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REVIEW

Intramolecular Involvement of an Oxygen-containing Nucleophilic Group in Epoxy Ring Opening

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Abstract—The objective of the review is analysis of reactions occurring in epoxy compounds with additional oxygen-containing group (carbonyl, epoxy ring or alcohol group) attached to its skeleton, and the description of the biological aspects of the reactions. The mechanisms of the reactions, the stereo- and regioselectivity of transformations are discussed.

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INTRODUCTION

Epoxy rings that fairly readily form at a double bond oxidation constitute structural fragments of quite a number of biologically active substances, both natural and synthetic [1]. Due to high reactivity the epoxides undergo various transformations in a wide range of environments when treated both with electrophilic and nucleophilic reagents. The preparation and reactions of epoxy compounds are described in several reviews [2–9]. However the behavior of epoxides containing an additional functional group was systematized save the articles on transformations of α,β-epoxy ketones where the reactions at epoxy and carbonyl groups were treated separately [10], and on α,β-epoxyalcohols [11].

We discuss here the transformations of epoxy derivatives having in the molecule an additional oxygen-containing functional group, epoxy, hydroxy, or carbonyl one. These polyfunctional compounds attract interest because the intramolecular nucleophilic attack of the oxygen leading to the opening of the epoxy ring may result in formation of various carbocyclic and heterocyclic substances. The transformations treated in the review concern epoxycarbonyl compounds with the functional groups separated with one or more carbon atoms, α,β-epoxy ketones with a pronounced reciprocal influence of functional groups, isomerizations of diepoxy compounds and epoxyalcohols where the functional groups were also separated with one or more carbon atoms. The final result

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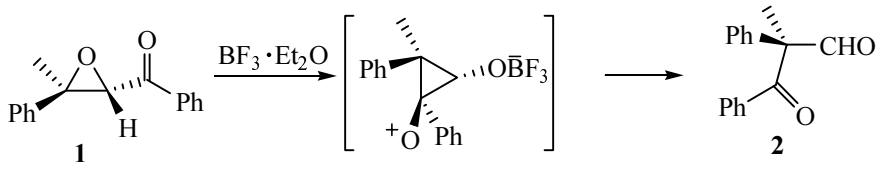
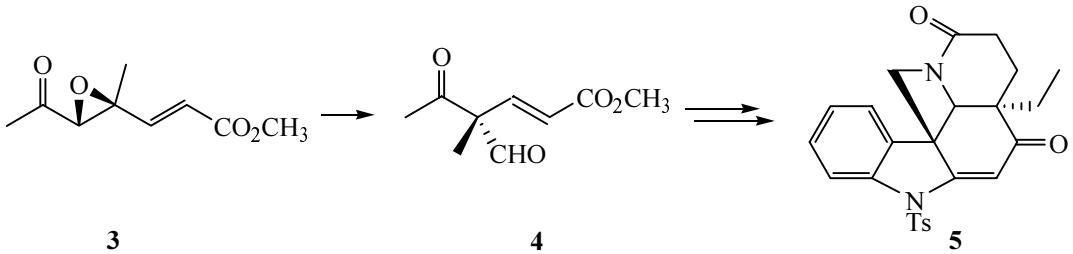
Scheme 1.



Scheme 2.



of transformations is discussed as influenced by the mutual position of the functional groups and the reaction conditions.

INTRAMOLECULAR TRANSFORMATIONS OF EPOXYCARBONYL COMPOUNDS ISOMERIZATION OF α,β-EPOXYCARBONYL COMPOUNDS

Epoxy group is very sensitive to acid reagents; therefore in the presence of acids the α,β-ketoepoxides undergo isomerization into the corresponding dicarbonyl compounds. The process involves a migration of an adjacent group (H, alkyl, acyl etc.) to the electron-deficient carbon atom arising at the epoxy ring opening [12, 13].

The growing interest to the enentioselective synthesis promoted development of procedure for α,β-epoxyketones rearrangement into 1,3-dicarbonyl compounds affording products of enentiomeric purity of 90% and more. For instance, the opening of the ring in 1,3-diphenyl-2,3-epoxybutan-1-one **1** effected by boron trifluoride etherate in dichloromethane solution furnished a single enantiomer **2** in 97% yield [14]. The anantioselectivity was attributed by Bach and Domalaga to the formation of a cyclic transition state (Scheme 1).

Proceeding from α,β-epoxyketone **3** 1,3-dicarbonyl compound **4** was obtained [15] that was used as a chiral building block in designing polycyclic compound **5** possessing antitumor activity (Scheme 2).

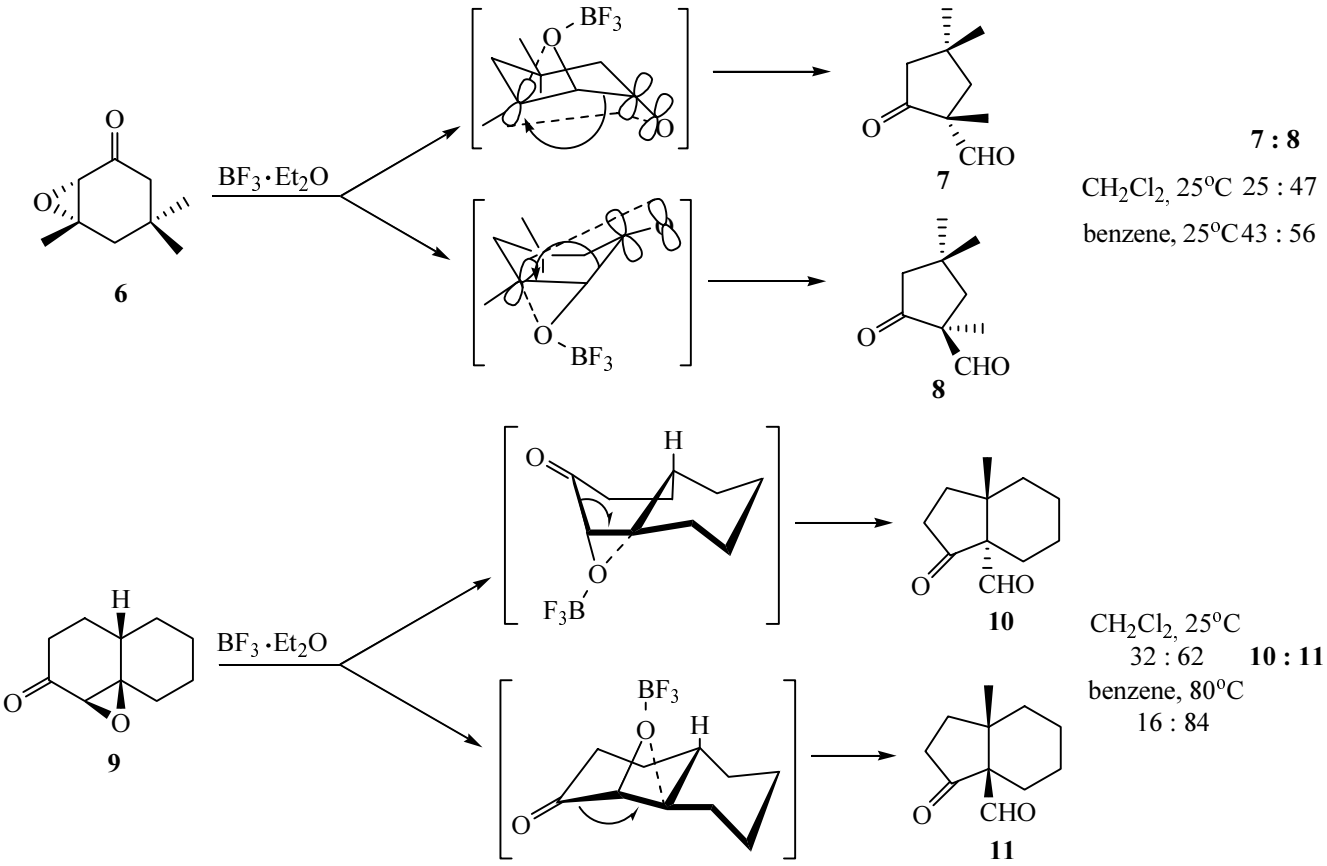
In the isomerization of cyclic epoxyketones with the oxirane ring fused to the cycle or is in a spiro position thereto the C~C-migration resulted in ring contraction or ring expansion respectively. The isophoron epoxide **6** trans-formation catalyzed by boron trifluoride etherate led to ring contraction yielding a mixture of enentiomers **7** and **8** [16] (Scheme 3). The optical isomers ratio varies depending on the solvent used. The isomerization of compound **9** also proceeded with contraction of the cyclohexane ring to cyclopentane one and resulted in a mixture of ketoaldehydes **10** and **11** [17].

The cycle expansion was observed in conversion of isopulegone epoxide **12** into compound **13** [18], and in the synthesis of the naturally occurring humulenone **15** from compound **14** [19] (Scheme 4).

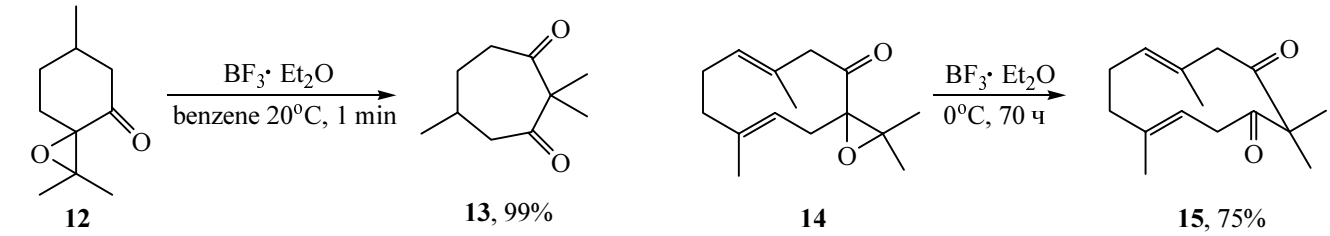
The epoxy ring opening was catalyzed not only by boron trifluorate etherate. In [20, 21] a mechanism was outlined of epoxycarbonyl compounds transformations catalyzed by metal cations. The α,β-epoxyketones were shown to undergo a rearrangement into 1,3-dicarbonyl compounds characterized by high stereo- and regiospecificity in the presence of Lewis acids like $LiClO_4$ (where the Li^+ cation played the role of the acid) or $InCl_3$. The rearrangement involved the *1,2*-migration of a C–C bond. The oxygens of the epoxy ring and the carbonyl group coordinate simultaneously to the Lewis acid, the electron density shifts to the epoxy group oxygen, and the rupture of the C–O bond occurs with a cationic center formation. The subsequent acyl group migration affords the 1,3-dicarbonyl compound. The key point of the procedure is the use of the above catalysts instead of the most common Lewis acids (BF_3, $SnCl_4$) providing the possibility to carry out the reaction under milder conditions (Scheme 5).

The opening of the epoxy ring in α,β-epoxyketones makes possible preparation of difficultly availably spirocyclic 1,3-dicarbonyl compounds. Based on epoxyketones **16** spiro compounds **17** were obtained in 70–

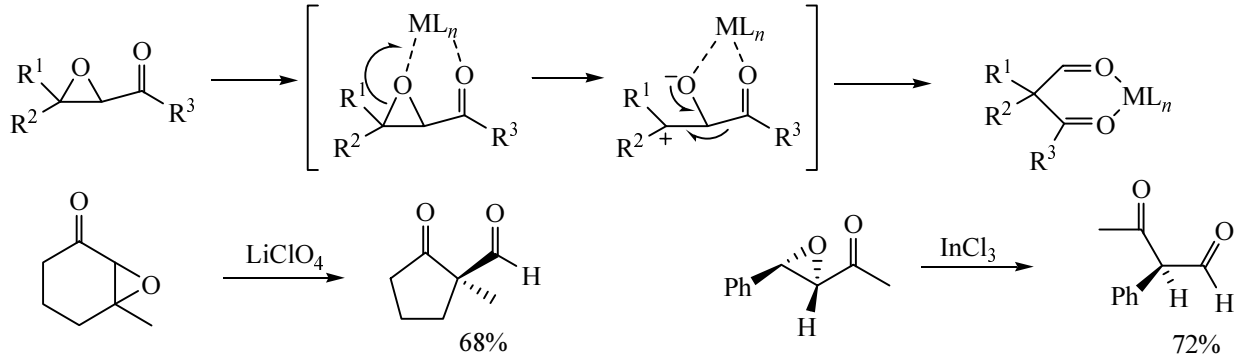
Scheme 3.



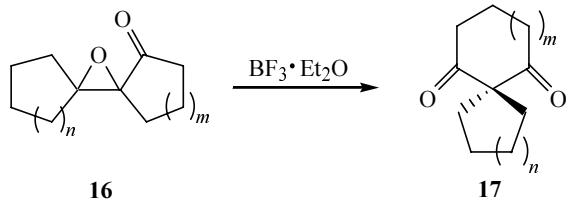
Scheme 4.



Scheme 5.



Scheme 6.



16 **17**

n = 1–4, m = 1, 3.

91% yield and with enentiomeric purity 98–99% [22] (Scheme 6).

The isomerization of the cyclic α,β-epoxyketone **18** into 1,3-dicarbonyl compound **19** was the key stage in the synthesis of an insect pheromone (–)-frontaline **20** and of the naturally occurring antibiotic (–)-malyngolide **21** found in sea organisms [23] (Scheme 7).

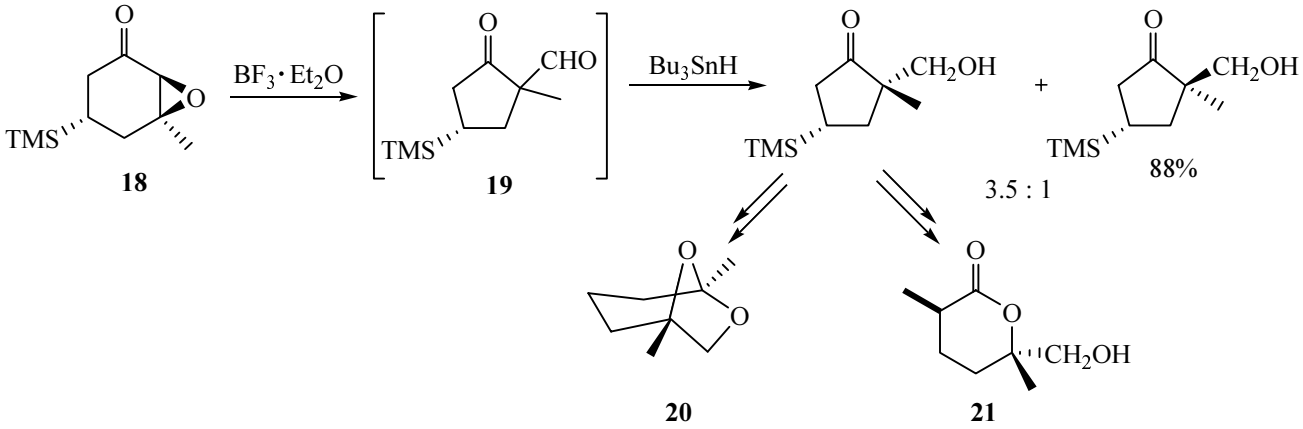
REARRANGEMENTS OF COMPOUNDS WHERE THE EPOXY AND CARBONYL GROUPS ARE SEPARATED BY ONE OR MORE CARBON ATOMS

The epoxy group opening in compounds with the carbonyl and epoxy groups separated by one or several carbon atoms affords either dicarbonyl compounds or carbo- and heterocycles arising from the intramolecular interaction of these functional groups.

1,4-Dicarbonyl compounds resulting from β,γ-epoxyketones under acid catalysis are intermediates in the synthesis of furan derivatives. For instance, in [24] the behavior of some epoxyketone **22a–22d** was studied in the presence of protic acids (*p*-toluenesulfonic acid in chloroform, 100°C, 1–2 h) and Lewis acids (boron trifluoride etherate in dichloromethane, 20°C, 15 min). The initial compounds were transformed into substituted furans **23a–23d**. In some cases the intermediately formed dicarbonyl compounds were isolated (Scheme 8). The isolation of diketones from the reaction mixture was considered by Cormier et al. as a proof that the furan derivatives formed via preliminary isomerization of the epoxy group into a carbonyl.

A series of tandem reactions involving the epoxy ring opening and aldol condensation resulting in intramolecular cyclization products was reported in [25]. The epoxy group isomerization into a carbonyl occurred in the presence of Pd(0) tributylphosphine complex, and addition to the reaction mixture of a weak base (sodium hydrogen carbonate) initiated the aldol condensation (Scheme 9). These reactions furnish conjugated unsaturated ketones

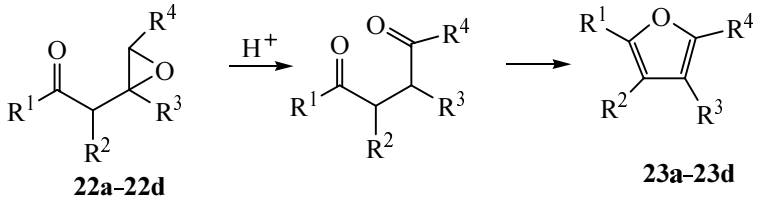
Scheme 7.



18 **19** **20** **21**

TMS is tetramethylsilyl

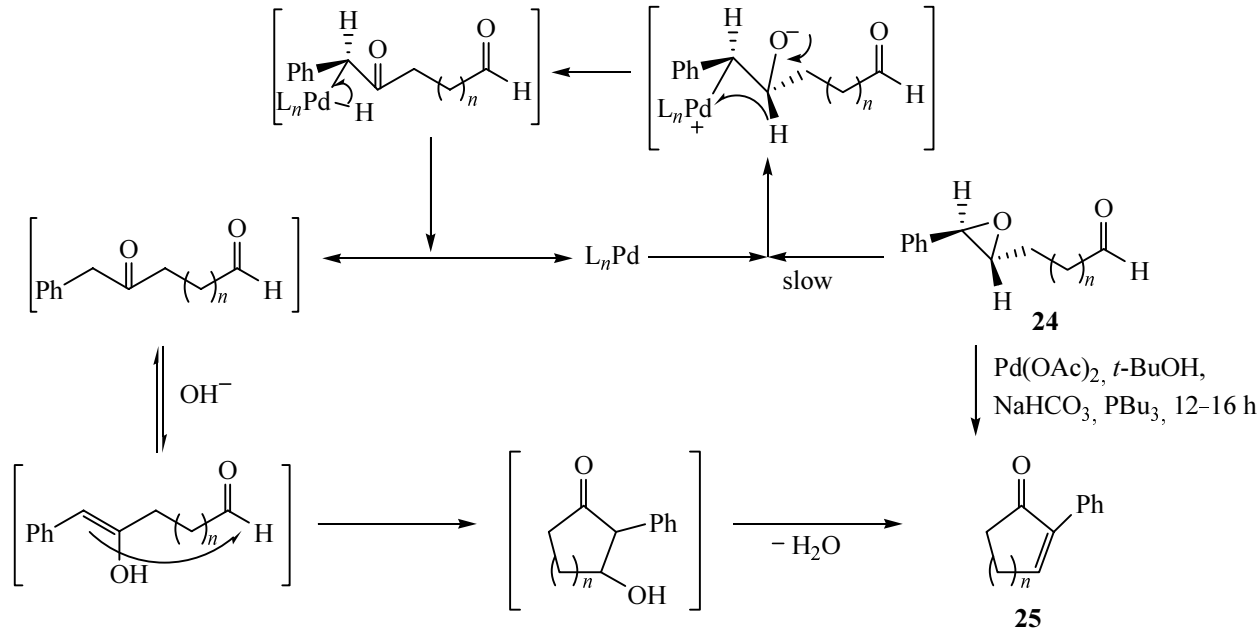
Scheme 8.



22a–22d **23a–23d**

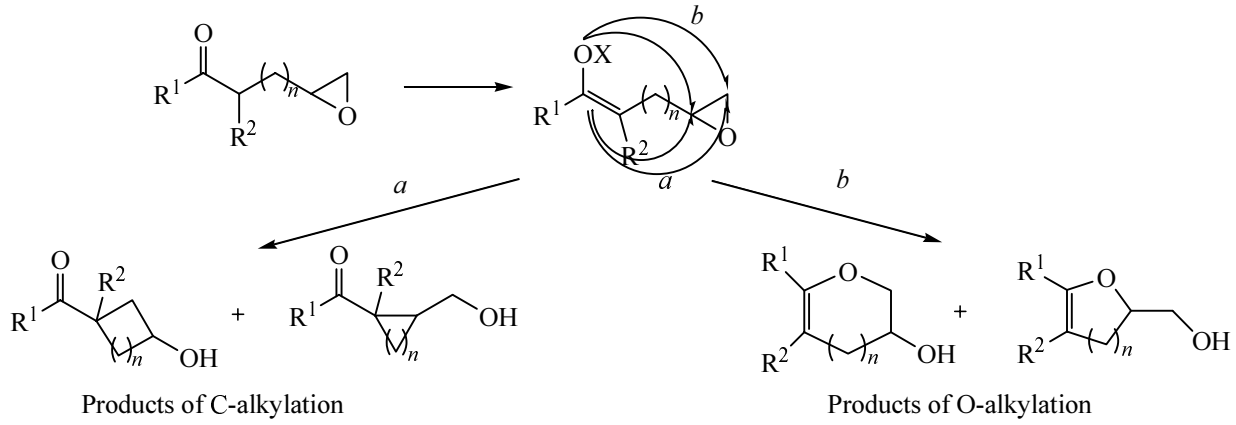
R^1 = Et (**a, b**), H (**c**), Me (d), R^2 = H (**a–c**), Me (**d**), R^3 = Me (**a**), H (**b–d**), R^4 = H (**a, b, d**), Et (**c**).

Scheme 9.



n = 1, 80%; 2, 78%.

Scheme 10.



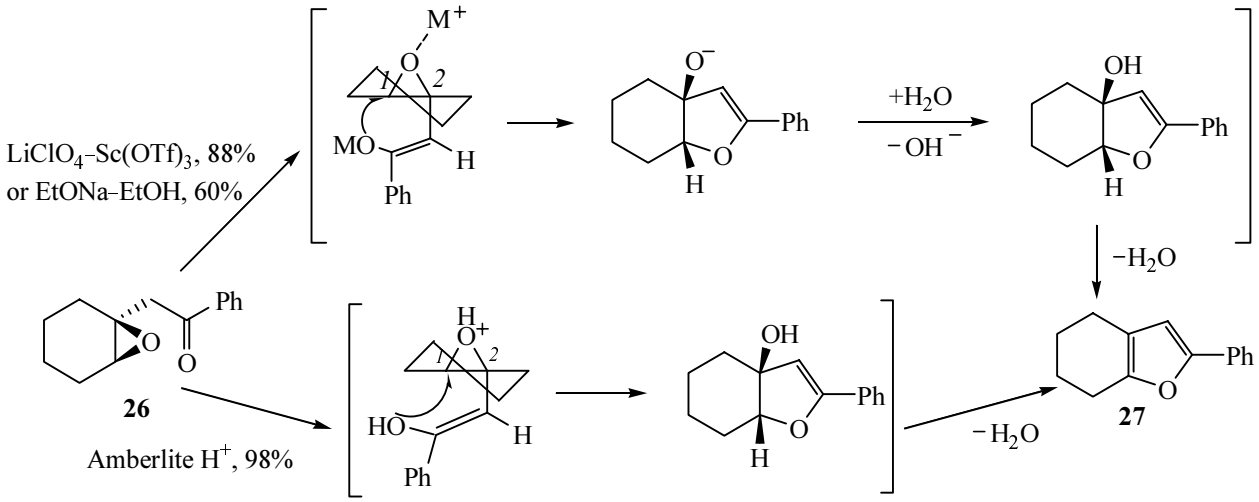
X = H, metal, n = 1–3

with five-membered and six-membered rings **25** from epoxycarbonyl compounds **24**.

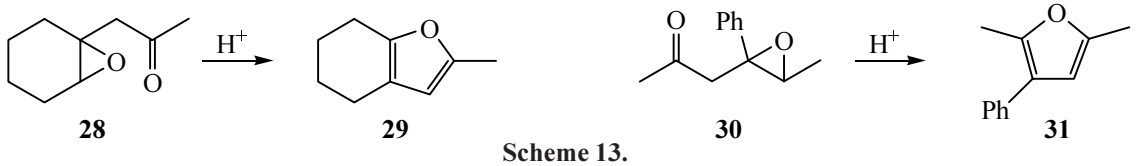
2.2.1. Formation of C- and O-alkylation products. The intramolecular reaction between the carbonyl and epoxy groups can occur in two ways: In acid or alkaline media arise enols or enolate anions respectively. Further interaction of the enol fragment with the epoxy ring results in carbocyclic compounds (cyclopropanes, cyclopentenes etc., Scheme 10, path *a*) in case of the C-alkylation, or in oxycompounds (cyclic ethers, furan derivatives etc.) at O-alkylation (path *b*).

Note that due to the high sensitivity of the epoxy ring to acid reagents the O-alkylation products prevail in the acid media. In the alkaline media where the epoxy ring is relatively stable the ratio of the C- and O-alkylation products depends on the spatial arrangement of the atoms in the transition state. Besides the reaction often affords a single enentiomer suggesting that the process may be regarded as enantioselective one. The O- and C-alkylation occurs both with epoxides from acyclic precursors and those containing a cyclic fragment in a molecule. There-

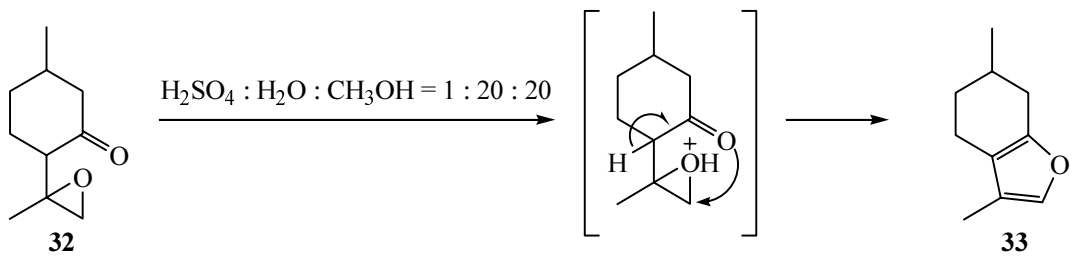
Scheme 11.



Scheme 12.



Scheme 13.



fore they can be applied to building up complex polycyclic structures.

β,γ-Epoxycarbonyl compounds (where the keto and epoxy groups are separated by a single carbon atom) provide furan derivatives both in acid and alkaline media. In alkali the oxygen of the enolate attacks the epoxy ring, and in the acid medium the enol form of the carbonyl group attacks the carbon atom of the protonated epoxy ring. For instance, epoxyketone **26** formed compound **27** [26] with a furan ring as a result of O-alkylation followed by elimination both in acidic and alkaline media (Scheme 11).

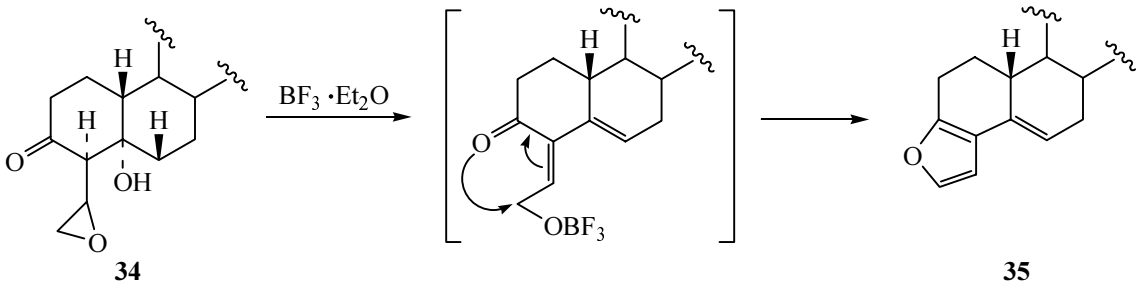
Acetonylepoxides **28**, **30** (β,γ-epoxyketones) cyclized into 2-methylfuran derivatives **29, 31** in the presence of dilute sulfuric acid [27] (Scheme 12).

The conversion of isopulegone oxide **32** into menthofuran **33** in 13% yield was carried out under mild conditions close to natural [28] (Scheme 13).

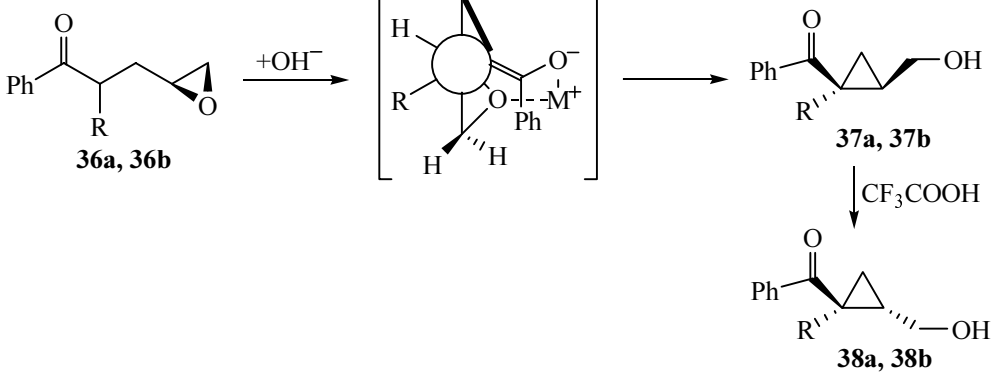
Epoxyketols of cholestane series **34** were also prone to rearrangement into furan derivatives **35** [29]. The reaction is catalyzed by BF_3 that acts simultaneously as a dehydrating reagent (Scheme 14).

The carbocyclization of β,γ-epoxyketones in basic medium is one of the preparation methods of cyclopropane derivatives. For instance, it was shown in [30] that compound**я** **36a, 36b** in various media [$LiClO_4$/$Sc(OTf)_3$/toluene, *t*-BuOK/*t*-BuOH, NBS/DMSO–H_2O/KOH] underwent cyclization to yield cyclopropane derivatives **37a, 37b** with only *cis*-position of substituents in the cyclopropane ring; no traces of presumable *trans*-

Scheme 14.

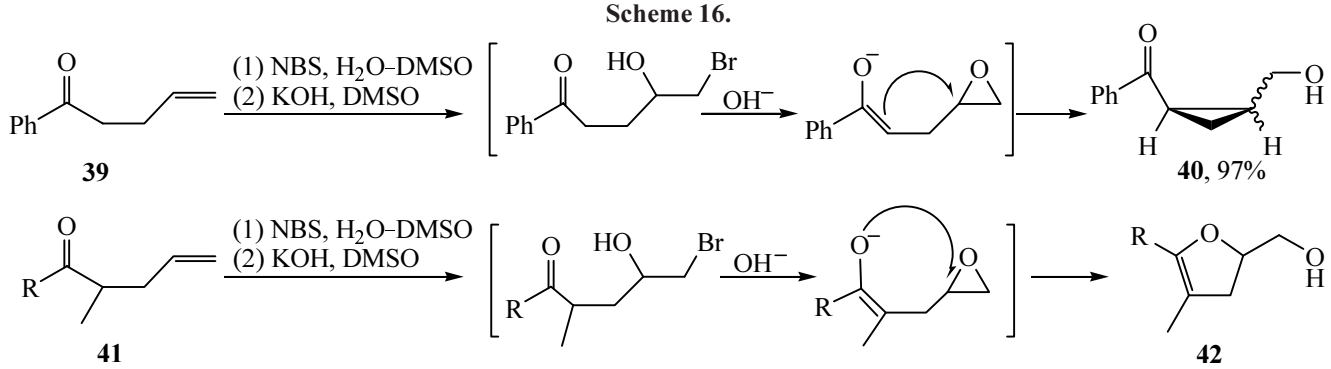


Scheme 15.



R = H, 0°C, 2 h, 94% (**a**); CH_3, 0°C, 3 h, 86% (**b**).

Scheme 16.

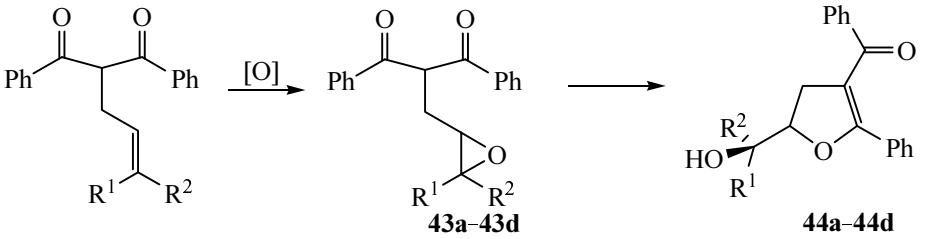


R = Ph, 67%; *t*-Bu, 49%.

diastereomers **38a, 38b** or O-alkylation products were found (Scheme 15) [31]. Dechoux *et al*. ascribed the formation of only compounds **37a, 37b** to the high stereospecificity of the cyclization process where the efficient coordination of the enolate and epoxy oxygens to the metal (Li^+, K^+, Sc^{3+}) prevented any possibility of *trans*-isomers **38a, 38b** formation. The latter can be prepared by compounds **37a, 37b** isomerization in the trifluoroacetic acid (Scheme 15). The conversion of compoundя **36a** in methanol in the presnce of sodium methylate yielded a single product **37a** of optical purity over 99% [31].

Sometimes the C- and O-alkylation reactions occur already in the process of the synthesis of epoxycarbonyl compounds. It was shown in [32] that in reaction of bromosuccinimide with unsaturated ketone **39** followed by bromohydrine treatment with KOH–DMSO an epoxy ring formed and the carbonyl group underwent enolization (Scheme 16). However the reaction was not completed at this point and further interaction occurred between the two functional groups to furnish cyclo-propane derivatives **40** with the ratio of the *cis* to *trans* isomers equal to 99:1. The reaction of compound **41,** structural analog of compound **39** distinguished only by the presence

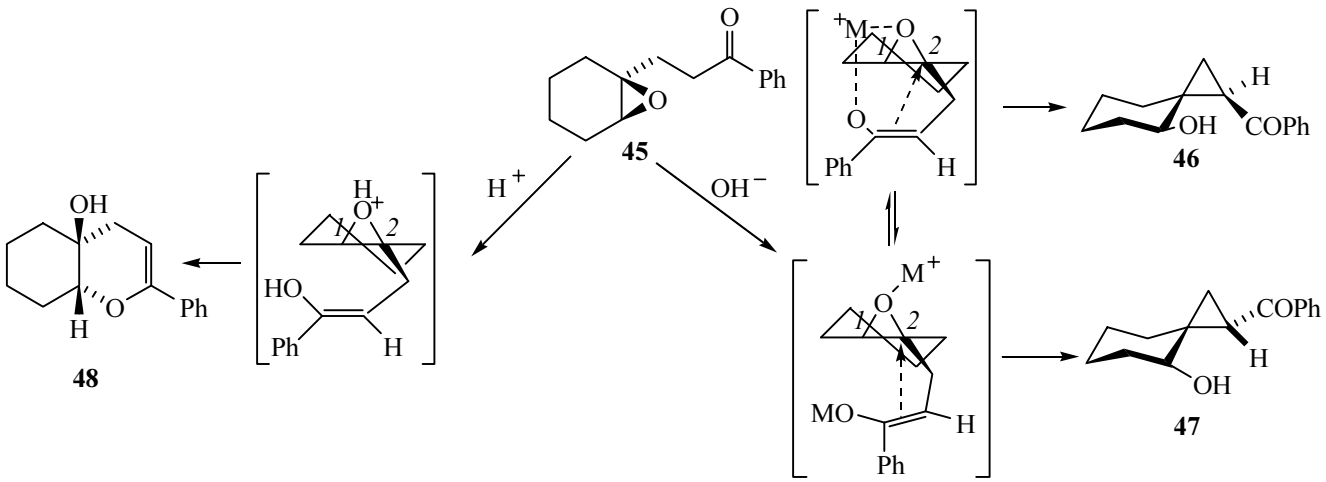
Scheme 17.



43a–43d **44a–44d**

R^1 = H, R^2 = H (**a**), Me (**b**), Ph (**d**); R^1 = Me, R^2 = Me (**c**).

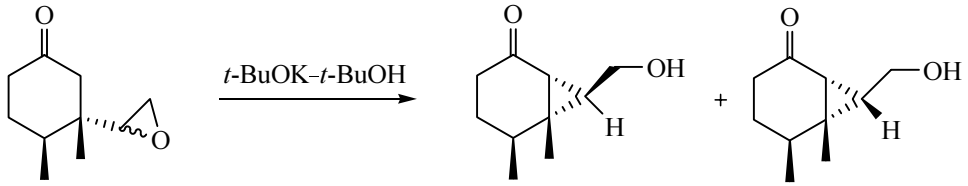
Scheme 18.



45 **46** **47** **48**

$M^+ = Li^+, Sc^{3+}, Na^+$.

Scheme 19.



49 **50** **51**, 71%

2.5 : 1

of a methyl group in the α-position to the carbonyl under the same conditions yielded the O-alky-lation products **42**. The different behavior of compounds **39** and **41** was probably caused by shielding of the enol C–C bond in the latter compound by the methyl group hampering the attack on the epoxy ring.

Under alkaline catalysis (with NaH or Na_2CO_3) epoxydiketones **43a–43d** were converted into dihydrofuran derivatives **44a–44d** in 75–96% yield [33] (Scheme 17). The dependence of the conversion on temperature was investigated to demonstrate that the reaction products could be obtained avoiding isolation of the epoxydiketones **43a–43d** from the reaction mixture.

When the epoxycarbonyl compound already contains in its skeleton a carbocycle the interaction between the epoxy and carbonyl groups provides bicyclic compounds with rings fused or in a spiro junction. For instance, in [26] was reported preparation of diastereomer C-alkylation products **46** and **47** by cyclization of epoxide **45** in alkaline medium ($LiClO_4$–$Sc(OTf)_3$–toluene) in a ratio **46**:**47** = 3:1 (Scheme 18). The predominant formation of compound **46** is apparently due to the chelating effect of metal cation (Li^+, Sc^{3+}) in the transition state. The isomerization of the same epoxyketone **45** in the presence of sodium alcoholate afforded the same products in another ratio: **46**:**47** = 1:6. In an acid medium only O-alkylation occurred furnishing bicyclic compound **48**.

Bicyclo[4.1.0]heptanes **50** and **51** obtained by compound **49** isomerization in alkaline medium arise from a stereospecific *cis*-junction of six-membered and three-membered rings by a C-alkylation process [34] (Scheme 19).

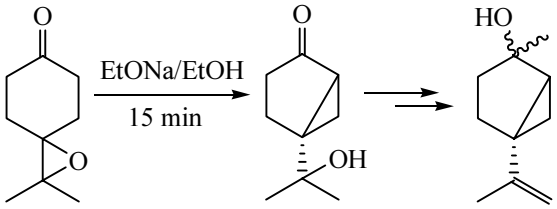
The carbocyclization of γ,δ-epoxyketone **52** affording a cyclopropane ring in compound **53** constitutes the principal stage in the synthesis of terpene compounds belonging to thujane group that has been developed in [35] (Scheme 20).

The formation of bicyclo[5.1.0]octanone **55** from 4,5-epoxyoctan-1-one **54** was described in [36] (Scheme 21).

The reaction of ethyl acetoacetate metal derivatives with β-bromoepoxides **56** resulted in formation of epoxycarbonyl compounds with the functional groups separated by three carbon atoms [37]. The intramolecular interaction of the epoxy and carbonyl groups in these epoxydiketones afforded dihydropyran derivatives **58** (Scheme 22). The preparation of the cyclic compounds was carried out without isolation of compound **57** from the reaction mixture.

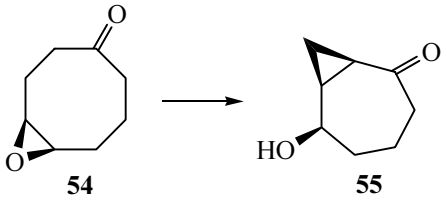
The transformations of acyclic β,ε-epoxyketones **59** where between the keto and epoxy groups three carbon atoms were present were studied in basic media [30]. It was shown that only O-alkylation products **60** and **61**

Scheme 20.



52 **53**, 90%

Scheme 21.



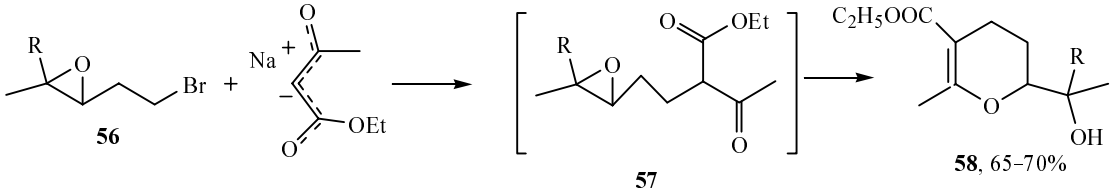
54 **55**

K_2CO_3–DMF 89%, *t*-BuOK–Et_2O, 90%.

were obtained (Scheme 23). No carbocyclization products were detected in the reaction mixture, and it was ascribed to the low stability of the transition state required for the C-alkylation.

The behavior of epoxyketones **62** and **63** containing an epoxy group fused to a cyclohexane ring was studied both in basic [$LiClO_4$–$Sc(OTf)_3$–toluene] and acid (Amberlite H^+) media [26]. The final product of

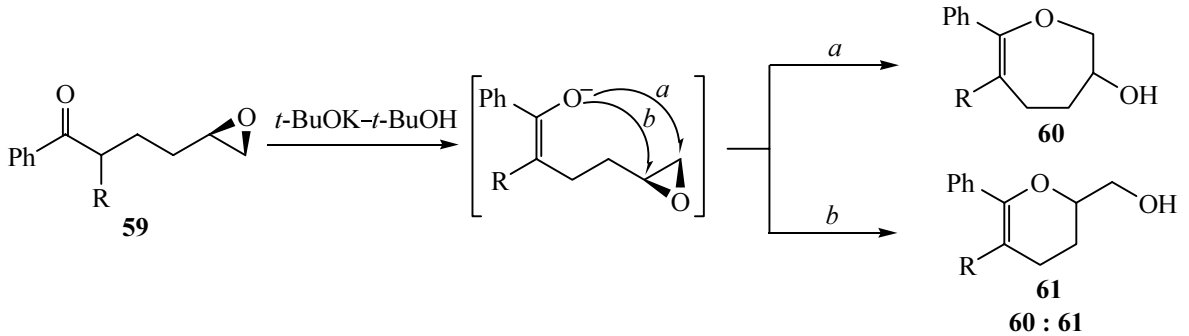
Scheme22.



56 **57** **58**, 65–70%

R = H, MeONa, MeOH, CH_3, EtONa, EtOH.

Scheme 23.

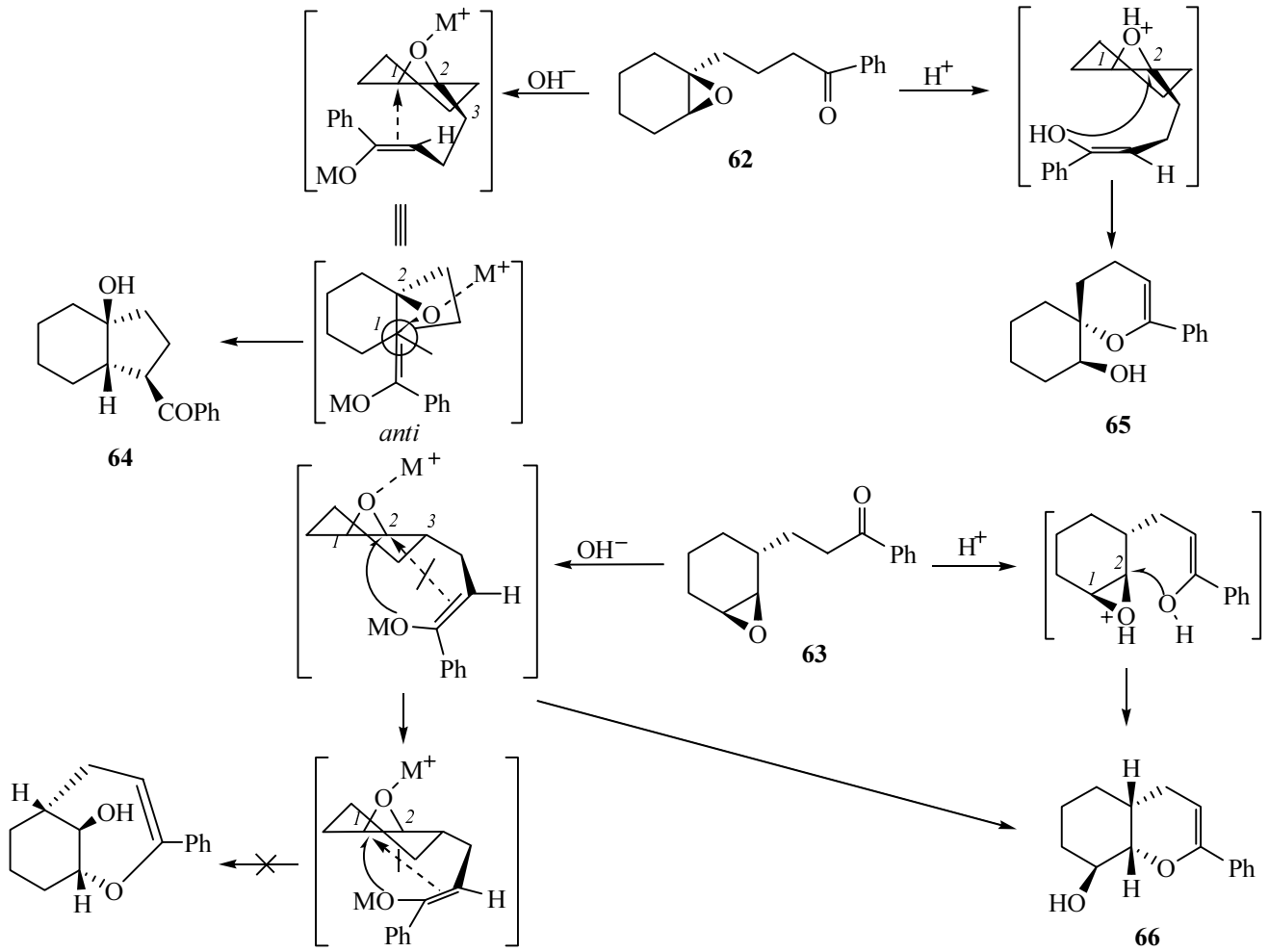


59 **60** **61**

60 : 61

R = H, 80°C, 3 h 23 : 77
R = CH_3, 80°C, 3 h 17 : 83

Scheme 24.

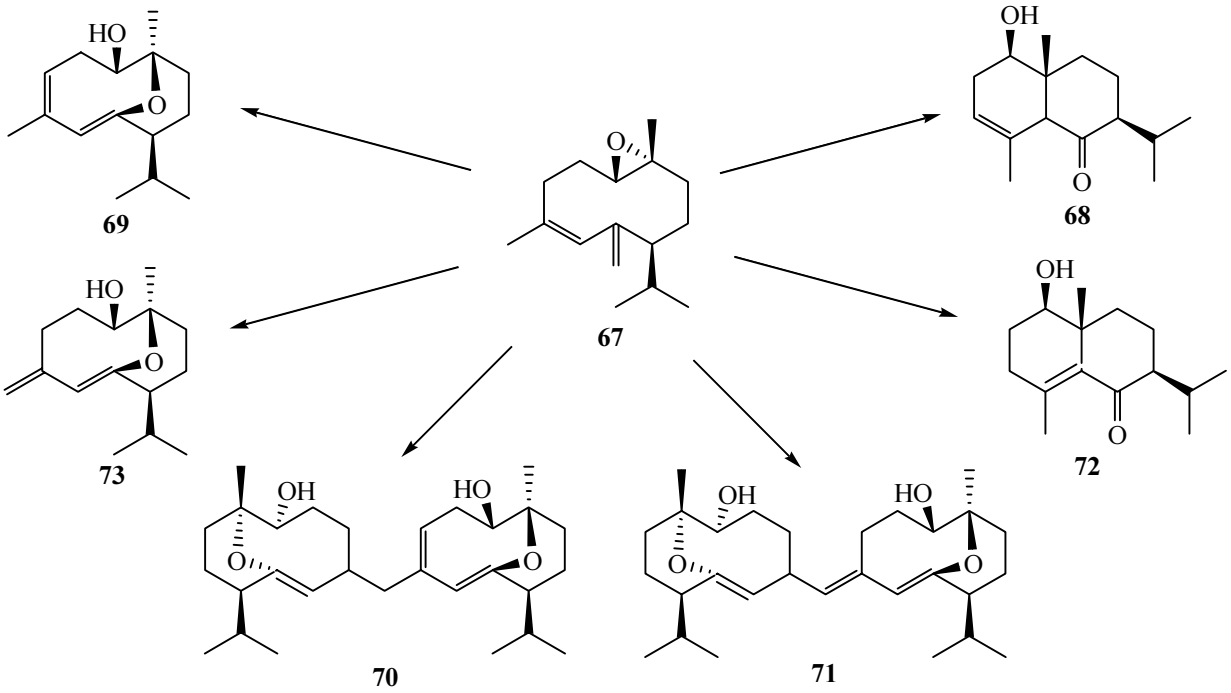


$M^+ = Li^+, Sc^{3+}$.

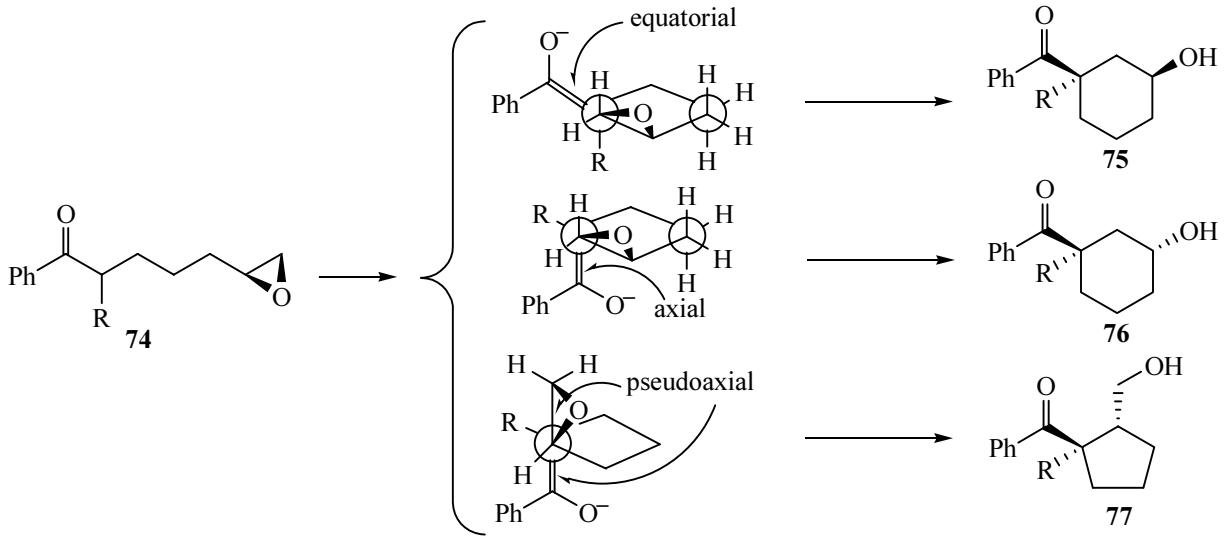
epoxyketone **62** conversion depends on the reaction conditions: in the basic medium only C-alkylation product was obtained (bicyclic hydroxyketone **64**), and in acid environment formed also the product of O-alkylation (spiro compound **65**). The compound **64** formation occurs through the classic most stable *anti*-transition state by the attack of the C–C bond of the enol fragment on the C^1 atom. In the acid medium the oxygen of the enol group attacks the C^2 atom since the six-membered cyclic transition state is more favorable than seven-membered (Scheme 24). Epoxyketone **63** both in acid and alkaline medium furnished only the O-cyclization product, compound **66**. Both conformations did not enter into the C-alkylation because the interaction between a double bond and an epoxy group required a four-membered or a five-membered transition state, but in contrast to compound **62** the fragment $C^1C^2C^3$ was rigidly fixed, and the distance between the reaction sites was too large. At the same time in the concurrent O-alkylation the nucleophilic attack on the C^2 atom of the epoxy ring occurred via a six-membered transition state leading to compound **66**. Hence in this case the direction of the reaction essentially depended on the structure of the initial β,e-epoxyketone.

The transformations of epoxyisoacoragermacrone **67** as an example of competing O- and C-alkylation were studied in [38]. The isomerization of epoxyketone **67** in formic acid cooled to –20°C afforded carbocyclization product **68** in 34% yield (Scheme 25). The rearrangement of compound **67** in the presence of Al_2O_3 occurred with the epoxy ring cleavage and intramolecular hetero-cyclization resulting in compound **69** and dimerization products **70** and **71** in 18 : 47 : 33 ratio respectively. Catalysis of epoxyketone **67** transformations with potassium *tert*-butylate in butanol afforded bicyclic compound **72** in 75% yield; and isomerization in the presence of basic alumina furnished compound **73** as the main reaction product.

Scheme 25.



Scheme 26.

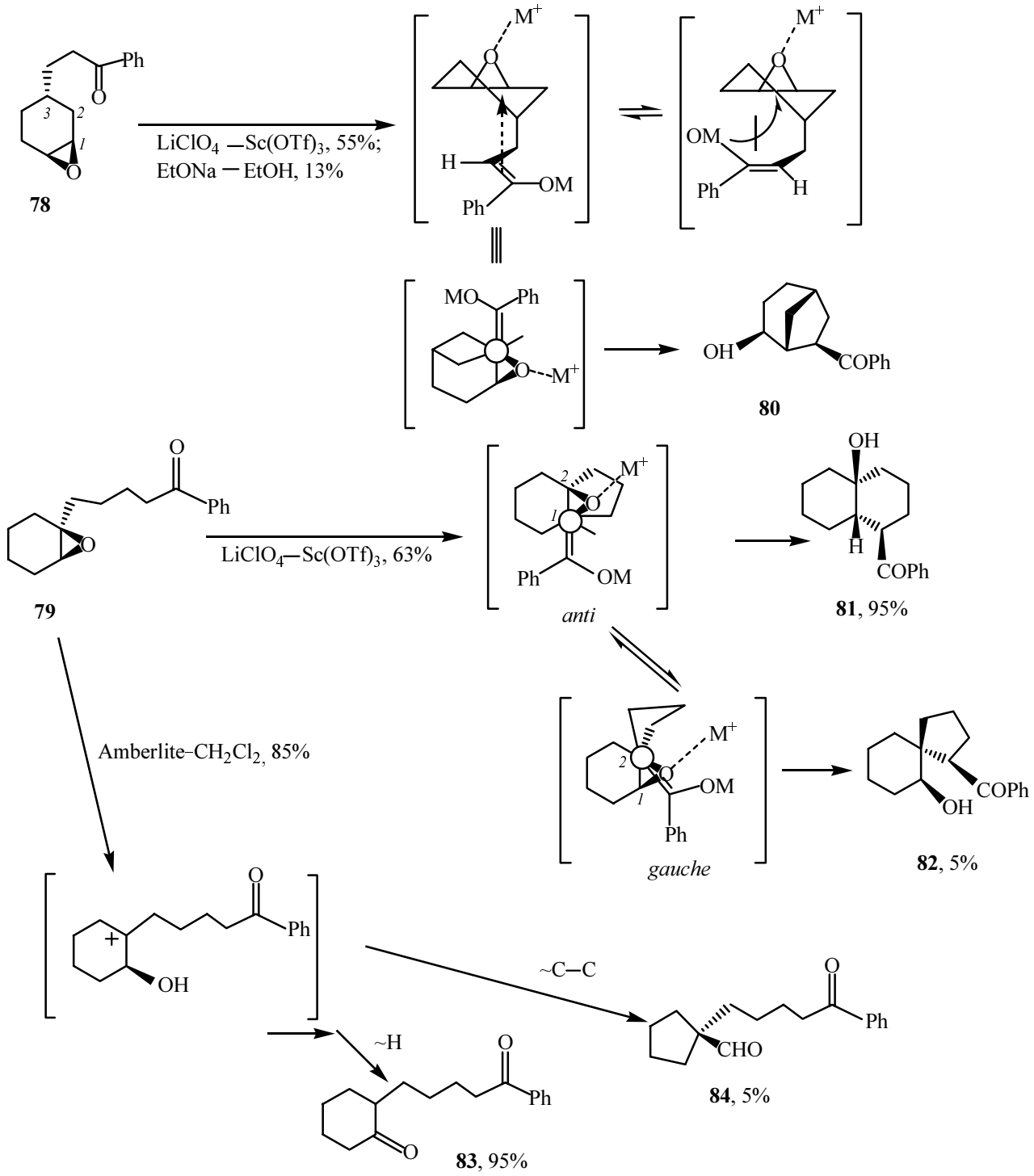


R = H, CH_3.

Let us consider the rearrangements of epoxyketones whose structure contains epoxy and keto groups separated by four carbon atoms. The cyclization of epoxyketones **74** in basic media reported in [30]afforded diastereomers mixture **75, 76** and compounds **77** (Scheme 26). It was shown that isomerization in the presence of $LiClO_4$–$Sc(OTf)_3$–toluene provided products **75** and **76** in a ratio **75**:**76** of 85:4, and also 12% of compound **77.** In the *t*-BuOK–*t*-BuOH medium formed only compounds **75** and **76** in the 73:27 ratio. The prevailing formation of cyclohexane derivative was ascribed to the higher stability of the six-membered transition state compared to the five-membered, and also to the feasibility of the attack on the less hampered primary carbon atom of the epoxy ring. The higher yield of compound **75** is due to its formation via the most stable transition state where the enol bond is in the equatorial position.

The behavior of epoxyketones **78** and **79** where the epoxy ring was fused to a cyclohexane ring and the carbonyl group was located in the acyclic side chain was studied in [26] (Scheme 27). The rearrangement of

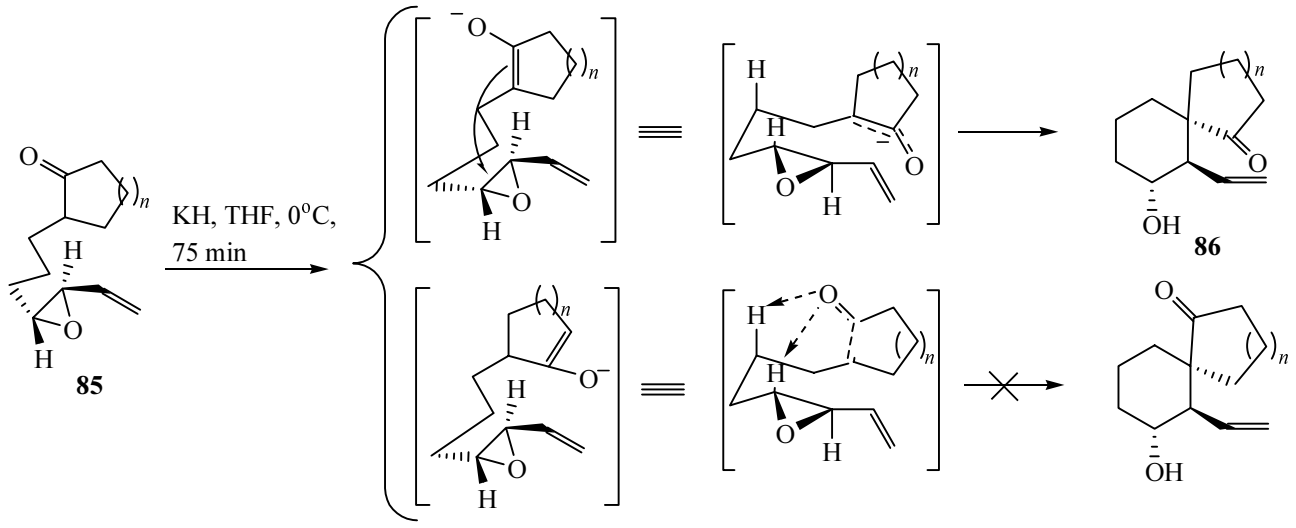
Scheme 27.



$M^+ = Sc^{3+}, Li^+$.

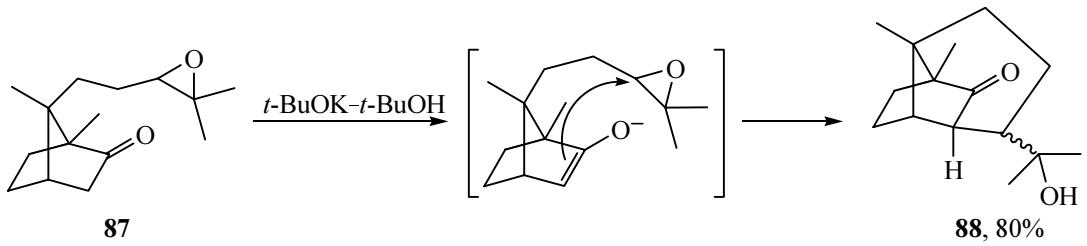
compound **78** in alkaline media gave rise to C-alkylation product **80.** The formation of this substituted bicyclo-[3.2.1]octane was ensured by a five-membered transition state with the *anti*-location of the unsaturated system and the C–C bond of the epoxy ring. No O-alkylation products was detected in rearrangements of compound **78** both in alkaline and acid media for this process required formation of at least seven-membered transition state. Epoxyketone **79** in alkaline media yielded only C-alkylation products. Bicyclic hydroxyketone **81** and

Scheme 28.



n = 1, 95%; 2, 50%.

Scheme 29.



spirohydroxyketone **82** arise from the nucleophile attack on the C^1 or C^2 atoms of the epoxy ring, and the prevailing formation of compound **81** is due to the higher stability of the *anti*-transition state as compared to the *gauche*-transition state. The lack of the O-alkylation products may be apparently ascribed to requirement for their formation of unfavorable seven- or eight-membered transition state. Only compounds **83** and **84** resulting from the epoxy ring opening were obtained in the acid media. The obvious difference in behavior of compounds **78** and **79** is due to the presence in the former of a rigid structural fragment $C^1C^2C^3$ between the epoxy and keto groups, whereas in the skeleton of epoxyketone **79** these functional groups are connected by a conformationally flexible carbon chain.

In contrast to above mentioned examples compound **85** contains the carbonyl in the ring and the epoxy group in a side chain. Epoxyketones **85** were shown [39] to undergo cyclization in THF in the presence of KH affording spirocyclic compounds **86**. *trans*-Location of the vicinal vinyl and hydroxy group resulted from the epoxy ring opening under the given conditions, and the selectivity at formation of the quaternary asymmetric center was due to the sterical requirements of the transition state: The 1,3-diaxial interaction was the most feasible in the *pseudochair* conformation (Scheme 28).

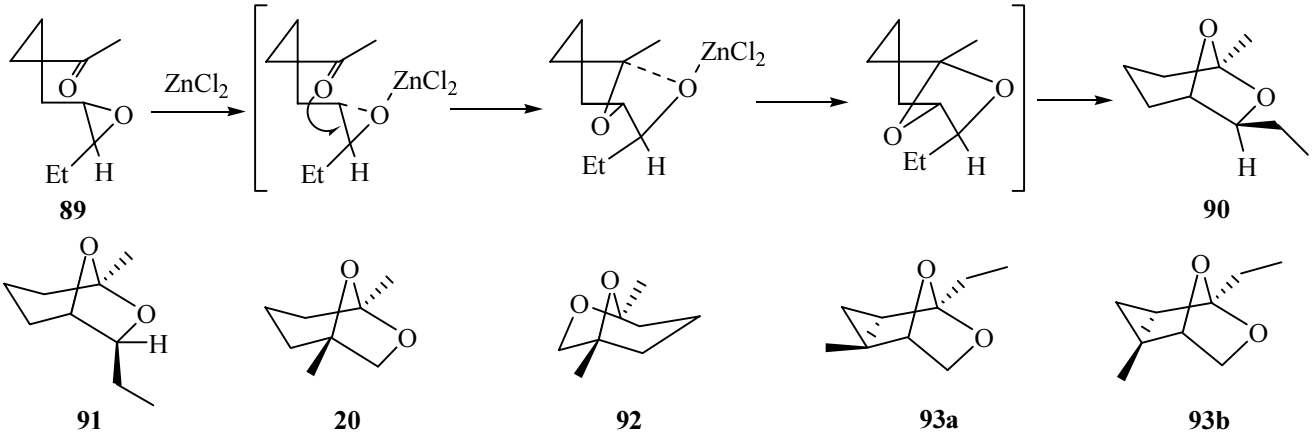
In [40] an example was described of epoxyketones application in the synthesis of complicated polycyclic structures **88** starting with bicyclic compound **87** (Scheme 29).

Hence we have shown in this section that the transformations of epoxycarbonyl compounds give rise to formation of versatile carbo- and heterocyclic compounds, and these compounds belond to different classes of cyclic substances: Bicyclic, spiro and/or oxaspiro compounds that are difficultly available by the other synthetic procedures form here with high stereo- and regioselectivity.

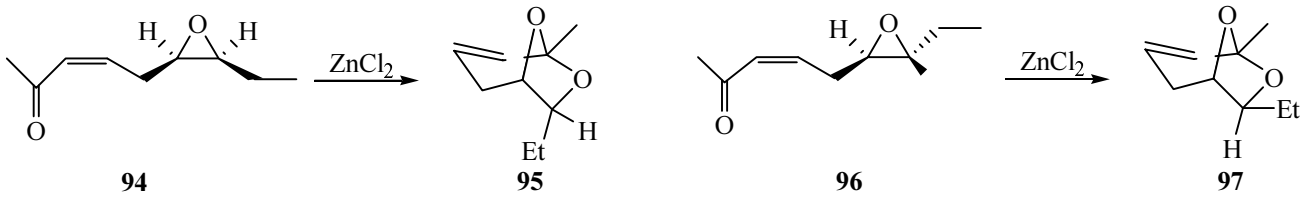
DIOXABICYCLIC COMPOUNDS FORMATION

The transformation of epoxycarbonyl compounds in acid media is among the main procedures for preparation of substances with a dioxabicyclic skeleton. The class of bicyclic ketals attracts much attention since these

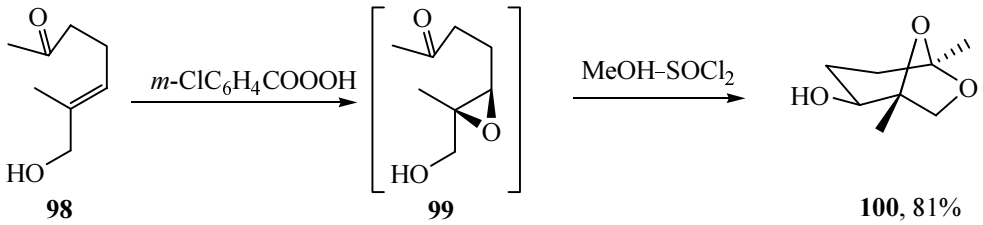
Scheme 30.



Scheme 31.



Scheme 32.



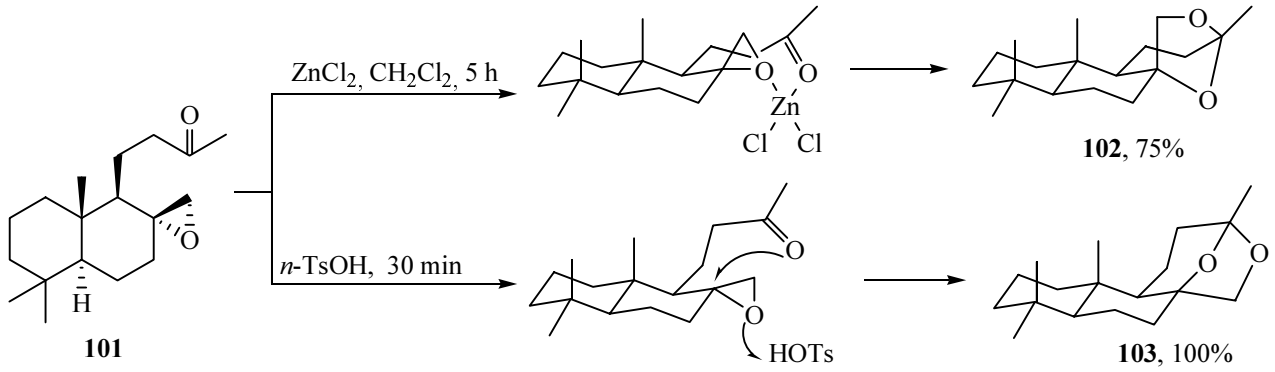
compounds are fundamental components of some insect pheromone compositions [41], they are fragrant substances, and methods have been developed to prepare therefrom six- and seven-membered cyclic ethers. The bicyclic ketals are obtained by treatment with various acid reagents (protic or Lewis acids) of epoxycarbonyl compounds where the epoxy and keto groups are separated by two, three, or four carbon atoms. The intramolecular epoxide opening involving the carbonyl often affords a single isomer.

It was shown in [42] that the opening of the epoxy ring in compound **89** and its structural analogs δ,e-epoxyketones furnished bicyclic ketals belonging to the series of 6,8-dioxabicyclo[3.2.1]octane **20, 90–93a, 93b**. The mechanism of formation of the compounds involves a protonation of the epoxy group or its complexing with a Lewis acid and an attack of the unshared electron pair of the oxygen from the carbonyl group occurring with the configurational inversion of the epoxy ring carbon (Scheme 30). Compounds prepared by isomerization of δ,ε-epoxyketone (*exo*-**90** and *endo*-brevicomin **91** [43], (–)-**20** and (+)-frontalin **92**, α-**93a** and δ-multi-striatin **93b** [44]) are characteristic components of phero-mone compositions controlling the aggregation of bark beetles belonging to genera *Dendroctonus* and *Dryocoetes.*

The unsaturated analogs of epoxyketone **89,** compounds **94** and **96,** undergo cyclization under the treatment with Lewis acids affording the multipurpose pheromone of domestic mice *Musmusculus* **95** and its isomer **97** respectively [45] (Scheme 31).

It was shown [45] that the dioxabicyclic compounds could be obtained also at the use of the other acids (TsOH, $BF_3 \cdot Et_2O$) but only the application of $ZnCl_2$ ensured the stereoselectivity of the reaction and nearly quantitative yield.

Scheme 33.



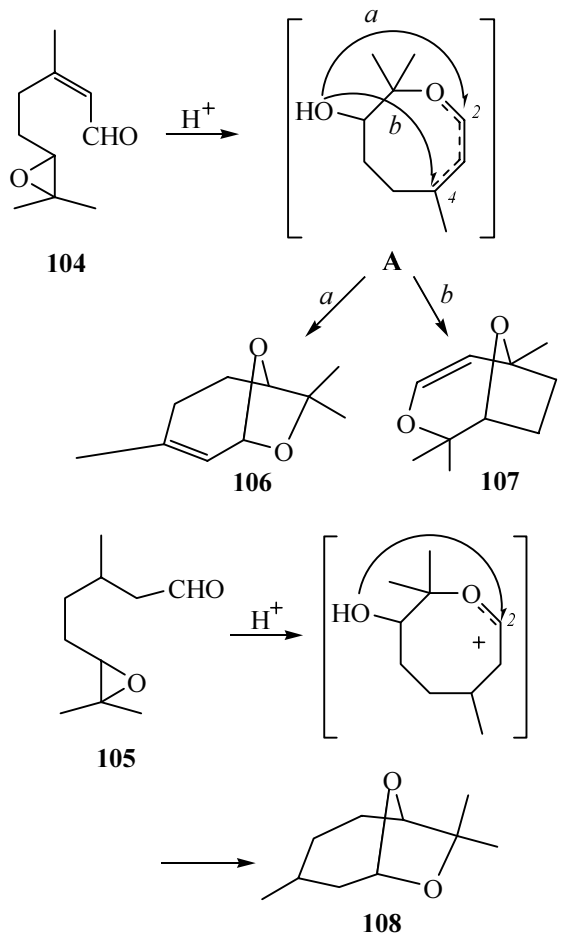
The treatment of unsaturated ketoalcohol **98** with the *m*-chloroperbenzoic acid gave rise to a labile epoxyketone **99** that in the system methanol–$SOCl_2$ was converted into bicyclic alcohol **100** as the main reaction product [46] (Scheme 32).

An interesting example was reported in [47] where the transformations of epoxyketone **101** were described occurring under the treatment of various acid agents. The cyclization catalyzed by $ZnCl_2$ furnished compound **102** with a strong wood odor. Isomeric compound **103** prepared in the presence of *p*-toluenesulfonic acid was odorless. The stereospecificity of the reaction resulted from coordination on $ZnCl_2$ both of carbonyl and epoxy oxygens, and therefore the quaternary asymmetric center was formed from the α-side; in the case of compound **103** formation the nucleophilic attack of the unshared electron pair of the carbonyl oxygen on the carbon atom of the protonated epoxy group occurred from the β-side (Scheme 33).

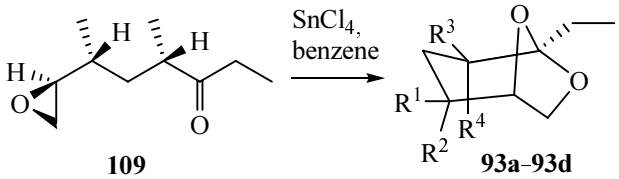
This example demonstrates that it is possible in some instances to control the reaction direction for selective preparation of a single one among possible isomers by varying the acid catalyst.

The epoxides of acyclic terpenoids, neral **104** and citronellal **105,** were shown [48] to undergo on heterogeneous catalysts (montmorillonite, zeolite-β) isomerization into dioxabicyclic compounds (Scheme 34). The probable mechanism involves the interaction of a cationic site arising at opening of the epoxy ring with an aldehyde group resulting in a cyclic cation. The attack of the oxygen unshared electron pair on the C^2 atom gives respectively compounds **106** and **108.** With **A** cation containing an allyl fragment the attack can take place both at the C^2 and C^4 yielding in the latter case compound **107**; therewith the relative amount of the reaction products depends on the type of the catalyst used.

Scheme 34.

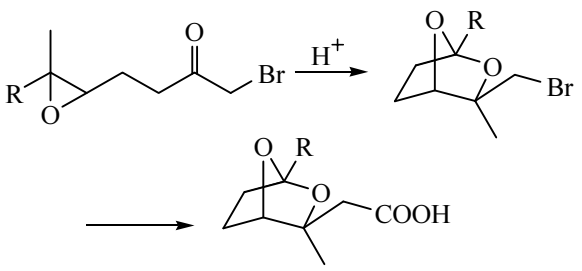


Scheme 35.



$R^1, R^3 = H, R^2, R^4 = CH_3$ (**a**); $R^1, R^4 = CH_3, R^2, R^3 = H$ (**b**); $R^1, R^3 = CH_3, R^2, R^4 = H$ (**c**); $R^1, R^4 = H, R^2, R^4 = CH_3$ (**d**).

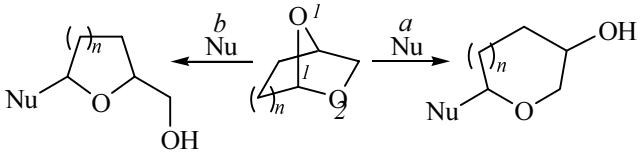
Scheme 36.



110

R = Alk.

Scheme 37.



$n = 1, 2$

The reaction of 4,6-dimethyl-7,8-epoxynonan-3-one **109** catalyzed by $SnCl_4$ gave rise to a mixture of isomers **93a–93d** β- in a ratio 9:13:1:2 respectively [49]. Dioxacarbocyclic compound **93a** is the active substance of the attractant of the small European bark beetle of the genus *Scolytus Multistriatus* (Scheme 35).

The key stage in preparation of compound **110** possessing a high biological activity consists in formation of a substituted 2,7-dioxabicyclo[2.2.1]heptane [50] (Scheme 36).

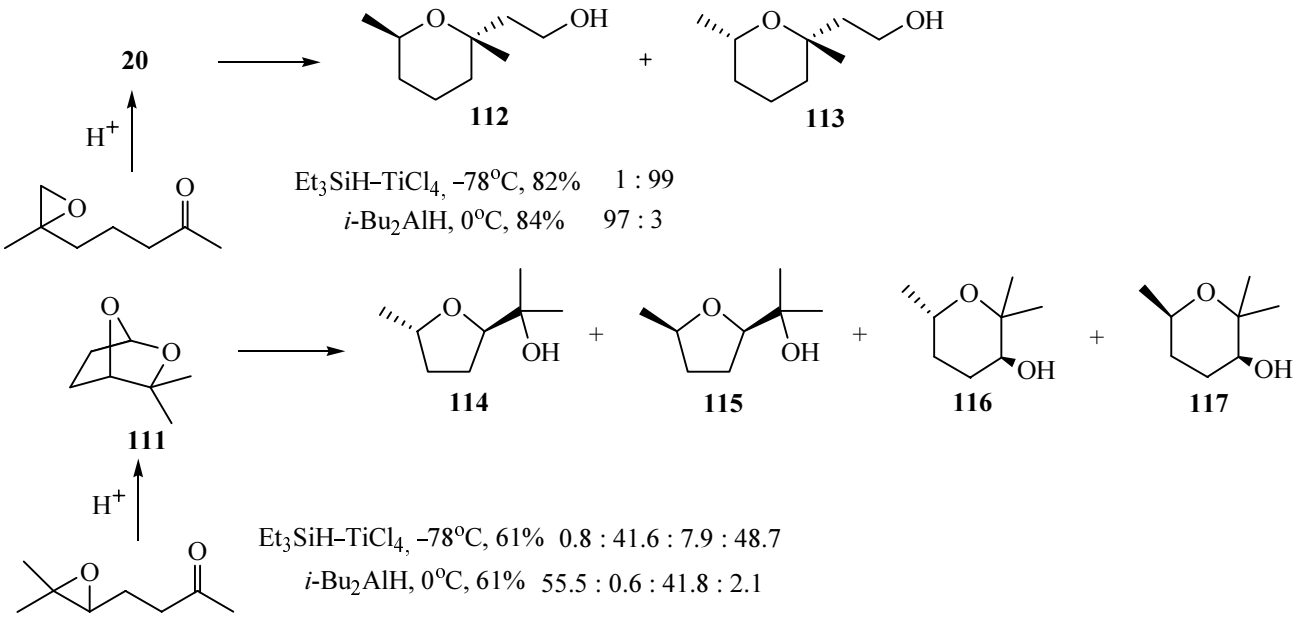
An important application of bicyclic acetals consists in their use as intermediate compounds in the synthesis of difficultly accessible cyclic ethers [51]. For instance, the nucleophilic cleavage catalyzed by Lewis acids occurs either at the C^1–O^1 bond (path *a*, Scheme 37) or at the C^1–O^2 bond (path *b*). When $n = 2$ (the initial compound contains a structural fragment of 6,8-dioxabicyclo-[3.2.1]octane) the process along path *a* affords seven-membered cyclic oxygen-containing systems. This structural block is an important fragment appearing in the natural polycyclic ethers [52]. As nucleophiles may serve compounds like triethylsilane, triethylsilylallyl, and trimethylsilyl cyanide in combination with Lewis acids, or diisobutylaluminum hydride.

The stereoselective opening of dioxabicyclic ethers **20** and **111** prepared from epoxycarbonyl compounds was reported in [53]. It was demonstrated that the use of the triethylsilane combined with Lewis acid afforded compounds with a *cis*-position of the substituents with respect to the heterocycle **113, 115,** and **117** (Scheme 38). The opening of the bicyclic ethers effected by the diisobutylaluminum hydride (*i*-Bu_2AlH) resulted in compounds with the *trans*- position of the substituents **112**, **114,** and **116**.

Treating epoxyketone **118** with the boron trifluoride etherate furnished dioxabicyclic compound **119**. The latter in reaction with the trimethylsilyl cyanide afforded compounds **120** and **121**; therewith on raising the reaction temperature the ratio of reaction products **120** : **121** changed from 1 : 1.3 to 1 : 4 [54] (Scheme 39).

Thus the bicyclic acetals are interesting from the biological viewpoint as characteristic components of pheromone compositions of some insects and for

Scheme 38.



synthesis as initial compounds in preparation of cyclic ethers by cleavage of one of the C–O bonds at the acetal atom under treatment with nucleophilic agents.

DIEPOXIDES TRANSFORMATIONS

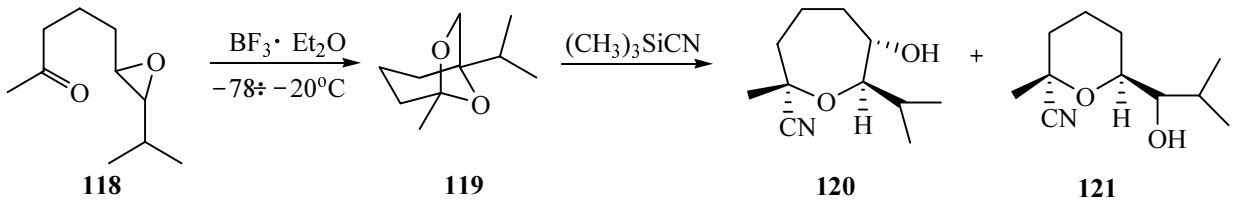
Transformation of compounds containing in their structure one or more epoxy groups may either result in formation of dicarbonyl compounds or due to the nucleophilic assistance of the epoxy group oxygen to the opening of the second oxirane ring may afford cyclic oxygen-containing compounds. It was shown in [25] that diepoxy compounds **122** and **123** underwent a tandem rearrangement involving epoxy groups opening into carbonyls followed by further intramolecular reactions resulting in cyclic unsaturated ketones **124** and **125** (Scheme 40). The reaction rate was slower than in transformation of epoxyaldehydes **24** (Scheme 9) because of higher aldehyde reactivity in aldol condensation compared with that of ketones. The intermediate products, epoxyketones and diketones, were isolated from the reaction mixture (Scheme 40).

The preparation of cyclic oxygen-containing compounds proceeding from di- and polyepoxy compounds is widely used in organic compounds designing. For instance, 1,5-hexadiene diepoxide **126** in the presence of acids furnished tetrahydrofuran derivative **127** [55] (Scheme 41).

Triterpene polyethers containing in their structure tetrahydrofuran and tetrahydropyran rings were isolated from sea algae [56], some higher plants [57], and from mollusks [58]. Therefore the reactions of diepoxy compounds resulting in cyclic ethers attract great interest. Biomimetic cyclization of diepoxy compounds isolated from the green sea algae *Botro-coccous braunit* were studied in [59]. The opening of one or another epoxy ring of compound **128** into a diol group gave two different intermediates; further attack of one of the hydroxy groups on the protonated epoxy ring led to cyclic compounds **129a, 129b** and **130a, 130b** in a ratio 1:1 and overall yield 84% (Scheme 42). Compounds **129a**, **130a** as well as **129b**, **130b** form enantiomer pairs.

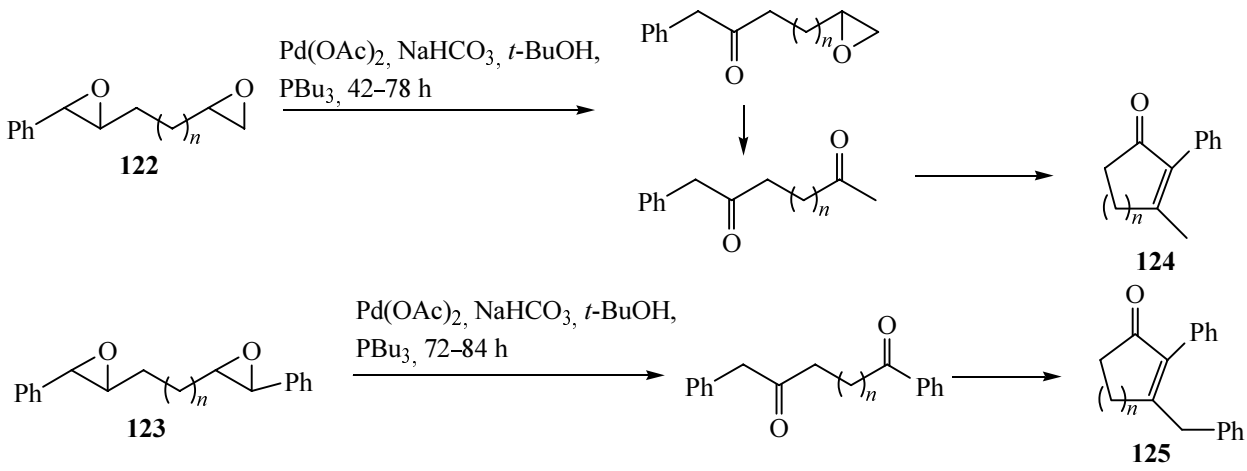
The transformations of diastereomers of compound **128,** diepoxides **131** and **132,** under the same conditions in keeping with Baldwin cyclization rules [60]

Scheme 39.



118 **119** **120** **121**

Scheme 40.

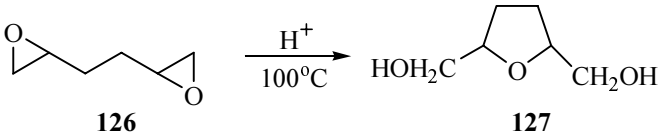


122 **124**

123 **125**

124, n = 1, 72%; 2, 33%; **125,** n = 1, 84%; 2, 35%.

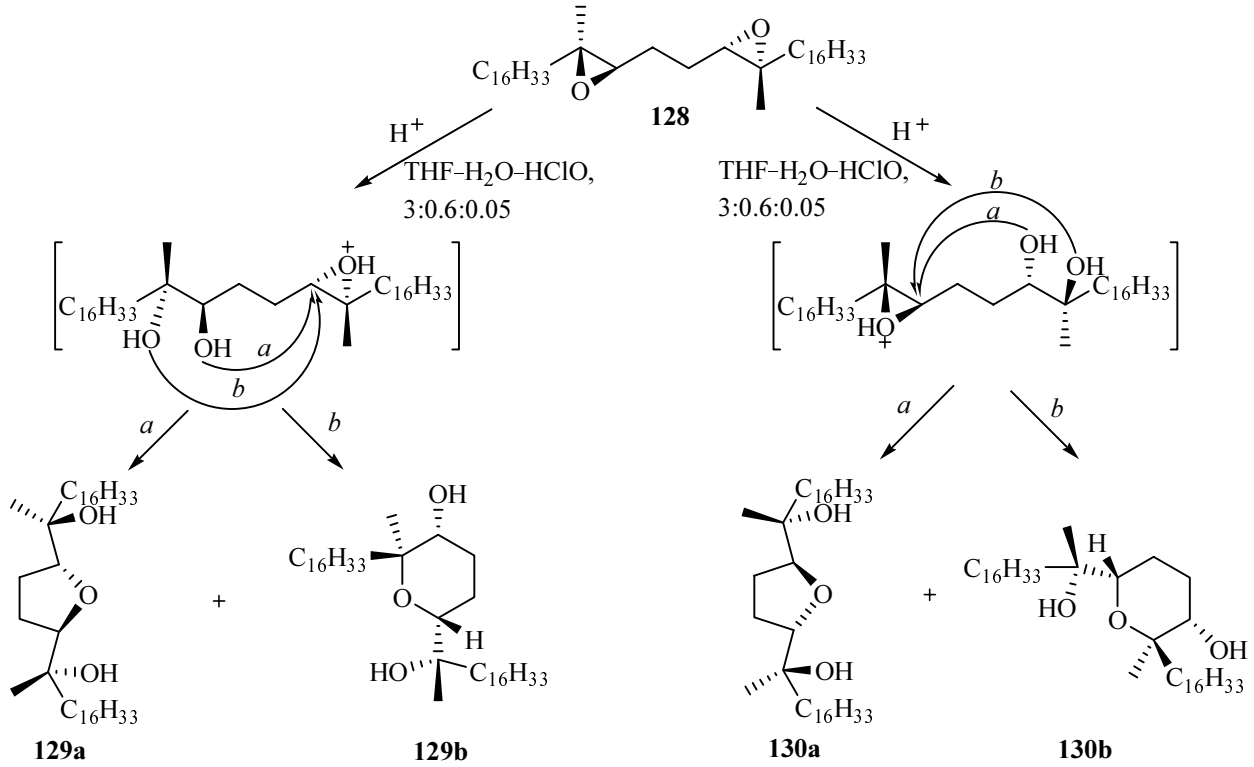
Scheme 41.



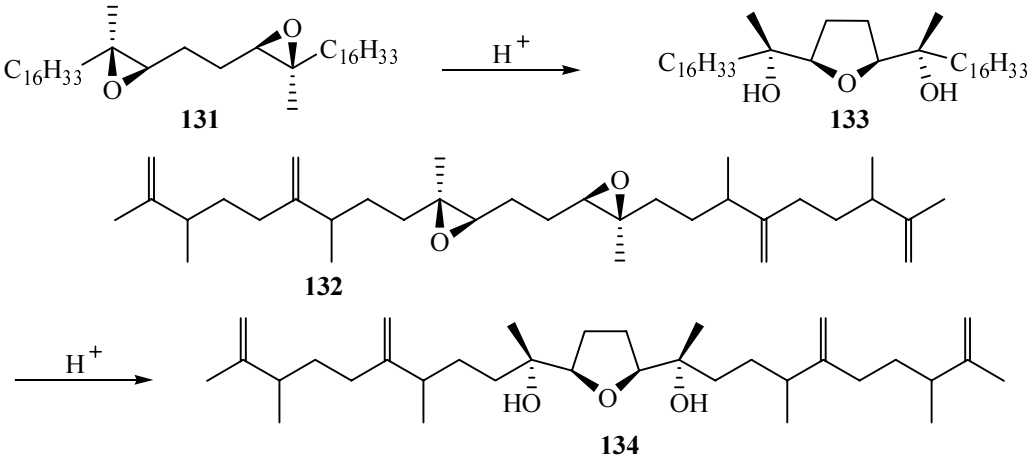
afforded only tetrahydrofuran derivatives **133** and **134** (Scheme 43).

Compound **135** transformation in diluted sulfuric acid was shown [61] to give mainly tetrahydrofuran derivatives **136**; however in the reaction mixture compounds were detected with six-membered **137**, **138** and seven-membered oxygen-containing rings **139** (Scheme 44).

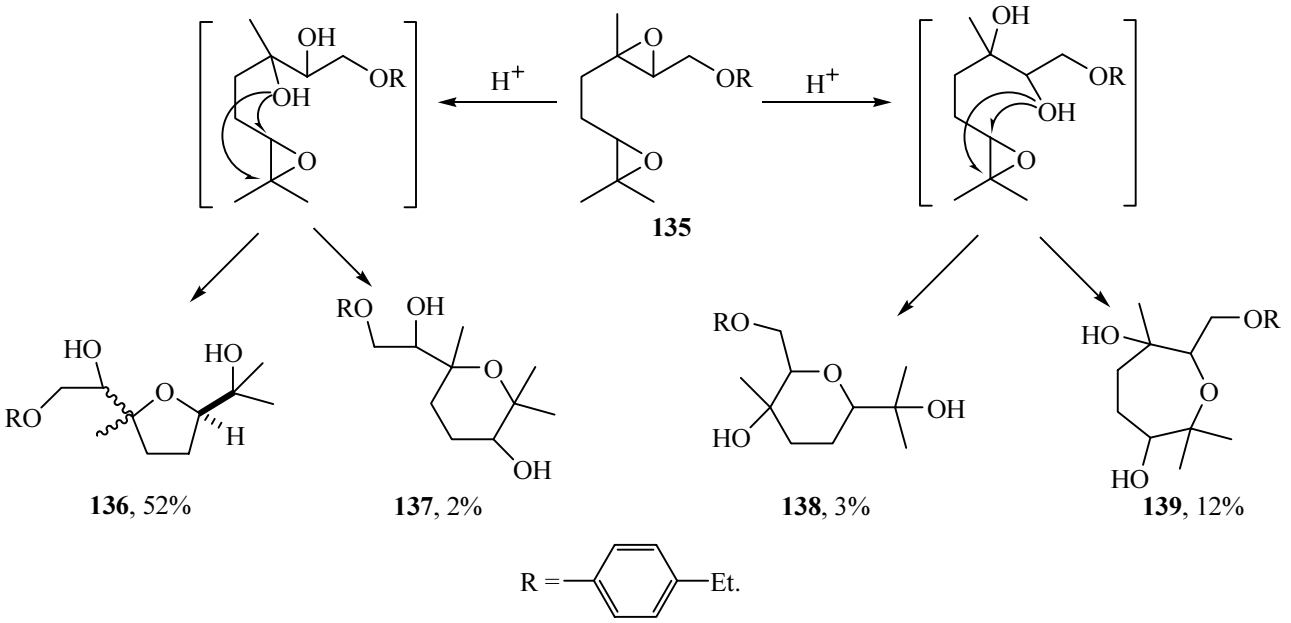
Scheme 42.



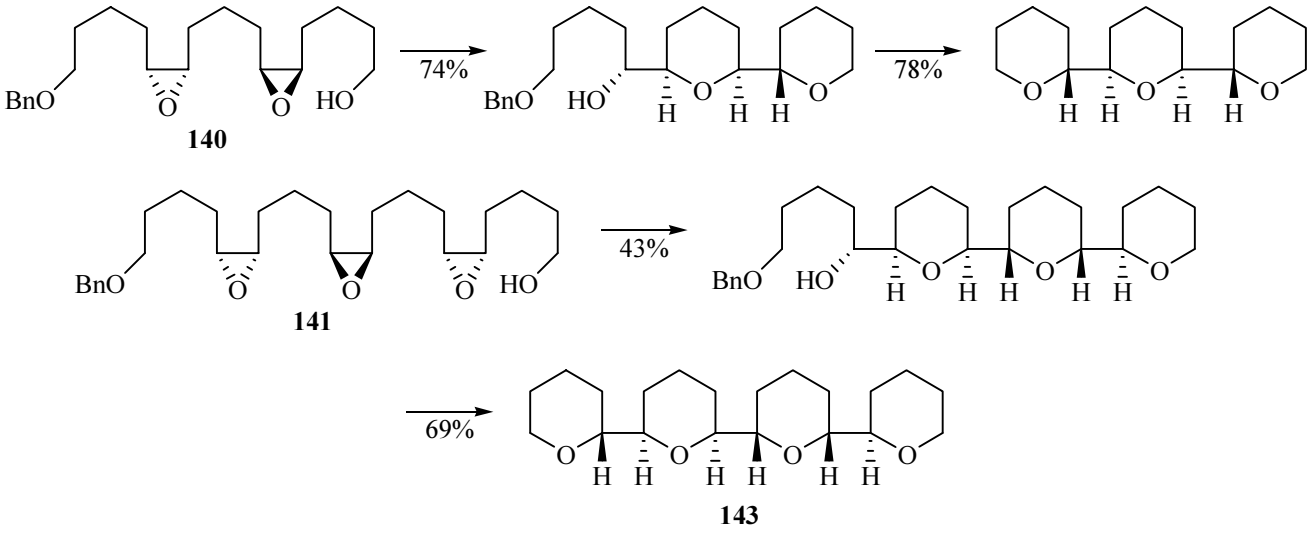
Scheme 43.



Scheme 44.



Scheme 45.



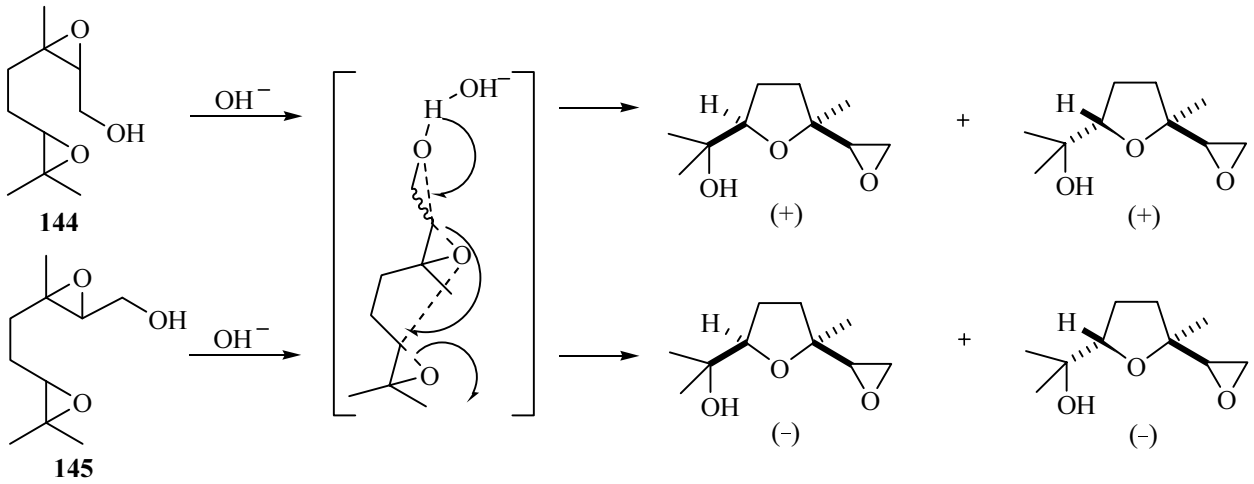
Intramolecular rearrangements of diepoxy **140** and triepoxy compounds **141** afforded polyether substances **142** and **143** [62] (Scheme 45).

Transformations of geraniol diepoxide **144** and nerol diepoxide **145** into tetrahydrofuran derivatives occurred under mild basic conditions [63] (Scheme 46). The formation of compounds containing an epoxy ring is caused by participation of the hydroxy group.

The conversion of diterpene diepoxy compound **146** into tetrahydrofuran derivative **147** occurred by concerted opening of the epoxy groups under acid catalysis conditions [64] (Scheme 47).

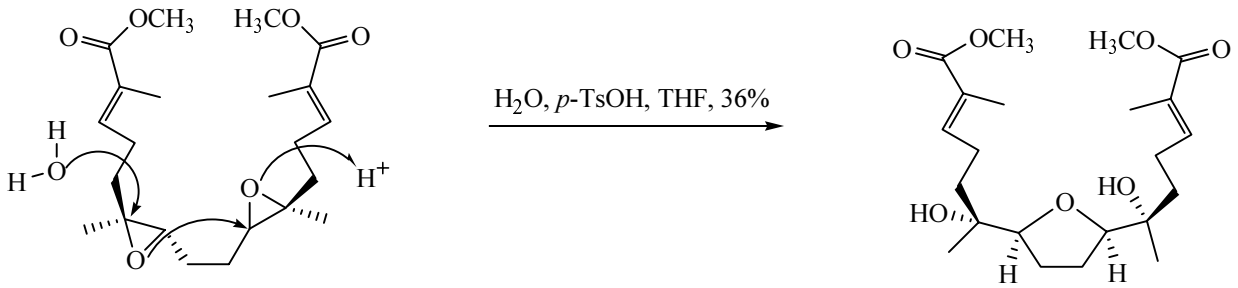
The opening of polyepoxy compounds to form cyclic ethers is used in the synthesis of structural fragments of many biologically active compounds. Bromodiepoxides **148** and **149** differing only in the reciprocal orientation of the epoxy groups under the action of silver triflate afforded *cis*-fused oxygen-containing heterocycles **150** and **151** respectively (Scheme 48) [65]. Compound **150** contains in its skeleton fused tetrahydropyran rings, and

Scheme 46.



144 **145**

Scheme 47.



146 **147**

the skeleton of compound **151** is constituted of fused tetrahydrofuran and tetrahydropyran rings. Thus the size of the second ring in the product depends on the stereochemical position of the epoxy groups in the initial compound. It was shown that the final products were formed via intermediate epoxytetrahydropyran compounds **152** and **153** respectively.

A number of optically active compounds isolated from sea microbes contain in their skeleton fused cyclic ethers [52]. Biomimetic transformations of polyepoxy compounds **154–156** performed by tandem oxocyclization to obtain *trans*-fused oxygen-containing compounds **157–159** were reported in [66] (Scheme 49). Cyclic compounds **157–159** are the structural fragments of the hemibrevitoxin B possessing very high biological activity. This compound is naturally formed at blooming of *Binoflagellate* alga and causes mass loss of life of fish and other sea inhabitants in Pacific and Atlantic Ocean.

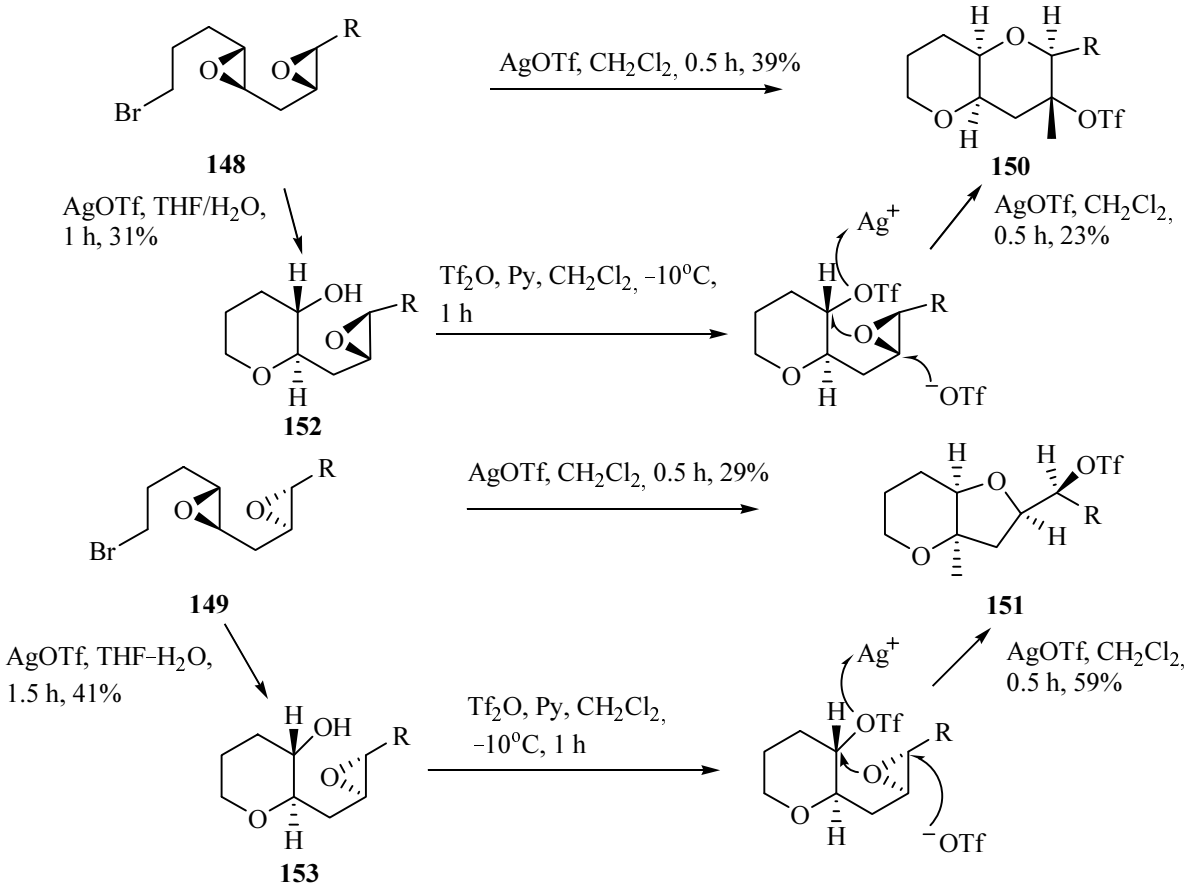
Reactions with boron trifluoride etherate of tri- **161** and diepoxy compound **162** prepared based on farnesol **160** also gave cyclic ethers with *trans*-junction **163** and **164** respectively [67] (Scheme 50).

The stereoselective cyclization of polyfunctional compound **165** containing in its molecule a carboxy and two epoxy groups occurred on molecular sieves 4A (Scheme 51). The tandem opening of the epoxy group was initiated by the carboxyl [68]. This reaction was used in a biomimetic synthesis of polyether antibiotics, like lonomycin A, monensin, lasalocid [69].

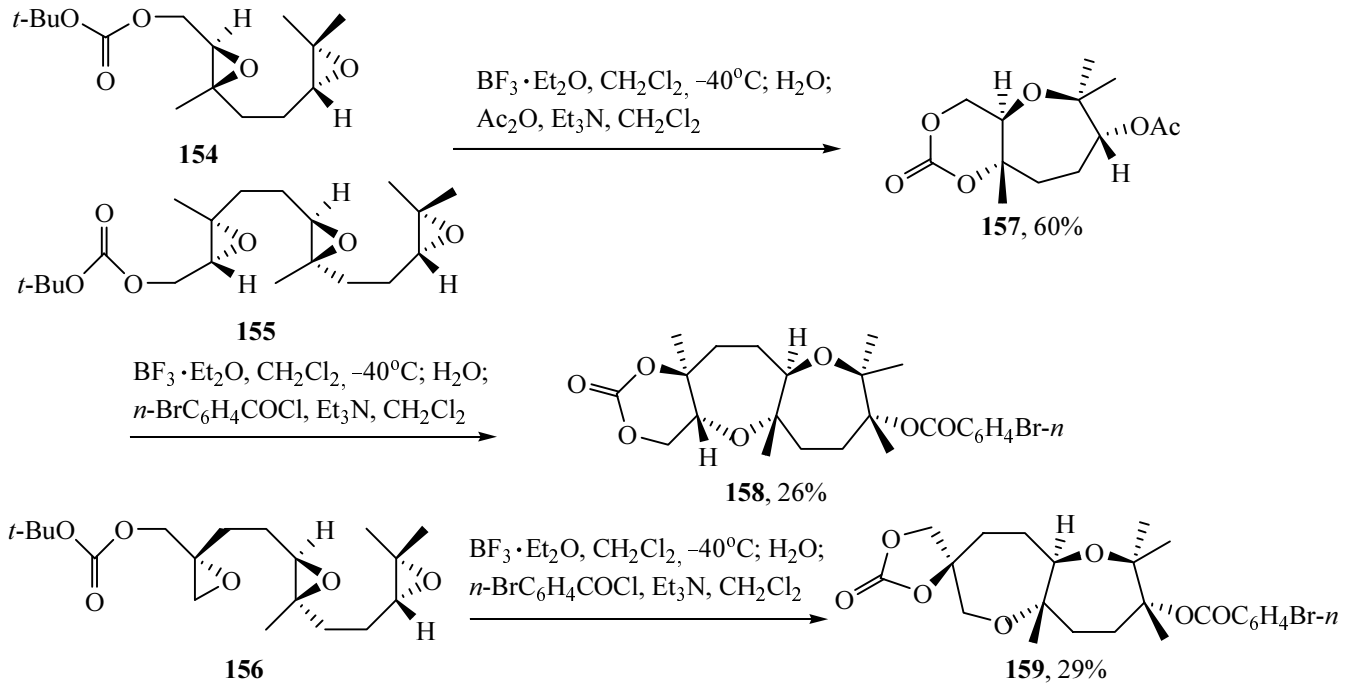
The transformations of the molecule of crotocin **166,** antimold antibiotic, that contains two epoxy groups of different reactivity, demonstrate the possibility to change the reaction direction by variation in the medium [70] (Scheme 52). In the acid medium the 4,13-epoxy ring is opened to give a tertiary cation, and the subsequent attack of the other epoxy group on the cationic site results in a tetrahydrofuran ring formation giving compound **167**. In the alkaline medium the reaction takes another path: As a result of a nucleophilic attack opens the 7,8-epoxy ring, and compound **168** arises containing a tetrahydroptran ring.

The transformations of caryophyllene diepoxide **169** and isocaryophyllene diepoxides **170** and **171** were discussed in [71] (Scheme 53). It was demonstrated that the introduction of the second epoxy ring into the molecule

Scheme 48.

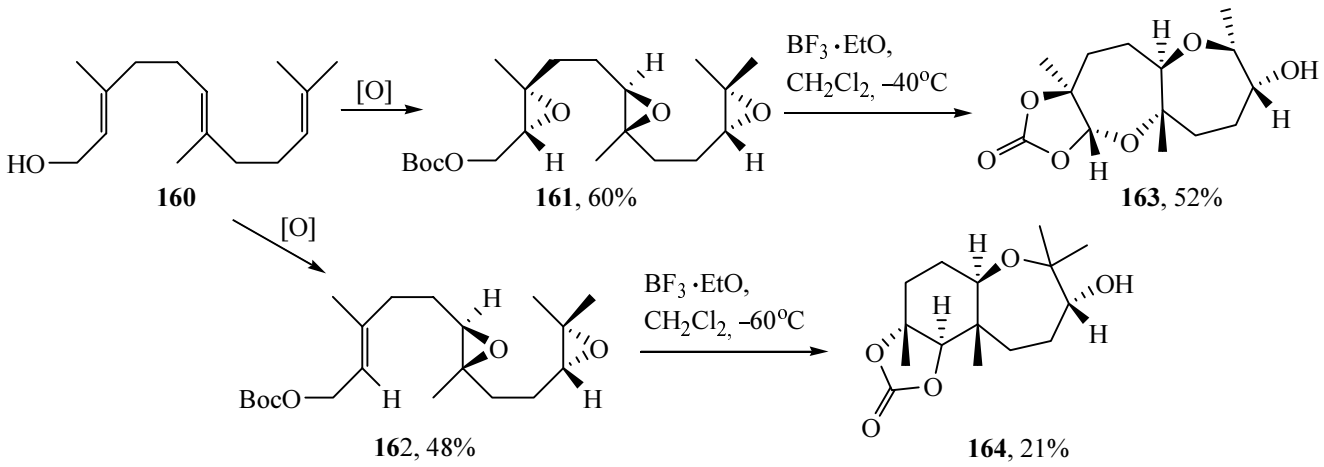


Scheme 49.



activated the cyclization reactions in alkaline media inasmuch as the 4.5-epoxides of caryophyllene and isocaryophyllene did not react in the alkaline media. In the diepoxides first the epoxy ring was opened obtained at the exocyclic double bond. Then the oxygen attacked the 4,5-epoxy ring at the C^5 with the configuration inversion. Therewith from diepoxides **169** and **170** formed compounds with tetrahydrofuran rings **172** and **173**, and diepoxide **171** gave rise to a compound with a tetrahydropyran ring **174**, for the 4,5-epoxy ring opening under the nucleophile action occurred by an attack of the hydroxy group the most close to the C^5 atom.

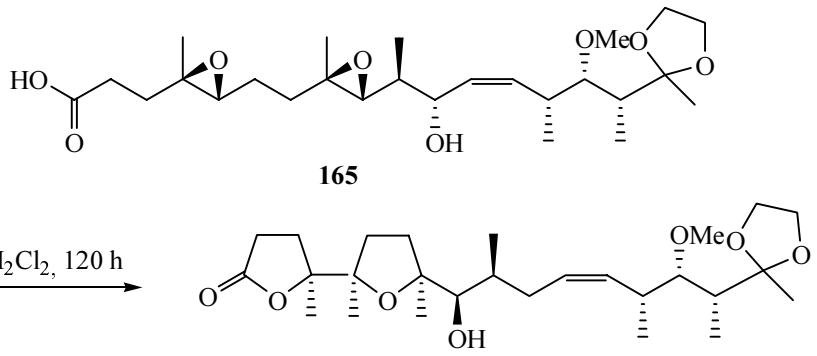
Scheme 50.



160 **161**, 60% **163**, 52%

162, 48% **164**, 21%

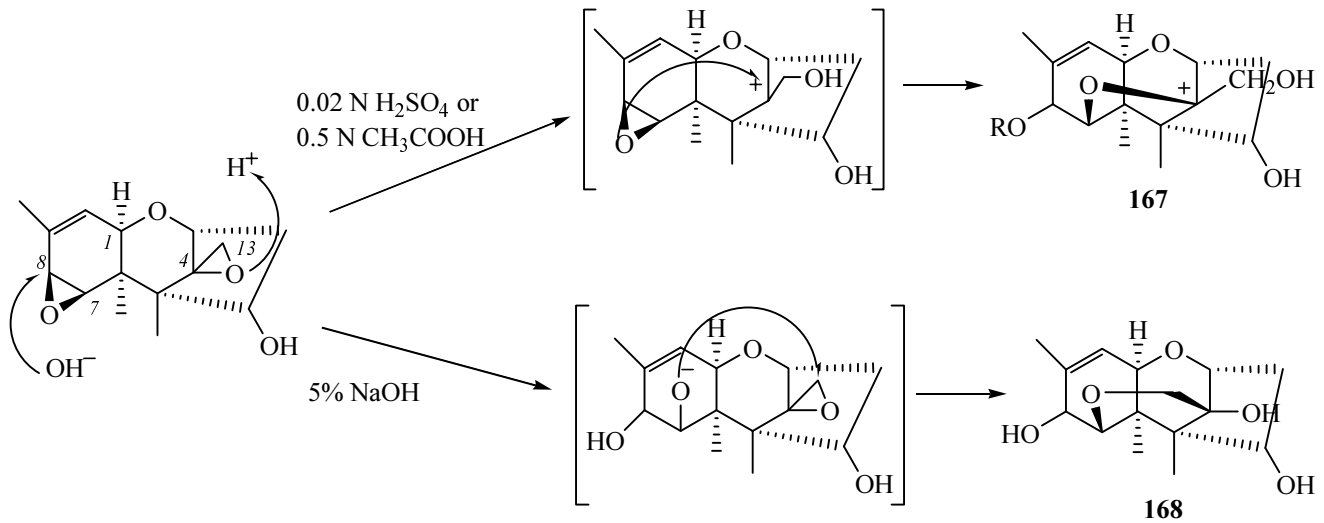
Scheme 51.



165

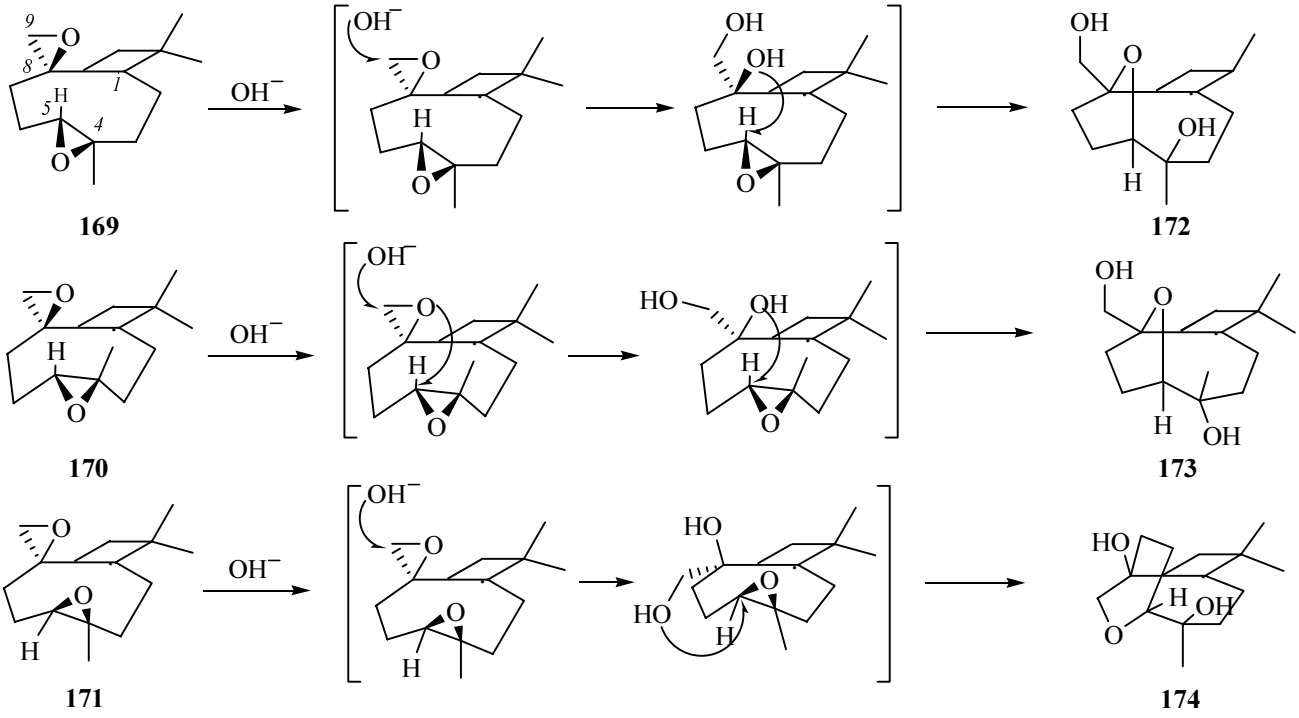
85%

Scheme 52.

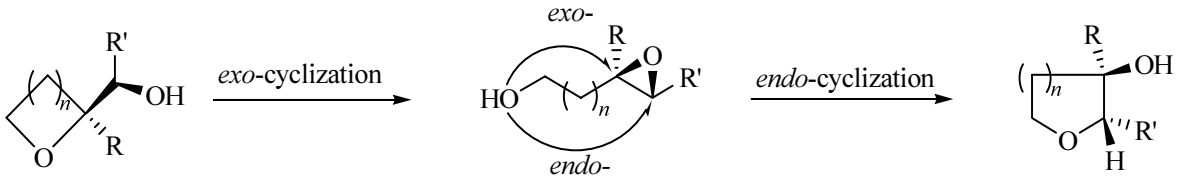


167 **168**

Scheme 53.

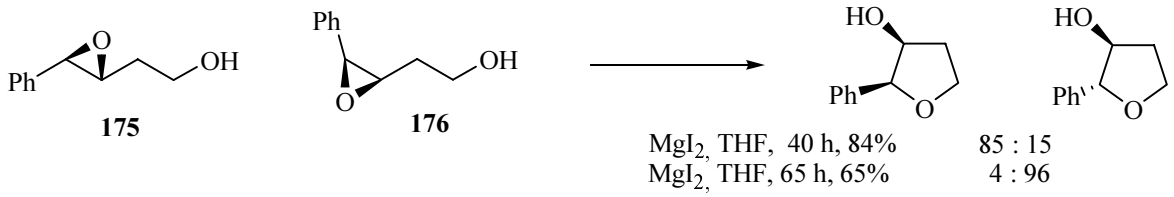


Scheme 54.



Exo; endo; exo-cyclization; *endo*-cyclization; n = 1-4

Scheme 55.



MgI_2, THF, 40 h, 84% 85 : 15
MgI_2, THF, 65 h, 65% 4 : 96

The direction of transformations observed in caryophyllene diepoxide **169** and isocaryophyllene diepoxides **170** and **171** demonstrated how the factor like the configuration of an epoxy group influenced the choice of the main reaction path.

Hence when the two epoxy groups in the molecule are reciprocally located in positions where they can influence each other the transformations of diethoxy compounds result in cyclic ethers. Tetrahydrofuran or tetrahydropyran derivatives are commonly obtained, but sometimes the reactions yield compounds with seven-membered and eight-membered rings. When the reactivity of the epoxy rings is not alike, the final reaction product depends on the reaction medium.

CYCLIZATION OF EPOXYALCOHOLS

Epoxyalcohols for a long time remain among the most important building blocks in organic chemistry. Recently owing to the efficient development of enantioselective procedures for allyl alcohols epoxidation [8] the reactions

of α,β-epoxyalcohols found application in many aspects of the organic synthesis [11]. In this section of the review we discuss the transformations of compounds containing the epoxy and alcohol groups separated by one or more carbon atoms.

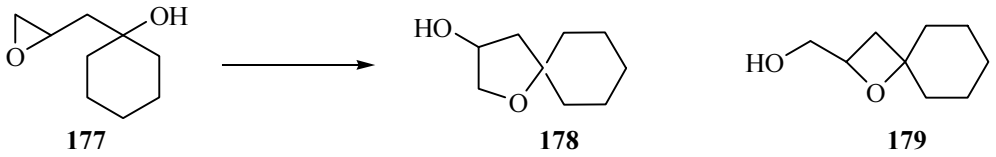
The intramolecular reaction of the epoxy and alcohol groups furnishes oxygen-containing cyclic ethers. The attack of the hydroxy group oxygen on the epoxy ring provides products of both *endo* and *exo* cyclization (Scheme 54). The relation between the rearrangement pathways depends on the applied catalyst and the substituents in the initial molecule.

When the alcohol and epoxy groups are separated by a single carbon atom the reaction products are usually five-membered oxygen-containing compounds. It was shown that rearrangement of epoxyalcohols **175** and **176** catalyzed by magnesium iodide resulted in formation of isomeric tetrahydrofurans [72] (Scheme 55).

The pathway of β,γ-epoxyalcohols transformations depends essentially on the basicity of the environment. For instance, 2,3-epoxypropyl-1-cyclohexanol **177** underwent cyclization effected by $MgBr_2$ affording mostly spiro compound **178** [72], and in a water solution of sodium hydroxide formed only compound **179** [73] (Scheme 56).

The reactions of epoxyalcohols **180** with the epoxy group located in an aliphatic substituent gave rise in alkaline media to spiro compounds and triols. When the epoxy group is fused to the carbocycle (compounds **181**) reactions under the same conditions afford spiro

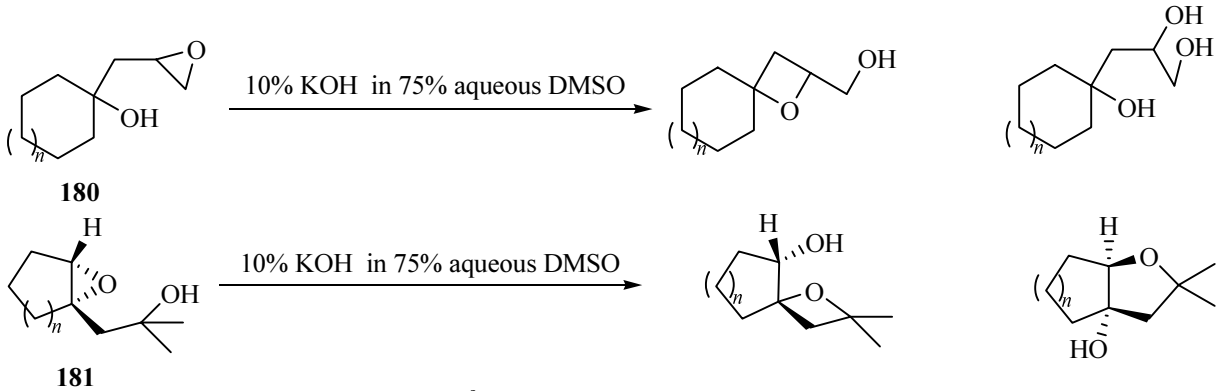
Scheme 56.



177 **178** **179**

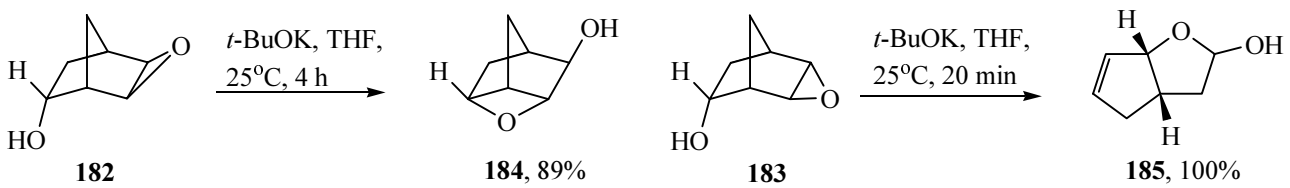
$MgBr_2$, THF, 20 ч, 69% 98 : 2
NaOH, H_2O 0 : 100

Scheme 57.



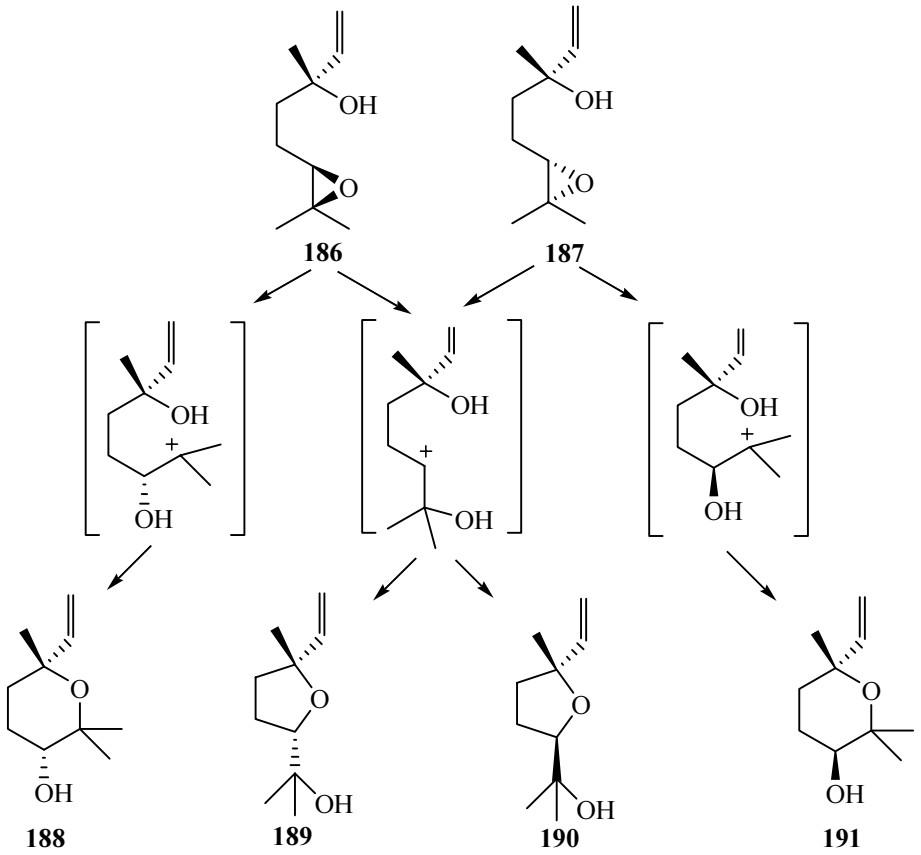
n = 1 (90 min, 135°C)	49%	32%
n = 2 (90 min, 135°C)	25%	55%
n = 3 (100 min, 80°C)	20%	60%

Scheme 58.



182 **184**, 89% **183** **185**, 100%

Scheme 59.



compounds and products with a skeleton containing fused rings with a *cis*-junction [74] (Scheme 57).

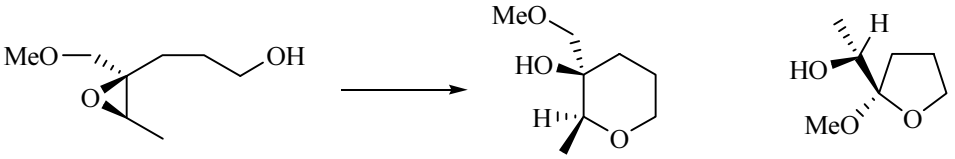
The direction of reactions occurring with β,γ-epoxyalcohols depends on the reciprocal stereochemical position of the hydroxy and epoxy groups. For instance, treatment with the potassium *tert*-butylate of compounds **182** and **183** possessing a bicyclo[2.2.1]octane skeleton resulted either in bicyclic or tricyclic compounds (Scheme 58). *exo*-Epoxy-*endo*-hydroxy compound **182** transformed into tricyclic compound **184** whereas *endo*-epoxy-*endo*-hydroxy compound **183** isomerized into bicyclic lactol **185** [75].

Among the most well known examples of intramolecular reactions between epoxy and alcohol groups a formation should be mentioned of stereoisomeric linalool oxides with tetrahydrofuran **189, 190** and tetrahydropyran **188, 191** rings in reaction with a protic acid of a mixture of (3*R*, 6*R*)- **186** and (3*R*, 6*S*)-6,7-epoxylinalools **187** (Scheme 59) [76, 77]. The same linalool oxides were obtained in the ratio **188:189:190:191** = 1:3:5:2 on a solid superacid ZrO_2–SO_4^{2-} [78].

Generally when the epoxy and alcohol groups are separated in the molecule by two carbon atoms the intramolecular reaction of these functional groups results in formation of oxygen-containing five-membered or six-membered rings. Here the main rearrangement path can depend on the applied catalyst. The rearrangement of compound **192** catalyzed by Lewis acids was shown [79] to afford substituted tetrahydropyran **193** or tetrahydrofuran **194** derivatives. The relative yield of products crucially depended on the catlyst used (Scheme 60). The isomerization of compound **195** distinguished from epoxyalcohol **192** by the absence of a methoxymethyl group at the epoxy ring furnished exclusively a tetrahydrofuran alcohol. Apparently this dissimilar direction of transformations is due to involvement of the methoxymethyl group into the intermediate complexing with the bidentate Lewis acids [$La(OTf)_3$].

The dependence of intramolecular cyclizations catalyzed by camphorsulfonic acid on the type of substituent attached to the epoxy ring was investigated in [80]. It was shown that depending on the electronic effect of the substituent at the carbon of the epoxy ring

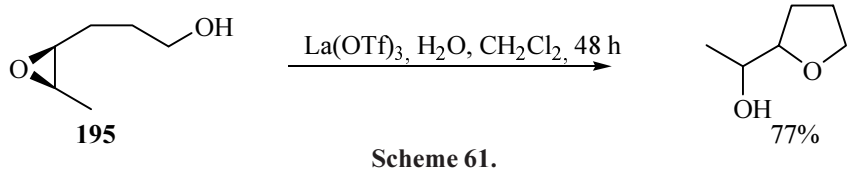
Scheme 60.



192 **193** **194**

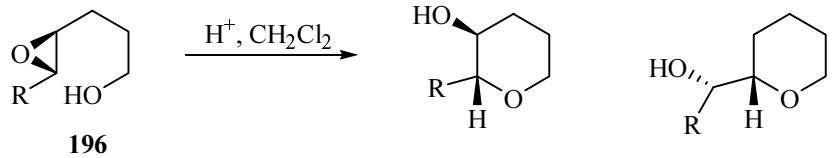
$La(OTf)_3$, H_2O, CH_2Cl_2, 48 h, 74% 82 : 18

BF_3OEt_2, CH_2Cl_2, 30 min, 95% 0 : 100



195 77%

Scheme 61.



196

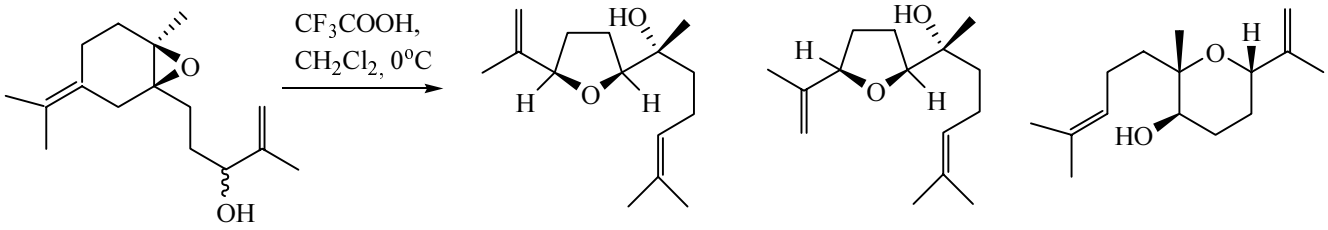
R = CH_2CH_2COOMe, 94% 0 : 100

R = CH=CHCOOMe, 96% 60 : 40

R = $CH=CH_2$, 95% 100 : 0

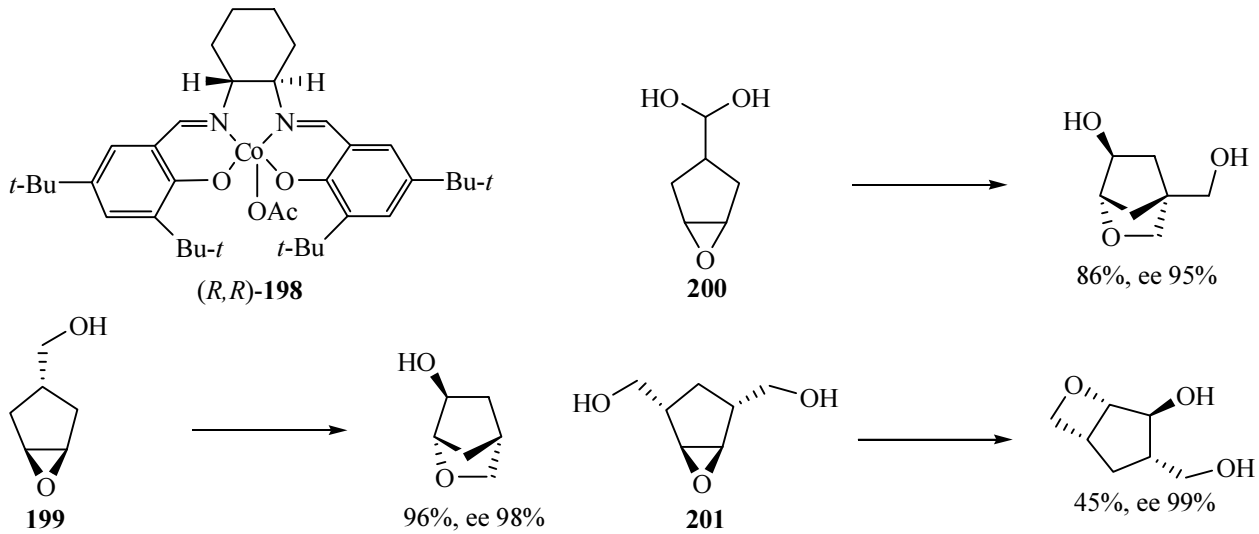
R = $CH=CBr_2$, 90% 100 : 0

Scheme 62.



197 45 : 18 : 37

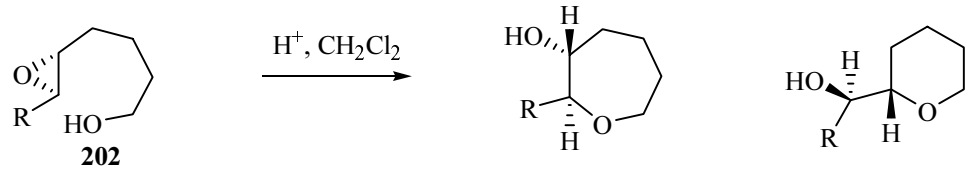
Scheme 63.



(*R*,*R*)-**198** **200** 86%, ee 95%

199 96%, ee 98% **201** 45%, ee 99%

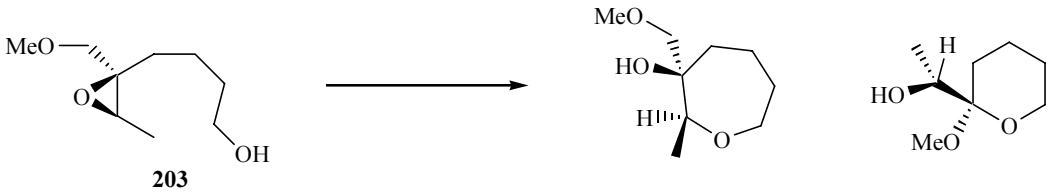
Scheme 64.



202

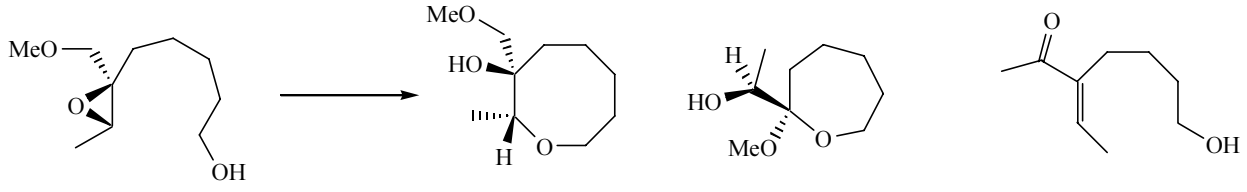
R = CH_2CH_2COOMe, 70%	0 : 100
R = CH=CHCOOMe, 75%	22 : 78
R = $CH=CH_2$, 75%	82 : 18
R = CH=CHCl, 75%	92 : 8

Scheme 65.



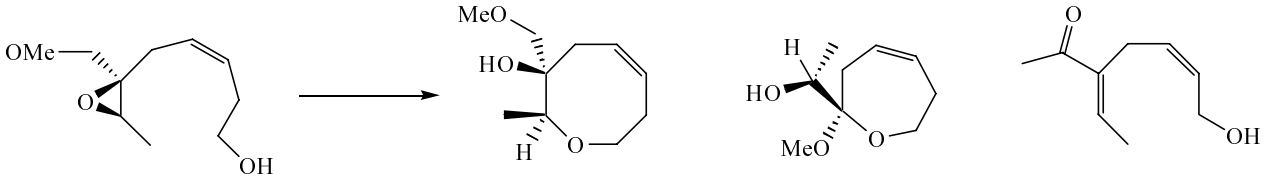
203

$La(OTf)_3$, H_2O, CH_2Cl_2, 72 h, 74%	92 : 8
BF_3OEt_2, CH_2Cl_2, 1 h, 61%	3 : 97



204

$Zn(OTf)_3$, CH_2Cl_2, 7 days, 14%	7 : 93
$La(OTf)_3$, CH_2Cl_2, 6 days, 23%	43 : 57



205

BF_3OEt_2, CH_2Cl_2, 17 h, 56%	22 : 78
$La(OTf)_3$, CH_3CN, 7 days, 40%	96 : 4

the isomerization of compound **196** yielded either tetrahydrofuran or tetrahydropyran compounds (Scheme 61).

The conversion of γ,δ-epoxyalcohols into compounds containing substituted tetrahydropyran rings are widely used in the total syntheses of biologically active compounds naturally occurring in the sea microbes [81].

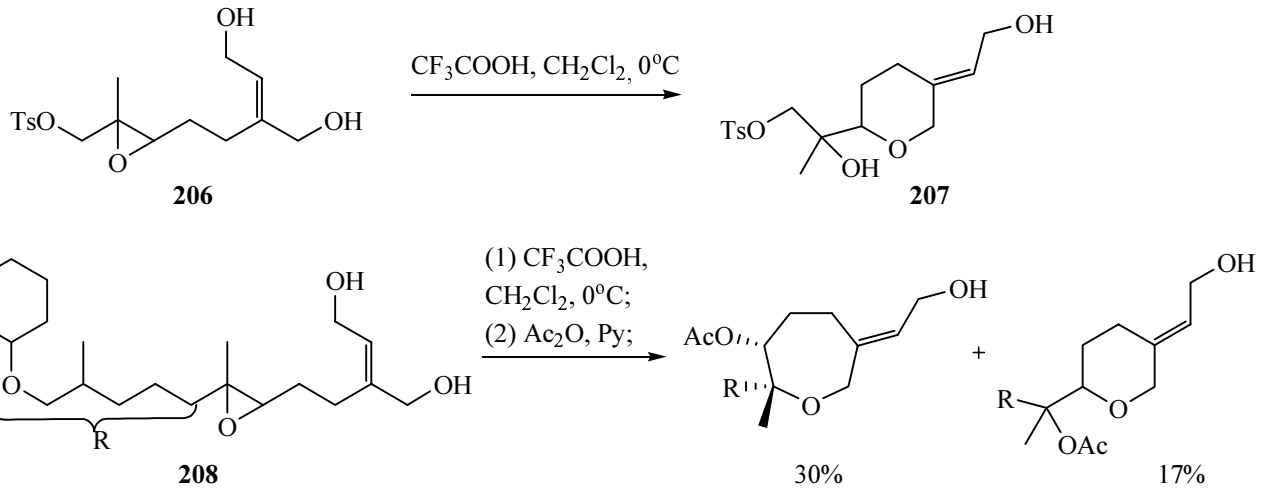
Under catalysis with the trifluoroacetic acid isomer mixture of epoxyaldehydes **197** was converted in tetrahydrofuran as well as tetrahydropyran compounds[82] (Scheme 62).

At the use of a chiral cobalt complex **198** as a catalyst of the intramolecular epoxy group opening in compounds **199–201** bicyclic substances were obtained characterized by a high enantiomer excess [83] (Scheme 63).

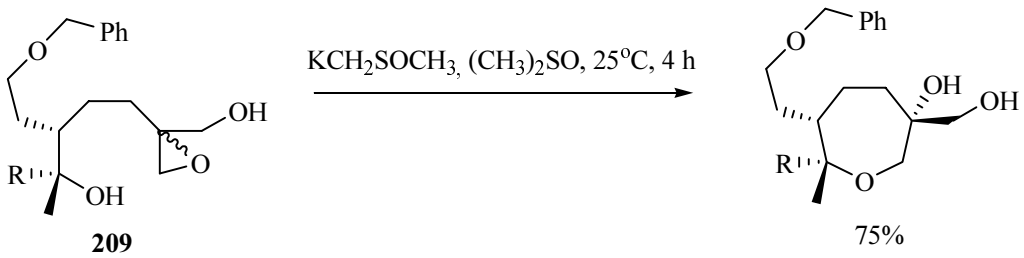
The epoxyalcohol compounds containing epoxy and alcohol groups ceparated by three carbon atoms undergo transformations in keeping with Scheme 54 affording six-membered or seven-membered oxygen-containing cyclic compounds. The dependence of the main path taken by the intramolecular cyclization of δ,φ-epoxyalcohols **202** on the electronic effect of the substituent linked to the epoxy ring was investigated in [84] (Scheme 64).

The dependence of the main path in transformations of the methoxymethyl-substituted epoxyalcohols with the

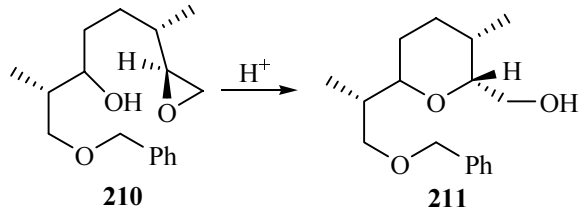
Scheme 66.



Scheme 67.



Scheme 68.



functional groups separated by three **203** and four **204, 205** carbon atoms on the kind of the applied Lewis acid was studied in [85] (Scheme 65).

The acid-catalyzed cyclization of epoxydiol **206** afforded as a single product crystalline pyrane derivative **207** in a 75% yield with no traces of any other oxygen-containing cyclic compounds. This result is due to the electron-withdrawing properties of the tosyl group [86] (Scheme 66). At the same time the cyclization of compound **208** resulted in formation of both seven- and six-membered oxygen-containing rings.

As already mentioned, the cyclic ether formation by reaction between an epoxy and an alcohol groups is widely used in the synthesis of naturally occurring biologically active substances. Compound **209** cyclization proceeded with a high stereoselectivity and is the key stage in the synthesis of zoapatanol, a natural substance isolated from a plant *Montanoa tomentosa* [87] (Scheme 67).

The cyclization of epoxy derivative **210** under catalysis with camphorsulfonic acid occurred with total regioselectivity (formation of solely tetrahydropyran ring) and stereoselectivity (inversion of configuration of the epoxy ring carbon) [88] [88] (Scheme 68). Hydroxytetrahydropyran derivative **211** that was a building block for the synthesis of polyether antibiotic X-14547A was obtained in 95% yield.

CONCLUSION

Summing up the discussion of the epoxy derivatives transformations we can state that the second nucleophile group (carbonyl, epoxy, or alcohol group) takes an active part in the opening of the epoxy ring. The isomerization of α,β-epoxyketones results in formation of 1,3-dicarbonyl compounds via migration of the neighbor group. In a particular case when the isomerization occurs with epoxy derivatives of unsaturated ketones containing the oxirane ring fused to the other ring or in spiro position thereto the C~C-migration leads to the contraction or expansion of the ring respectively. The intramolecular

reaction between the carbonyl and epoxy groups separated by one or more carbon atoms can afford products of either C- or O-alkylation. The published data indicate that β,γ-epoxycarbonyl compounds both in alkaline and acid media afford furan derivatives as a result of O-alkylation. The furan derivatives may also arise through the preliminary isomerization of the epoxide into a keto group. The carbocyclization of γ,δ-epoxyketones in a basic environment is one of the procedures for preparation of compounds with a cyclopropane ring. Therewith when the epoxyketone molecule already contains a carbocycle the reaction of epoxy and carbonyl group leads to bicyclic compounds with rings fused or in a spiro junction. The pathway of epoxyketones transformations when their carbonyl and epoxy groups are separated by two or three carbon atoms essentially depends on the catalyst (as a rule, acids promote O-alkylation, bases C-alkylation), the structure of initial molecules, and the stability of the transition state. The growing length of the carbon chain between the carbonyl and epoxy groups providing the chain is flexible brings about prevailing nucleophilic attack of a double bond arising from the carbonyl enolization on the epoxy ring thus affording the C-alkylation products. It should be noted that the reaction products belonging to various classes of cyclic compounds (bicyclic, spiro and/or oxaspiro compounds, difficultly available by alternative synthetic procedures) were obtained with high stereo- and regioselectivity. The reasoning behind the suggested mechanisms can be applied to predicting the character of cyclic compounds.

The acid-catalyzed cyclization of compounds with the carbonyl and epoxy groups separated by three carbon atoms provided 6,8-bicyclo[3.2.1]octane derivatives. Bicyclic acetals are interesting from the biological viewpoint as characteristic components of pheromone compositions of some insects and as initial compounds for preparation of cyclic ethers by cleavage of one of the C–O bonds at the acetal atom under treatment with nucleophilic agents.

The transformations of compounds containing in the molecule two epoxy group were reported in a limited number of recent publications. The analysis of the results of these studies shows that in case the epoxy groups are located so as their reciprocal influence is possible the rearrangement of the diepoxides results in cyclic ethers, usually a tetrahydrofuran or tetrahydropyran derivatives.

The intramolecular reaction of an epoxy and an alcohol groups affords cyclic ethers. The oxygen of the hydroxy group attacks the epoxy ring to furnish both products of *endo*- and *exo*-cyclization. The products ratio depends on the applied catalyst and the substituents in the initial compound. The transformation of compounds where the alcohol and epoxy groups are separated by one or more carbon atoms are used in the modern organic chemistry to synthesize structural fragments of the naturally occurring biologically active compounds.

Although the transformation pathways of epoxy compounds with oxygen-containing functional groups are diverse the appropriate choice of reaction conditions makes possible the preparation of the desired product, and therefore these reactions may be regarded as an interesting group of synthetic approaches worth applying to the synthesis of sufficiently complex substances.

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