme 32.



Scheme 33.



Scheme 34.



107, R = MeCH=CH; **108**, R = CH_2=CH; **109**, R = *o*-HOC_6H_4.

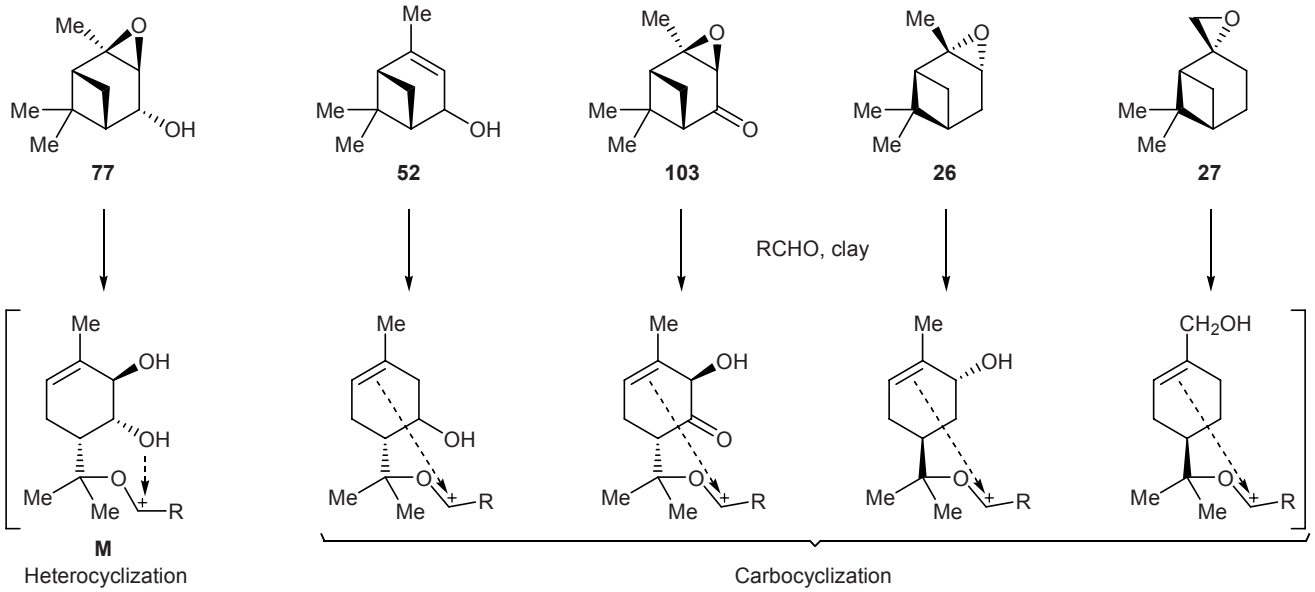
cule from intermediate campholenaldehyde analog (Scheme 33). Keeping of epoxide **103** over askanite–bentonite gave rise to α-hydroxy ketones **105** and **106** having *p*-menthane and camphane skeletons (22 and 36%, respectively), whereas no aldehyde **104** was detected in the reaction mixture [67].

The formation of camphane derivatives from oxygen-containing pinane terpenoids was not observed previously; such rearrangements are typical of only α- and β-pinenes themselves. Insofar as the corresponding *endo* isomer is formed exclusively, the mechanism of formation of compound **106** should inevitably include a formal epimerization step. The epimerization could occur during the rearrangement of the pinane skeleton into camphane. Heterocyclic α-diketones **107**–**109** (as the corresponding enols) were isolated together with the isomerization products from the reaction of verbenone epoxide **103** with acrolein, crotonaldehyde, and salicylaldehyde over clay [67] (Scheme 34). Despite the presence of several oxygen atoms in intermediate carbocation, its carbocyclization rather than heterocyclization turned out to be the most favorable in the final step of the assumed mechanism (as was observed for *cis*-verbenol epoxide **77**; Scheme 27).

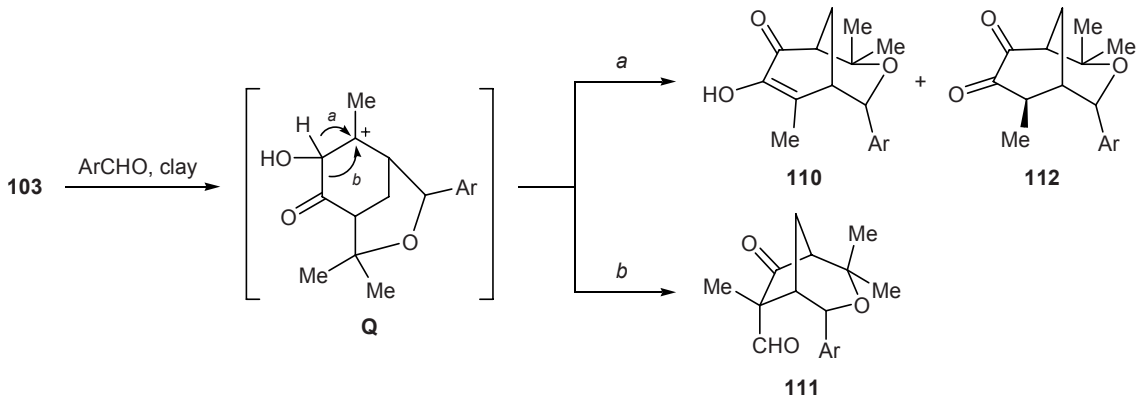
Scheme 35 shows that the structure of carbocationic species derived from verbenone epoxide **103**, *trans*- and *cis*-verbenols **52**, and pinene epoxides **26** and **27** in the course of their clay-catalyzed reactions are very similar to the structure of cation **M** which was presumed [54] to be formed from *cis*-verbenol epoxide **77**. Nevertheless, in the five cases, the products were compounds formed exclusively via carbocyclization in the final step, whereas epoxide **77** gave rise to only heterocyclization product. Thus, even relatively small changes in the terpenoid structure could result in radically different transformation pathways over montmorillonite.

A novel transformation pathway was observed in the reaction of verbenone epoxide **103** with *p*-methoxybenzaldehyde in the presence of clay: apart from

Scheme 35.



Scheme 36.



keto enol **110** (major product), keto aldehyde **111** was obtained. The latter is likely to result from ring contraction in intermediate carbocation **Q** as shown in Scheme 36 [67]. No analogous ring contraction was observed previously in the reactions of terpenoids with aldehydes, leading to bicyclic ethers. Diketone **112** (a tautomer of **110**) was also isolated from the reaction mixture, but compounds **110** and **112** were not converted into each other on heating to 40°C.

8. CONCLUSION

We can conclude that in the past decades considerable progress was achieved in the fields of studying transformations of pinane terpenoids in the presence of acid catalysts, understanding the nature of processes occurring therein, and developing effective procedures for the synthesis of some compounds of practical interest. Wide application of heterogeneous catalysts, mainly montmorillonite clays, made it possible to reveal a number of new transformation pathways leading to various optically active polyfunctional heterocyclic compounds. Despite generally moderate yields in acid-catalyzed transformations of pinane terpenoids, these reactions attract attention due to accessibility and relatively low cost of starting materials and reagents, as well as unique structures of the transformation products.

Strong dependence of the transformation pathways of pinane terpenoids upon the catalyst nature and its parameters gives grounds to believe that appropriate conditions for selective preparation of one or another target product could be found. The results obtained during the past decades open new prospects in the application of pinenes and their derivatives in fine organic chemistry.

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