

Methods and Mechanisms of Epoxy Compounds Reduction

L. I. Kas'yan^a, A. O. Kas'yan^b, and E. A. Golodaeva^c

^aDnepropetrovsk National University, Dnepropetrovsk, 49050 Ukraine

e-mail: cf@ff.dsu.dp.ua

^bProBioGen AG, Berlin, Germany

^cKirovograd State Pedagogical University, Kirovograd, Ukraine

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Abstract—Analysis was performed of reduction processes of epoxy derivatives obtained from unsaturated compounds belonging to various groups: alkenes, cycloalkenes, spiroalkanes, and substituted norbornenes. The regio- and stereochemistry was discussed of reactions between epoxides and complex metal hydrides, of catalytic hydrogenation, and some other processes. The mechanisms were considered of the reduction reactions, in particular, those involving radical and ion radical intermediates.

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1. INTRODUCTION. REDUCERS AND REACTION MECHANISMS

Epoxy compounds are practically promising and extensively investigated organic synthons underlying the

preparation of versatile pharmacologically active compounds, in particular, those related to the carcinogenesis problem [1, 2]. The reactions of oxiranes with nucleophilic reagents attract special attention owing to the crucially important biochemical aspects of similar transformations involved into metabolism processes of polycyclic aromatic compounds and other carcinogenic and mutagenic substances [3].

The reduction of epoxides into alcohols is a practically important target of organic synthesis that is achieved using various methods taking into account the regular trends in the known chemo-, stereo-, and regiochemical conversions of oxiranes. The existing reviews on the reactivity of epoxides [4–10] either describe their reactions with reducers only to a limited degree or are out of date to a great extent. The reduction of epoxy-norbornanes and spirooxiranes was compiled in reviews [11, 12] and a book [13] that were dedicated to the chemistry of alicyclic epoxy compounds. Some data are extracted from special reviews [14–17] on the action of certain groups of reagents.

In [18] three main mechanisms of epoxides reactions were discussed: selective nucleophilic substitution (path *a*); one-electron reduction of epoxides through radical intermediates (path *b*); and successive two-electrons reduction into the corresponding carbanions (path *c*) followed by addition of electrophilic reagents (Scheme 1).

The research performed confirms the applicability of every one of this mechanisms to the reduction. The



Kas'yan Liliya Ivanovna was born in the town Staryi Oskol, Belgorod Oblast'. She graduated from Odessa State University in 1960. Candidate of Chemical Sciences since 1970, Doctor of Chemical Sciences since 1990. Honored Worker of Science and Engineering of the Ukraine. Professor at the Chair of Organic Chemistry at the Dnepropetrovsk National University.

Field of scientific interests: chemistry of epoxy compounds, chemistry of cage-like compounds, mechanisms and stereochemistry of organic reactions.



Kas'yan Andrei Olegovich was born in 1966 in Dnepropetrovsk. In 1988 he graduated from Dnepropetrovsk State University. Candidate of Chemical Sciences since 1993. In 1996–2002 worked in Universities of Halle and Aachen (Germany). At present he is the Head of Laboratory at the ProBioGen Co (Berlin).

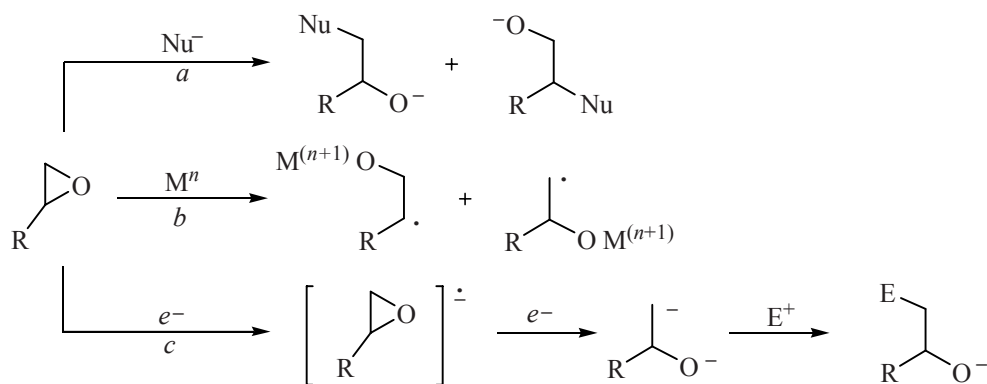
Field of scientific interests: chemistry of cage-like compounds.



Golodaeva Elena Anatol'evna was born in 1977 in Sverdlovsk. In 1999 she graduated from Dnepropetrovsk State University. Candidate of Chemical Sciences since 2003. Assistant Professor of Kirovograd State Pedagogical University.

Field of scientific interests: chemistry of cage-like compounds.

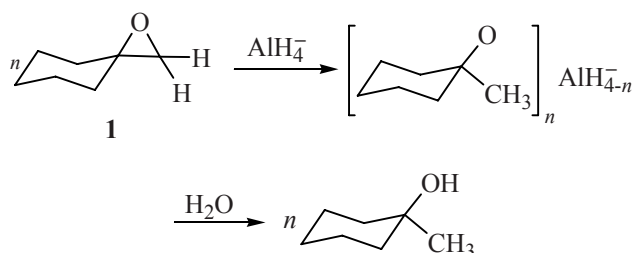
Scheme 1.



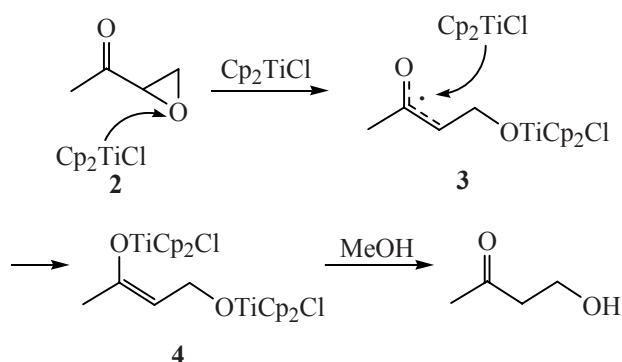
mechanisms of the first group are characteristic of oxiranes reactions with complex metal hydrides, first of all, with lithium aluminum hydride. In these reactions hydride anion (H^-) serves as nucleophilic reagent, and all features of bimolecular nucleophilic substitution are conserved; the substrate is presumed to be activated by aluminum hydride present in the reducer as impurity. The epoxymethylenecyclohexane reduction yielded a tertiary alcohol as a result of the nucleophilic attack on the primary sterically more accessible carbon atom of the terminal epoxide **1** [19, 20] (Scheme 2).

The second mentioned mechanism (*b*) concerns the epoxy compounds reduction along the radical processes

Scheme 2.



Scheme 3.

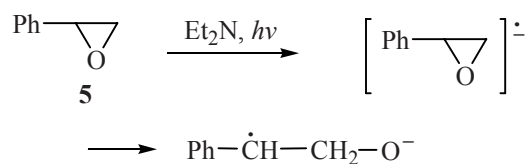


with the homolysis of the carbon-oxygen bond under the action of bis(cyclopentadienyl)titanium(III) chloride [21, 22]. The reaction involves a one-electron transfer from the titanocene to oxirane **2**. Radical intermediate **3** reacts apparently with the second equivalent of the reagent, and the protonation of the enol form of β -alcoholate **4** provides in the final reaction product (Scheme 3).

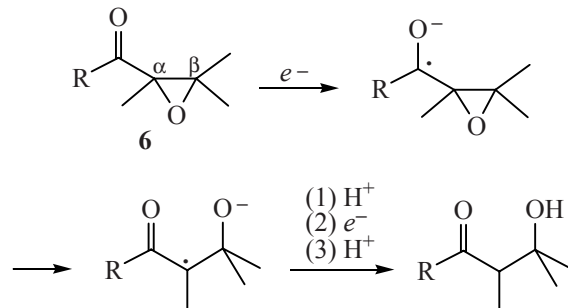
The third mechanism (*c*) is characterised by a successive transfer of two electrons to the substrate molecules and by the intermediate formation of an anion radical. Boyd et al. [23] regard as the key stage of a photochemical process the electron transfer from the triethylamine molecule to epoxide **5** that further undergoes epoxy ring opening forming a more stable radical (Scheme 4).

A photoinduced transformation of α,β -epoxyketones **6** into β -hydroxyketones occurred in the presence of dimethyl-2-phenylbenzimidazole and acetic acid [24] (Scheme 5).

Scheme 4.

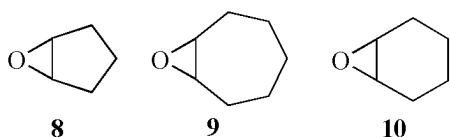


Scheme 5.



Besides the three above kinds of mechanism of epoxides reduction schemes were suggested involving the formation of a cyclic intermediate state. For instance, H.C. Brown suggested such a mechanism of epoxides reaction with lithium triethylborohydride based on studies of kinetics and kinetic isotope effect [25] (Scheme 6).

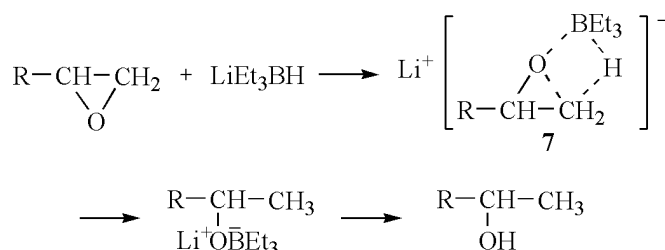
The transition state **7** of the reaction cannot be indifferent to the degree of the steric strain in the substrate [25], therefore epoxycyclopentane **8** and epoxycycloheptane **9** are considerably more active than epoxy-cyclohexane **10**, and the steric strain energy of these alicyclic epoxy compounds decreases just in this order [26–30].



On the other hand, in the reaction with the lithium aluminum hydride in the boiling ether the activity sequence is reversed: the most reactive substrate is epoxy-cyclohexane **10** [31, 32], and significantly less active are epoxycyclopentane **8**, epoxycycloheptane **9**, and epoxides of cyclic hydrocarbons C_{10} , C_{12} , C_{15} . It is also shown [33] that at the use as reagent of a combination of lithium aluminum hydride and aluminum chloride in a molar ratio 2:1 the activity sequence of the epoxides remains the same ($10 > 8 > 9$), and the increased electrophilic assistance to the opening of the epoxide ring leads to the shorter reaction time. The same activity series was observed also in the other reactions of alicyclic epoxy compounds, in particular, in the aminolysis on the surface of alumina [34], in the epoxides polymerization under the action of aluminum compounds [35], and also in methanolysis and the other reactions involving the activation of the epoxide oxygen that facilitated the nucleophile attack on the electrophilic carbon sites of the oxirane.

The character of the influence of the steric strain of epoxides depending on the electrophilic activity of the oxygen in the substrate molecule is supported to a certain extent by the results of quantum-chemical calculations. It was shown in [36–38] that in the absence of epoxide substrate protonation a late transition state formed with a considerable degree of the epoxy ring opening; the formation of this transition state should be favored by high steric strain in the substrate. The early transition state based on the protonated substrate is characterized

Scheme 6.

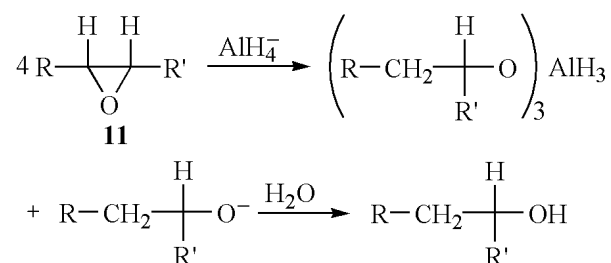


by a smaller degree of the ring opening; the effect of the strain should not be the governing factor in the process in acid medium.

2. GENERAL PATTERN OF EPOXY COMPOUNDS REDUCTION BY LITHIUM ALUMINUM HYDRIDE

The reduction of epoxy compounds with lithium aluminum hydride occurs according to Scheme 7:

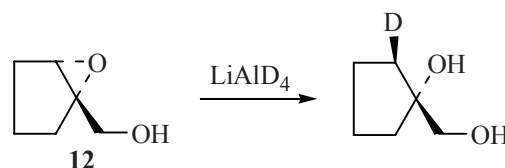
Scheme 7.



In theory the reduction of 1 mol of epoxide **11** requires 0.25 mol of the reagent, but in practice it should be used in a larger amount (up to 0.5 mol), especially when the steric hindrances exist due to the presence of cyclic systems. In event of conformationally rigid bulky systems (in most cases bicyclic) the reduction cannot occur under common conditions (boiling in ethyl ether) [31, 32], but requires heating in higher boiling solvents (THF, dimethoxyethane etc.).

Many examples are reported of regioselective and stereoselective reduction of epoxides with lithium aluminum hydride [39]; in particular, the reduction of epoxide **12** (Scheme 8).

Scheme 8.



On the other hand, *trans*-oxiranes **13** and **14** of similar structure give on reduction different regiochemical results [40] (Scheme 9).

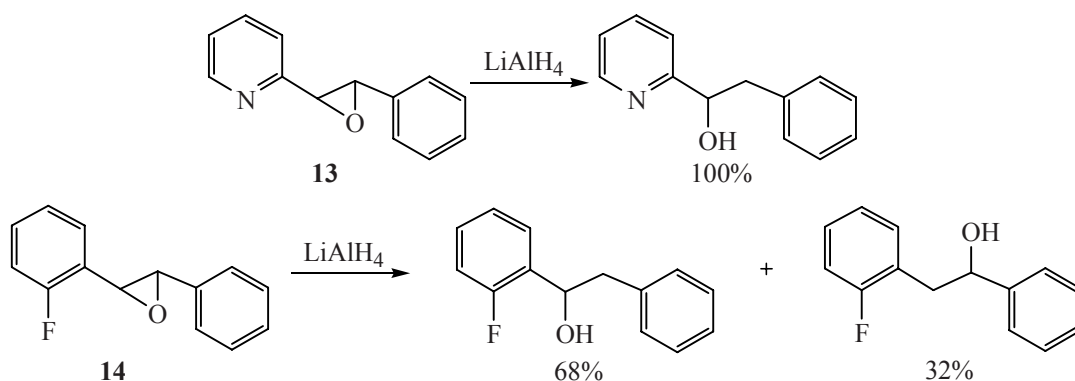
The regio- and stereochemistry of epoxycyclohexanes reduction with lithium aluminum hydride was studied in detail by Chini, Macchia et al. [41–44], and also by Germain et al. [45]. It was suggested later that the reaction mechanism is much more complicated than a simple S_N2 -opening of the epoxide ring [4]. First of all the partial (10%) epimerisation of the hydroxy group in the course of the reaction cast some doubt. Schwab [46] investigated the products of epoxycyclohexane reduction with lithium aluminum deuteride applying NMR spectroscopy on ^1H and ^2H nuclei. The reaction products were identified by comparison with [2,2,6,6- $^2\text{H}_4$]cyclohexanol. The stereochemistry and the ratio of the side products (1:1) obtained alongside the main and expected cycloalkanol **15** indicate their formation by the reduction of ketone **16** (Scheme 10).

Reactions of lithium aluminum hydride with stereoisomeric 1,2-anhydrosugars **17** and **18** were described in [47] (Scheme 11). The high stereospecificity of the reaction was established by 2D NMR spectroscopy.

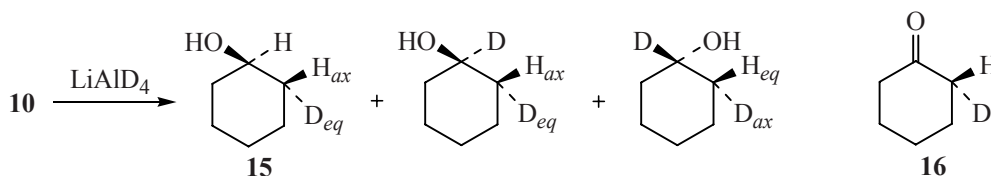
In [41–44] the reduction of *cis*-(4-benzyloxy)-1,2-epoxycyclohexane and its analogs with lithium aluminum hydride was classed among the processes involving the formation of chelates through interaction of lithium ions with the oxygens of the substituent and of the epoxy ring. The contribution of the bidentate chelates into the regiochemistry of the process was revealed by the comparison with the reduction in the presence of a catalyst, 12-crown-4.

The reduction of unsubstituted 1,2-epoxycycloalkanes and 1,2-epoxyalkanes with lithium aluminum hydride was performed in order to reveal the effect of the ring size [31, 32]. Inasmuch as the reduction of a number of epoxides occurred very slowly Andrejevic et al. [33, 48] modified the reducer by adding aluminum chloride. The

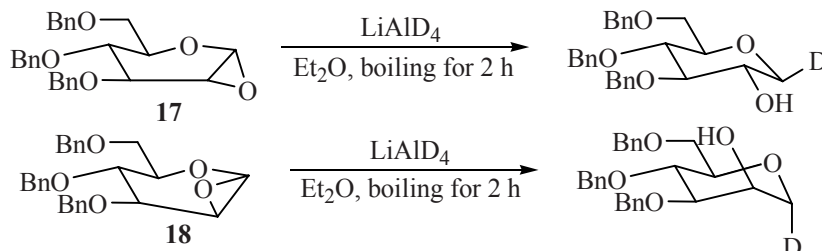
Scheme 9.



Scheme 10.



Scheme 11.



necessity of aluminum chloride addition in reduction of tetrasubstituted oxiranes, e.g., of terpinolene-4,8-oxide **19** was shown in [49] (Scheme 12).

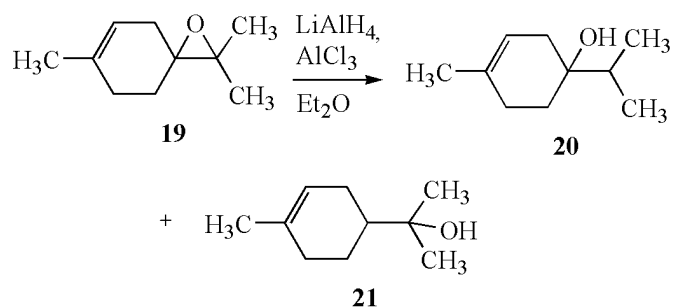
By an example of this epoxide the optimum ratio of the reducer and the catalyst (3:1) was determined providing a plausible yield of compounds **20** and **21** (68 and 22% respectively). Other ratios (9:1, 1:1, 1:3) led to the considerable decrease in the yield of compounds **20** and **21**.

The reduction of alkyl-substituted epoxides is governed both by steric and electronic and also by conformational effects [50].

The dependence of regioisomers ratio on steric interactions is clearly seen both in reduction of *trans*- and *cis*-3-methyl-1,2-epoxycyclopentanes **22** and **23** [50] and in reactions of the other cyclic epoxides **24–26** [51, 52] (Scheme 13).

The reduction with lithium aluminum hydride was often used for confirmation of the structure and for establishment of the absolute configuration of naturally occurring substances [53, 54]. For instance, a reduction

Scheme 12.

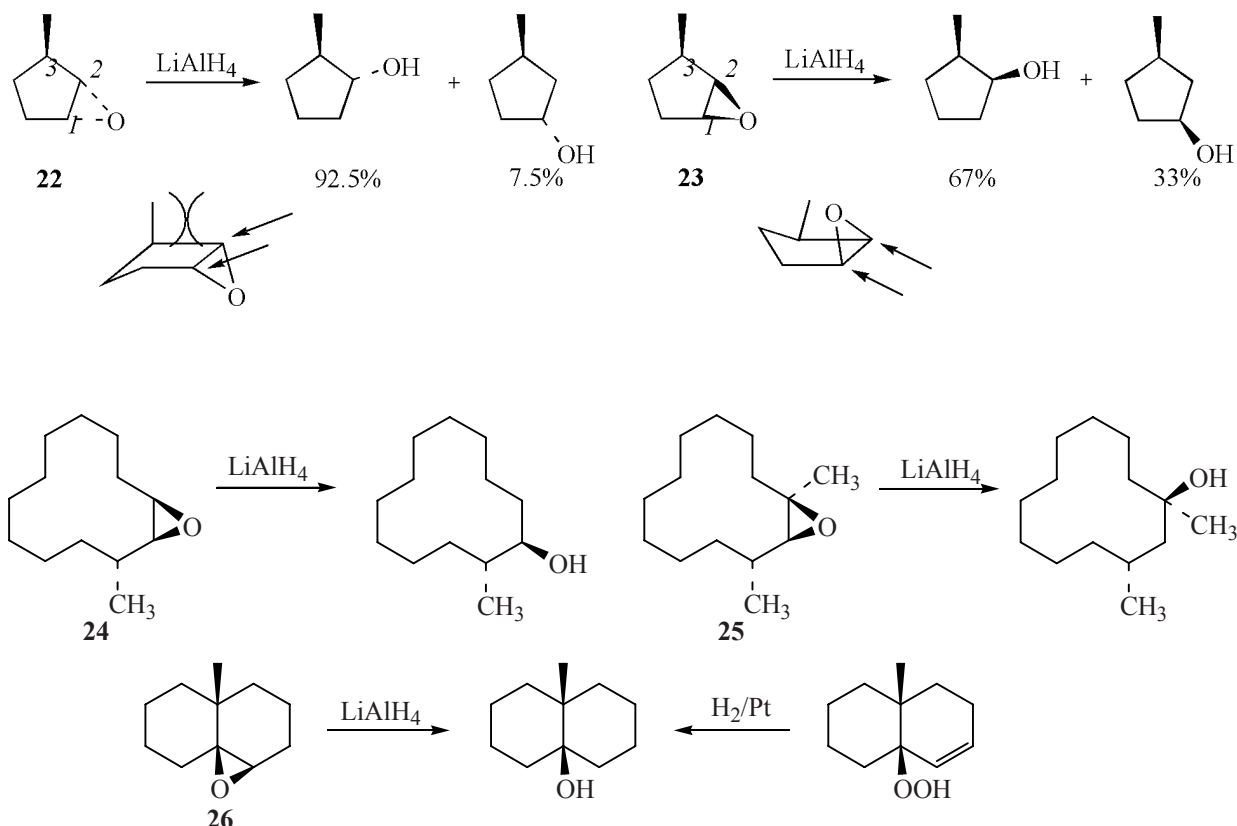


of optically active epoxide epoxide **27** was studied in [23] (Scheme 14).

In some cases (compounds **28** and **29**) the reduction of epoxides involved also a transformation of other functional groups [13] (Scheme 15).

Double bonds can be retained, as has been observed in the regioselective reduction of 8-oxabicyclo[5.1.0]-octa-2,4-diene **30**,—epoxy derivative of cycloheptatriene (Scheme 16).

Scheme 13.



The course of reaction is affected by the stereochemical relations of the functional groups of substrate [13] (Scheme 17).

In the first reaction yield of 1,2-*cis*-diol **31** amounted to 80%, and in the second 1,3-*trans*-diol **32**, 81% in the mixture of the reduction products. The prevailing formation of compound **31** compared to the other products was governed by the conformation of the hydroxy group and the corresponding complex with the metal hydride **33**; the formation of an impurity of *trans*-1,2-diol is due apparently to an intermolecular attack on the epoxide of a molecule of the complex hydride.

In the course of synthesis of active herbicides from the 1,7-dioxaspiro[5.5]undecane series [55] the isomeric epoxides **34** and **35** were shown to be converted into diol **36** at the reduction with lithium aluminum hydride (Scheme 18).

The reduction of epoxyethers **37** related to compound **35** occurred less selectively; methyl and benzyl ethers (R = Me, CH₂Ph) were converted into mixtures of β-

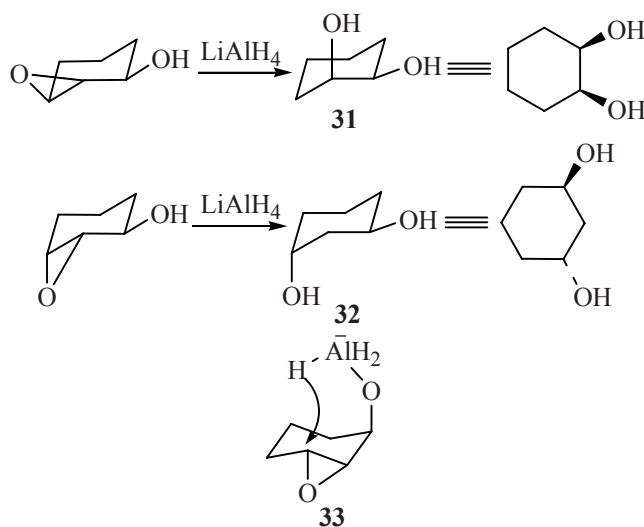
and α-alkoxyalcohols in the percent ratios 63 and 13, 51 and 17 respectively [55] (Scheme 19).

Special attention should be called to the difference in regiochemistry of reduction of epoxyacetal **38** by lithium aluminum hydride and by zinc mixed with chlorotrimethylsilane. These reactions were developed for preparation of 1,2- and 1,3-diones [56] (Scheme 20).

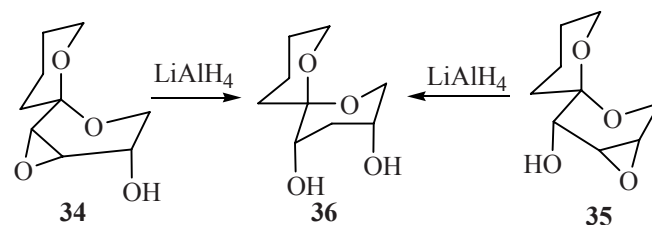
Analogously 2,3-epoxyacetals **39–42** were reduced in high yields.

The reduction can occur regio- and stereospecifically even in the cases where several factors can operate in compounds with several substituents, for instance, in the molecules of *cis*- and *trans*-epoxy derivatives of 6-*tert*-butyl (or 6-trimethylsilyl-, or 6-trimethylgermyl)-3,3-dimethylcyclohexenes [57].

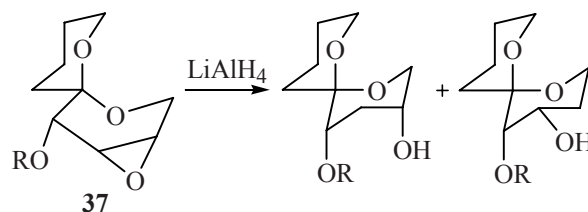
Scheme 17.



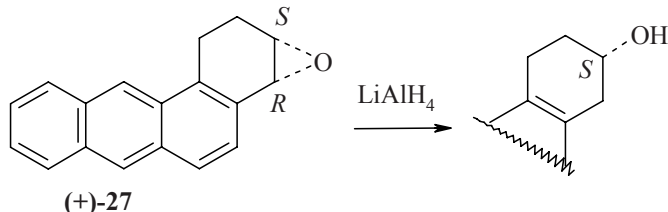
Scheme 18.



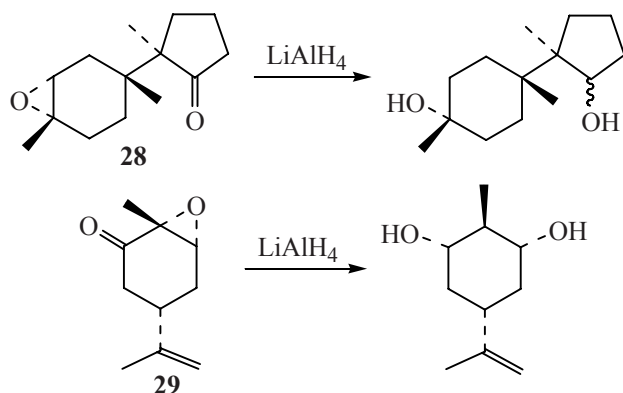
Scheme 19.



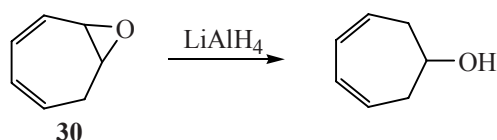
Scheme 14.

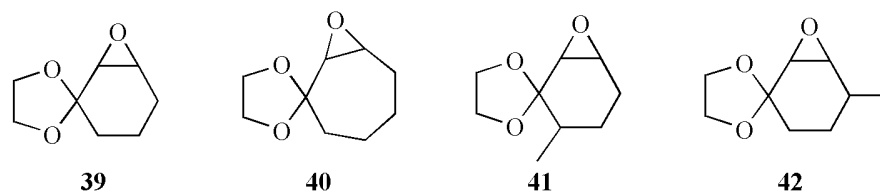


Scheme 15.



Scheme 16.

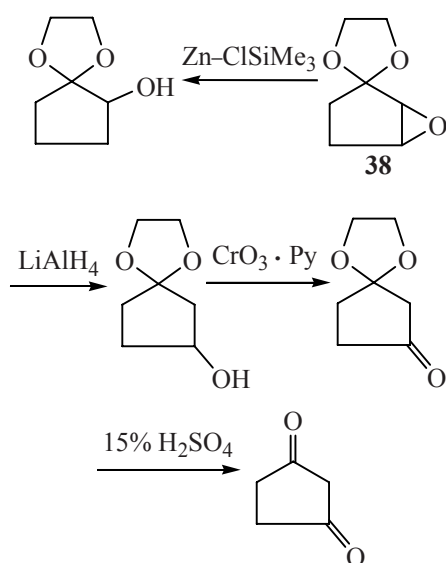




Stereoselectivity is also characteristic of the reduction of diepoxides. By an example of reduction of 1,4-cyclohexadiene *cis*- and *trans*-diepoxides it was shown that the direction of the attack was affected by the possibility of a complex formation between the intermediately formed organoaluminum derivative and

the intact epoxy ring. The reduction products obtained from the γ -terpinene *trans*- and *cis*-dioxides are essentially different [58]. *trans*-Dioxide **43** yielded a single reduction product, the reduction of *cis*-isomer **44** was a lot less selective (Scheme 21).

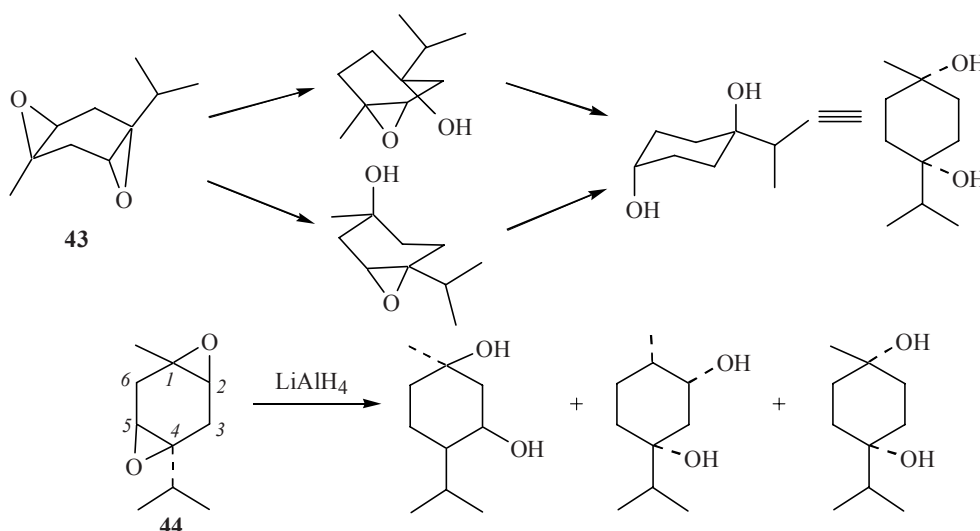
Scheme 20.



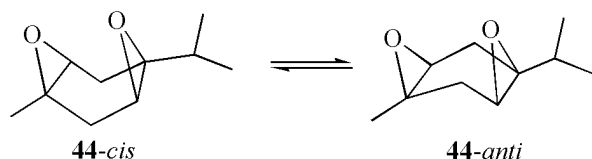
The lack of the fourth possible isomer in the latter reaction equation suggests that the primary attack of the hydride ion is directed prevalingly on the secondary carbon atom due to the steric hindrances to the approach of AlH_4^- anion to atoms C^1 and C^4 from the side of the methyl and isopropyl groups. The analysis of molecular models of the γ -terpinene *cis*-dioxide **44** showed that the attack of the anion met the least steric hindrances when directed on the atom C^2 of the *syn*-form of the diepoxide which evidently entered the reaction [58] (Scheme 22).

In certain instances the application of the lithium aluminum hydride had obvious disadvantages. For instance, in the presence of a carbonyl group the epoxy moiety was prevalingly inert [59] or entered into the reaction after the carbonyl and at more stringent conditions [60]. Rearrangements were observed in the reduction of epoxides **45** and **46** of a series of tricyclo[5.2.1.0^{2,6}]dec-8-ene [61] that yielded the same

Scheme 21.



Scheme 22.



diol **47** [R = Me, Bu, C₈H₁₇, CH₂(CH₂)₇OSiMe₂Bu-*t*] at different rates (Scheme 23).

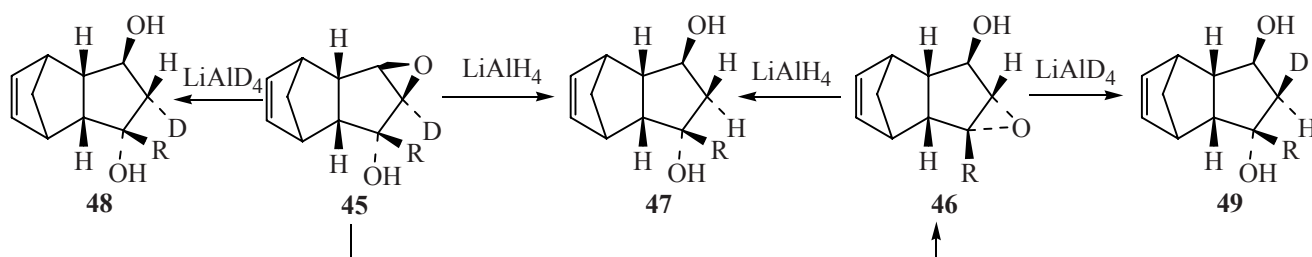
The reduction of the epoxides with the lithium aluminum deuteride was investigated. Epoxide **46** gave diol **49**, and reduction of its isomer **45** led to the formation of a mixture of compounds **48** and **49** in the ratio from 45:55 to 65:35 (Scheme 23). These data confirmed the existence of the rearrangement **45** → **46** and also the direct reduction of epoxide **45** occurring notwithstanding

the steric hindrances to the attack of the hydride ion from the *endo*-side of the tricyclic skeleton [61].

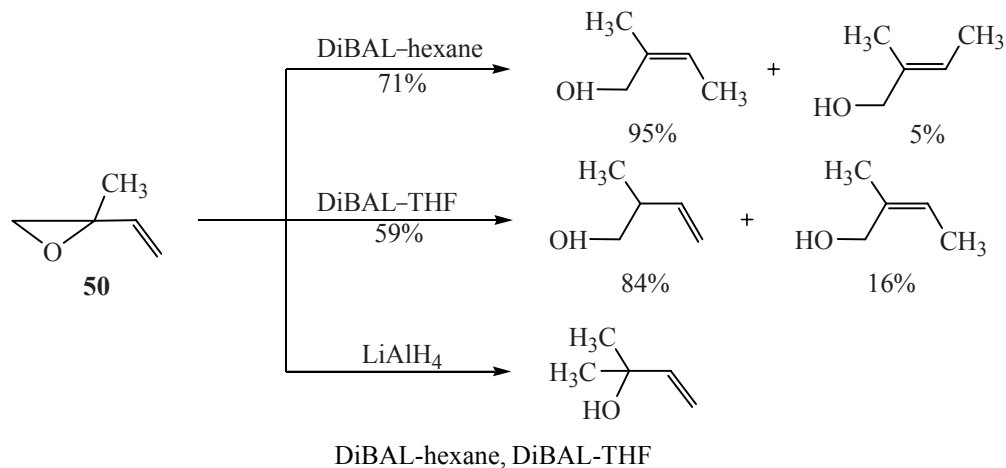
In order to prevent the electrophilic rearrangements, in particular, Wagner-Meerwein rearrangement, the lithium aluminum hydride was replaced by lithium alkyl- or alkoxyaluminumhydrides. Lithium alkoxyaluminumhydrides to a large extent were up to the expectations but the application of these compounds retained some shortcomings of the lithium aluminum hydride, in particular, insufficient yields and incomplete regioselectivity of reactions.

The application to the reduction of various organic compounds of diisobutylaluminum hydride (DiBAL) and triisobutylaluminum (TiBA) was treated in reviews [10, 15]. A part of the results obtained in reduction of epoxide **50** is shown in Scheme 24.

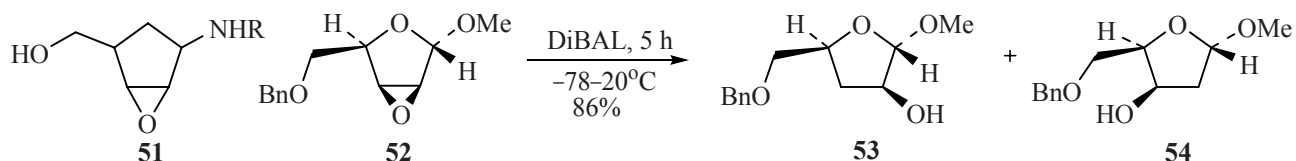
Scheme 23.



Scheme 24.



Scheme 25.



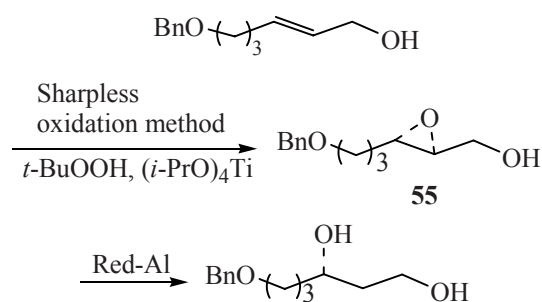
The reduction of epoxide **51** with lithium diisobutylaluminumhydride occurred to a low yield (25%) [62]. The reduction of epoxide **52** with diisobutylaluminum hydride gave the products in a ratio **53:54** = 1:2 (Scheme 25); with the lithium aluminum hydride (boiling in THF) the reduction took 12 h and provided the products in 88% yield in a ratio **53:54** = 13.5:1 [63].

Gadikota et al. demonstrated, that the use of DiBAL in reduction of the *tert*-butyldimethylsilyl derivative of alcohol **51** increased the yield to 85% and resulted in a regioselective conversion of the epoxide into diol. Among the convenient reducers of this group Red-Al [NaAlH₂(OCH₂CH₂OMe)₂] should be mentioned [63]. The regioselective reduction of epoxides with Red-Al was included in the new strategy of preparation of practically important 1,3-polyols from epoxide **55** [9] (Scheme 26).

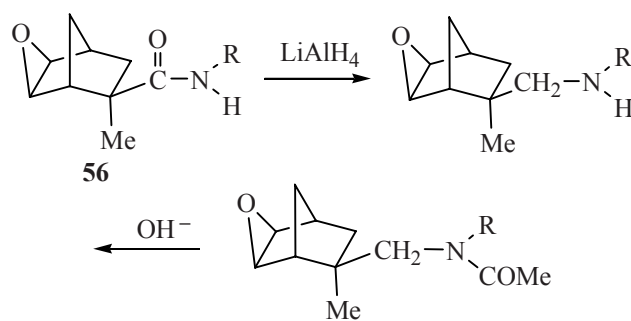
A special group of oxiranes make epoxynorbornanes that are usually inert in reactions with the lithium aluminum hydride in common solvents [4, 11, 13]. The specific geometry of the *exo*-epoxynorbornane moiety essentially hampers the bimolecular substitution in these rigid systems, and the sensitive to the steric effects reductive opening of the epoxy ring by lithium aluminum hydride is impeded in this series. In most cases it does not proceed in boiling ether with little exclusions from the rule. Some epoxides do not undergo reduction in boiling THF, *N*-ethylmorpholine, and dimethoxyethane [13]. The reductive opening of the epoxide ring in compound **56** was attained only at 105–110°C applying as solvent dibutyl ether [64] (Scheme 27).

The abnormal course of the reaction becomes more probable in the presence in the epoxide molecule of electron-donor groups, in particular, in epoxide **57** [11] (Scheme 28). In the reduction of functionally substituted epoxynorbornanes the governing factor is the mutual orientation of the groups [65]. The heterocyclization

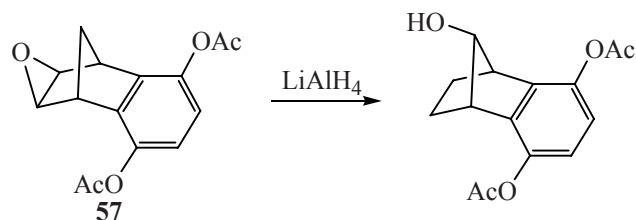
Scheme 26.



Scheme 27.

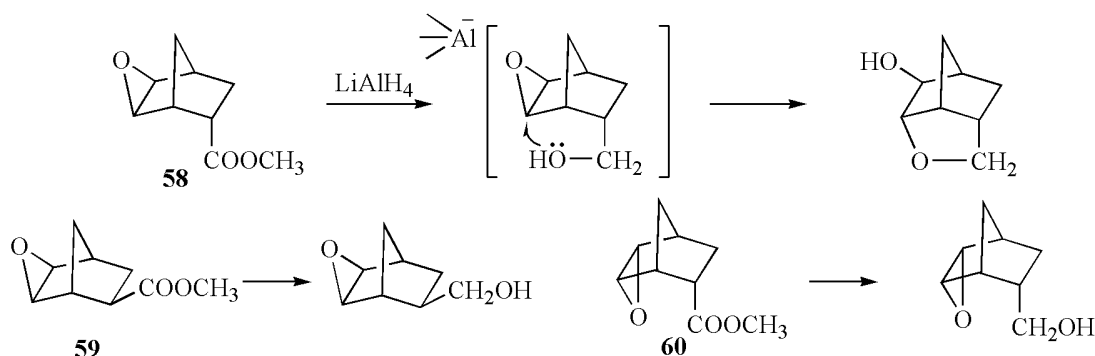


Scheme 28.



occurred only in the reaction of epoxide **58** as a result of a rear attack of the arising hydroxy group on the electrophilic sites of the epoxide. When this attack was impossible (epoxides **59** and **60**) a chemoselective transformations proceeded involving the other reactive sites of molecules leaving intact the epoxynorbornane fragment (Scheme 29).

Scheme 29.



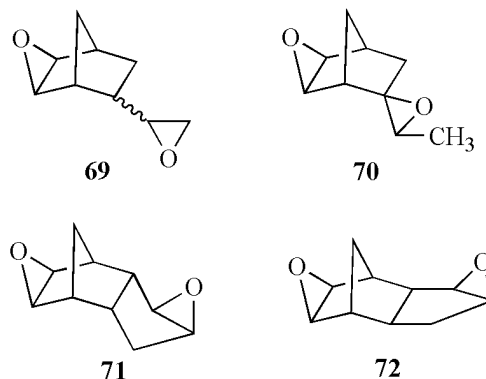
A heterocyclization was performed at the expense of the nitrogen of amino group arising at the chemoselective reduction of *endo*-nitrile **61**; *exo*-forms of amines **62** were not capable of heterocyclization [66] (Scheme 30).

The same reaction pattern was observed in the reduction of epoxy derivatives of acylated amines from the norbornene series **63** (R = Me, CH₂Ph, Ar) [67, 68] (Scheme 31).

Azabrendane system **66** analogous to the parent compound of the series **63** was obtained according to [69] by the reduction of epoxy derivatives of imides **65** (R = CH₂CH₂Ph). However recently applying aromatic imides (R = Ar) the formation under the same conditions of compounds **67** and **68** isolated by chromatography was proved by X-ray diffraction analysis [70] (Scheme 32).

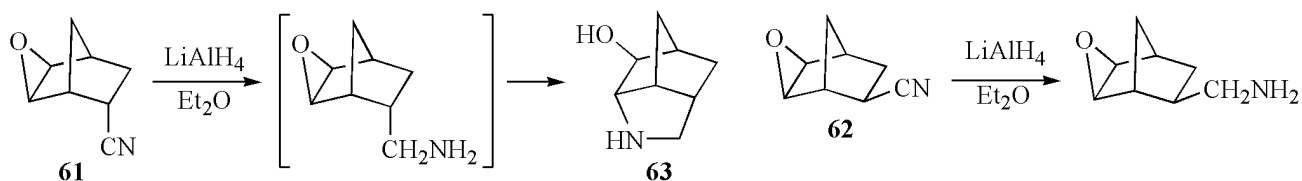
Evidently the intermediately formed carbinol attacked from the rear of the skeleton the electrophilic centers of the oxirane, and the spatial structure of the carbinol favored the intramolecular cyclization.

The high stability of the *exo*-epoxynorbornane fragment against the lithium aluminum hydride was also found in the study of the reduction of compounds **69–72** containing two epoxide rings each in different surrounding [65].

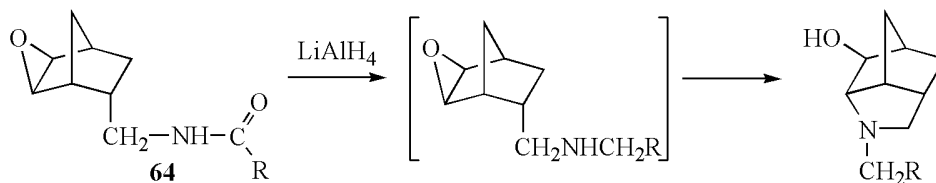


The high regio- and stereoselectivity of epoxide **71** reduction originates from steric reasons: from the hampered *endo*-attack on the carbon atom of the epoxycyclopentane fragment contiguous to the norbornane skeleton, and from the possibility of the attack on the distant atom of the epoxide ring. The stereoisomeric *exo*-dicyclopentadiene dioxide **72** where the epoxide rings were significantly remote from each other did not place these heavy demands on the attacking nucleophile; the nucleophile attack here was not regioselective, and the mixture of alcohols **73** was converted into ketones **74** and **75** that were isolated by chromatography on alumina (Scheme 33).

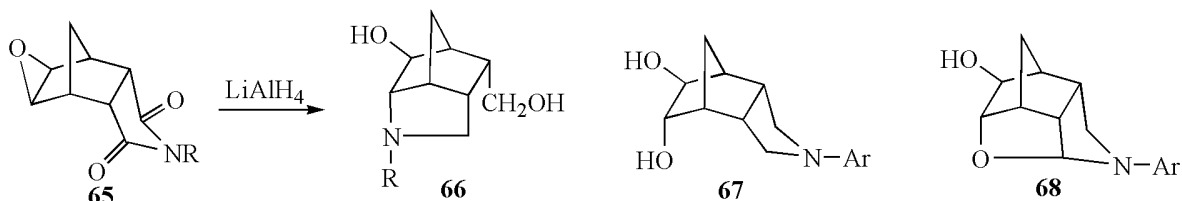
Scheme 30.



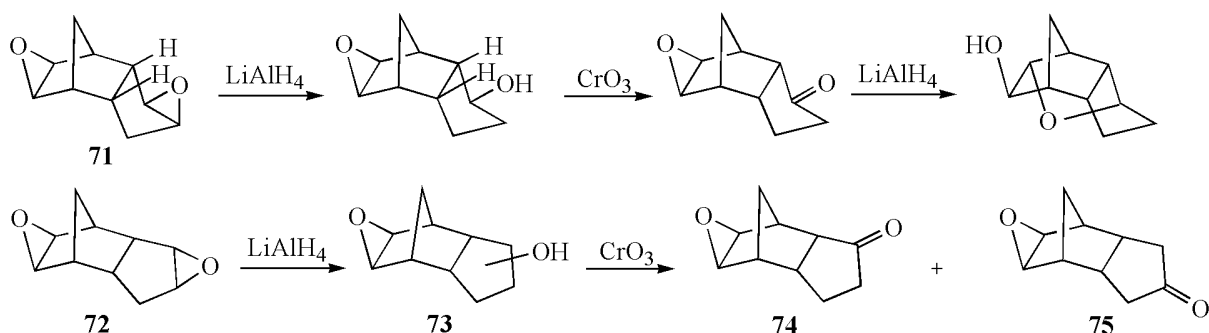
Scheme 31.



Scheme 32.



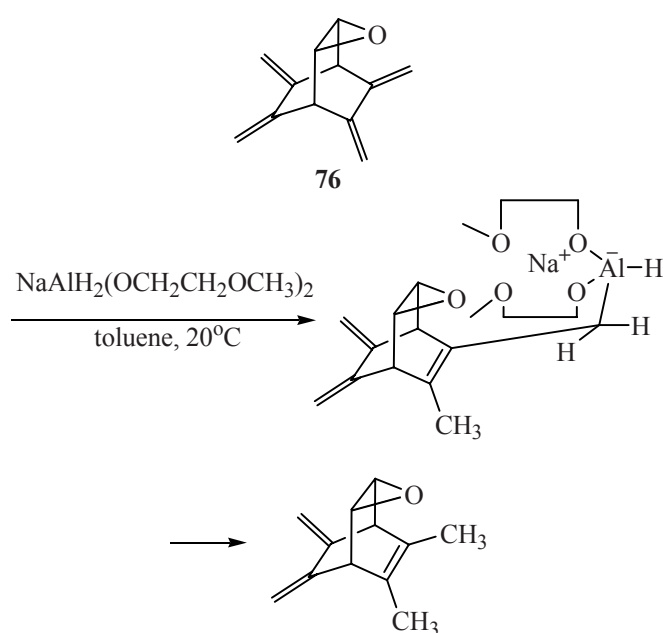
Scheme 33.



The effect of the epoxide ring on the reduction of the other substituents is thoroughly analyzed in [71].

The reduction of compound **76** with sodium bis(methoxyethoxy)aluminumhydride capable of reducing carbonyl, carboxy and ethoxy groups resulted only in the hydrogenation of the 1,3-diene system (Scheme 34). The chemoselectivity of the process originated from the involvement of the epoxide oxygen in the coordination of the sodium cation by the reducer molecule.

Scheme 34.



3. APPLICATION OF BORON-CONTAINING REDUCERS

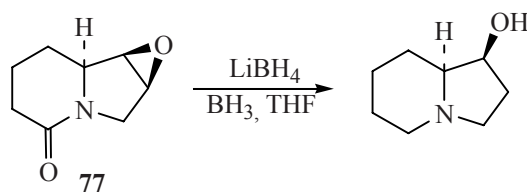
This group of reducers includes lithium, zinc, and sodium borohydrides, borohydride, boranes and related structures; the most important among them is evidently lithium borohydride [72]. The efficiency of the reagent is raised by adding triethylborane [73] and borohydride [74]. In the latter case the regio- and stereoselective functionalization of epoxide **77** and other, among them optically active substances, was performed (Scheme 35).

A regioselective reduction of 2,3-epoxy-1-alkanol derivatives was performed with lithium borohydride on a zeolite support [75].

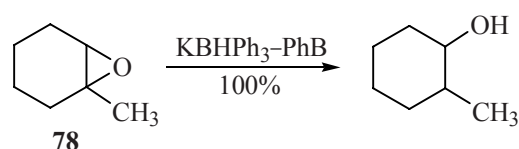
Epoxide **78** was regiospecifically reduced under the action of a mixture of potassium triphenylborohydride and triphenylborane, and the addition of the latter changed the regiochemistry of the process [76] to that previously found only under the conditions of radical reactions [77] (Scheme 36).

Recently a considerable reducing potential was discovered in lithium *N,N*-dialkylaminoborohydrides [78]. Reductions of cyclohexene and cyclopentene oxides to alcohols were quantitative in the presence of BH_3 and a nitrile (e.g., benzonitrile) as an additive. The replacement of one of the hydrogens by pyrrolidinyl

Scheme 35.



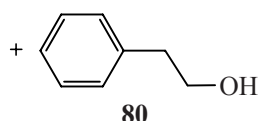
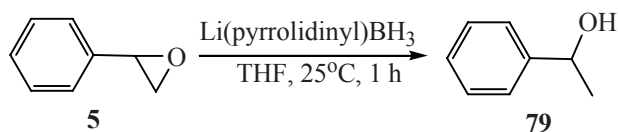
Scheme 36.



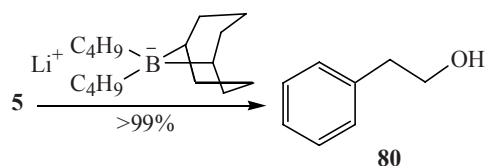
permitted preparation of the product with a significant prevalence of one isomer (**79:80** = 12:1) (Scheme 37).

The reversed regioselectivity is characteristic of the reduction of epoxystyrene **5** at the use of lithium 9,9-dibutyl-9-borabicyclo[3.3.1]nonane[4] (Scheme 38).

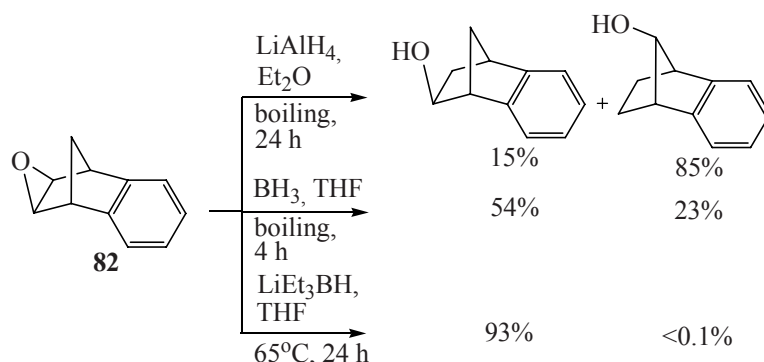
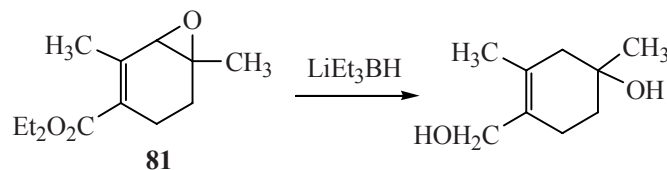
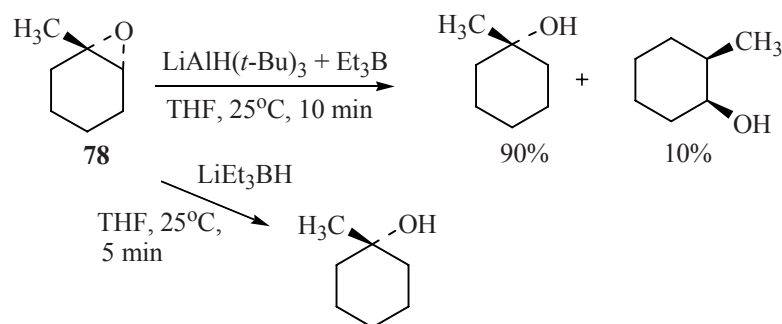
Scheme 37.



Scheme 38.



Scheme 39.



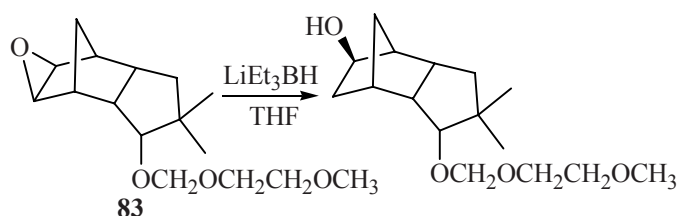
Alkyl-containing epoxides formed prevalingly (over 90%) secondary alcohols as a result of the reaction in keeping with Krasusky rule.

An invaluable breakthrough of Brown was introducing of lithium triethylborohydride (“*Super-Hydride*”) [25, 79]. This reagent found application both on the industrial scale and in kinetic and fine synthetic research, it showed high activity and excellent selectivity [25, 80]. The latter was decreased at the use of borane (BH_3) or its analogs [47] as catalysts. The reactions with the Super-Hydride permit the preparation of unrearranged products from epoxides **78**, **81** and **82** [11] (Scheme 39).

The Super-Hydride possessed a considerable capability to reduce regioselectively epoxynorbornane **83** [81] (Scheme 40).

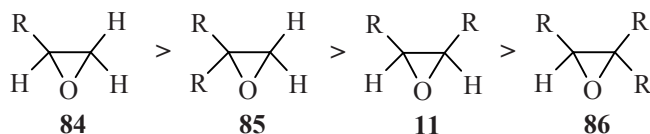
Among the complex metal hydrides sodium borohydride appears as very attractive: It is available, mild, safe in operation reagent used in reduction of ketones and aldehydes [20, 82]. The reduction of oxiranes with sodium borohydride proceeded very slowly save the compounds having neighboring nitro or hydroxy

Scheme 40.



groups [83]. Epoxy fragments are capable to be conserved in the course of transformation of the other groups [62].

In this connection the attempts to carry out chemoselective transformations of just the epoxy fragment in the presence of other reducible groups are especially valuable. Nowadays several convenient methods of chemoselective reduction of epoxides with sodium borohydride are developed. In earlier publications of Soai et al. [73, 84] the reduction was carried out in mixed solvents (*tert*-butanol–methanol or 1,2-dimethoxyethane–methanol), and it occurred in yields 73–100% and high regioselectivity (89–100:11–0) in favor of the more substituted alcohol. Individual solvents (methanol, *tert*-butanol) and mixtures (THF–methanol, hexane–methanol, benzene–methanol) are considerably worse than the above systems. The activity of epoxides **11**, **84**–**86** decreased in the series given below; terminal epoxides in the presence of trisubstituted oxiranes were reduced, the trisubstituted compounds being intact.



The reducing system is highly chemoselective and does not affect carbamoyl, carboxy, nitro, and cyano groups, and conserves phosphorus atoms in substrate, in particular, **87** [84, 85]. The application of potassium borohydride increases the selectivity, but decreases the yield of the target product (Scheme 41).

Further search for solvents showed that the high chemo- and regioselectivity was conserved when the reactions were carried out in ethanol or 2-propanol [83], and also in the presence of poly(ethylene glycol)-400 (PEG) [86]. In the latter case Santaniello et al. presumed that as reducer acted the complex $\text{Na}[(\text{OCH}_2\text{CH}_2)_n\text{OH}]_2\text{BH}_2$ ($n = 8, 9$), or $\text{Na}(\text{PEG})_2\text{BH}_2$. It should be noted that at the use of this method the reduction products from the disubstituted epoxides were obtained in low yield.

It was shown by an example of 2-furyloxirane [87] that the regiochemistry of the epoxide reduction both by sodium borohydride and lithium aluminum hydride essentially depended on the character of the solvent. Interesting findings were obtained in the study of reduction of epoxy derivative of isophorone oxime **88**, a mixture of *syn*- and *anti*-forms [88] (Scheme 42).

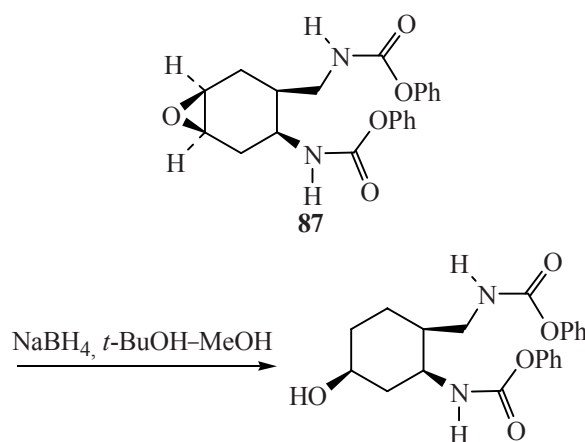
This scheme summarizes the effect of a number of factors on the composition of the reduction products, namely, of the ratio of the reactants, the nature of the complex hydride (NaBH_4 , LiAlH_4) and additives (MoO_3 , CeCl_3). The important result of the study was the development of a new procedure of preparation of valuable γ -aminoalcohols analogous to natural compounds.

In the presence of catalytic quantities of iron(III) chloride or of selenium the phenyloxirane but not its aliphatic analogs was reduced with sodium borohydride into a mixture of α - and β -phenylethylene alcohols in 30–35% yield and the α -isomer content 80–83% [89]. The simultaneous application of both catalysts resulted in deoxygenation and the formation of styrene (60%).

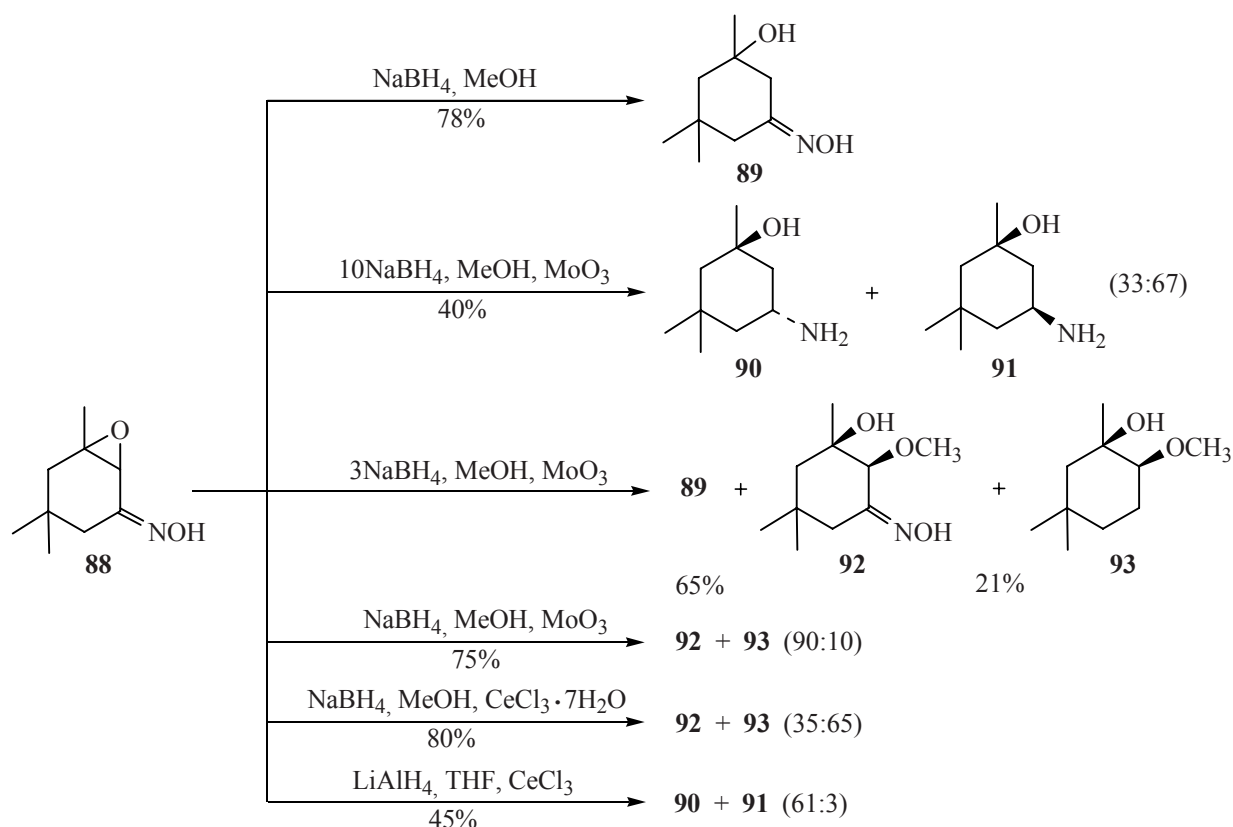
Procedures were developed for epoxides reduction with sodium borohydride in the presence of cyclodextrins in water environment [90, 91]. It was shown by kinetic study that two enantiomers of epoxystyrene reacted with different rates giving predominantly 1-phenylethanol. The enantioselectivity of the process could reach 46 *e.e.* Cyclodextrins accelerate the regioselective reduction of 1,2-epoxyindan, and the unreacted substrate possessed the optical rotation. The hydride anion attack on the benzyl atom in the 1,2-epoxyindan and 1,2-epoxyacenaphthene was proved in [92].

Applying sodium borohydride with a catalyst containing α -proline a regioselective reduction of epoxides was

Scheme 41.



Scheme 42.



performed, in particular, of 1-methyl-1,2-epoxycyclohexane; therewith from racemic epoxides optically active alcohols were obtained [93].

Sodium cyanoborohydride in the presence of zinc iodide was successfully used for regioselective opening of an epoxy ring (contrary to Krasusky rule). Among epoxides under study were compounds **94–96** etc. [94] (Scheme 43).

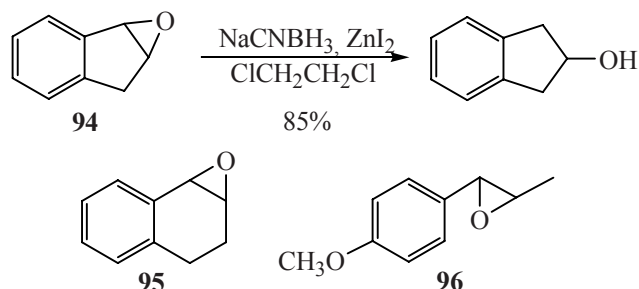
The reducer modification by introducing a cyano group into the hydride molecule made it possible to carry out an unexpected conversion of epoxyesters **97** into α -hydroxyesters (Scheme 44). The complex process

includes an isomerization of the epoxide in the first stage and the reduction of the carbonyl group in the second stage [95].

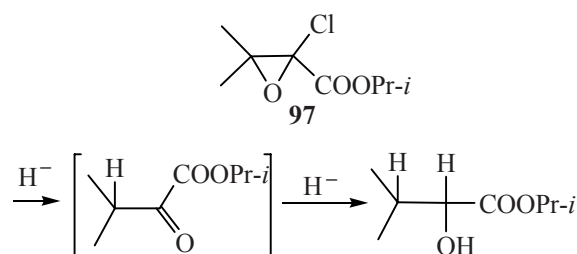
Uncommon route take epoxide reactions with a sulfurized sodium borohydride (a product of sodium borohydride reaction with three sulfur atoms) [96]. Although the general trends in the regio- and stereo-chemistry of the reactions are conserved (*trans*-opening of the ring with an attack on the less sterically loaded site) the reaction products **98** possess unusual structure (Scheme 45).

In the last decade among the reducers of a large synthetic potential appeared zinc borohydride [8, 97, 98]. The reagent is especially valuable with respect to the

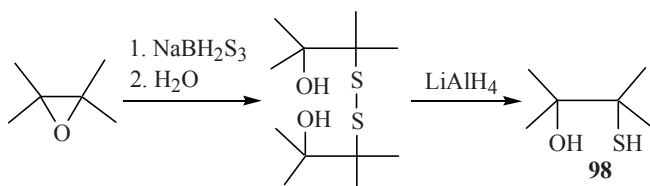
Scheme 43.



Scheme 44.

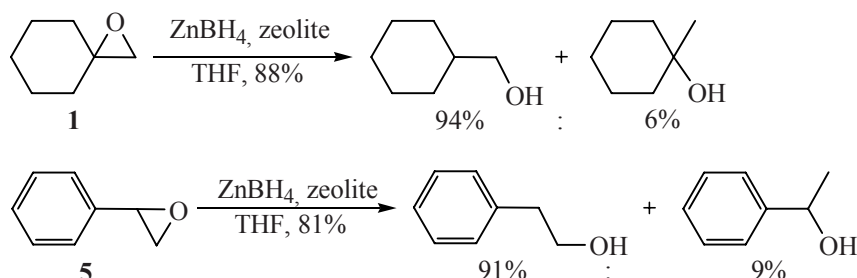


Scheme 45.



reduction of epoxides for it makes possible to perform regio- and stereoselective conversion of these compounds into less substituted alcohols. In [98] β - and γ -zeolites were used as catalysts but a complete regioselectivity was not attained, and the isomers ratio varied from 94:6 to 75:25 (Scheme 46).

Scheme 46.



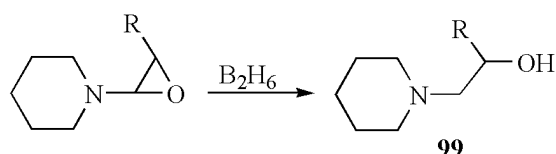
Diborane can be used as epoxides reducer [99, 100] leading to the formation of a group of very valuable *N*-hydroxyalkylpiperidines **99** (R = Me, Et) (Scheme 47).

In [99] aliphatic α,β -unsaturated epoxides **100** were used as substrate whose conversion into substituted allyl alcohols occurred through a cyclic transition state (Scheme 48).

The inertness of the epoxy derivatives of substituted norbornenes toward lithium aluminum hydride was already mentioned. A similar behavior of epoxides belonging to this and related groups with respect to less active complex hydrides seems natural. Recently a detailed study was published [101, 102] on the reduction of epoxyketone **101** resulting in stereoisomeric alcohols **102**, **103** (see the table, Scheme 49).

The inertness of epoxy fragments to reduction was also observed in other ketoepoxide groups: in compounds from acyclic series toward sodium hydride in the presence of calcium chloride [103], in α,β -epoxyketones of various structures with respect to a new hydride reagent containing tin (Bu_2SnFH) [104].

Scheme 47.

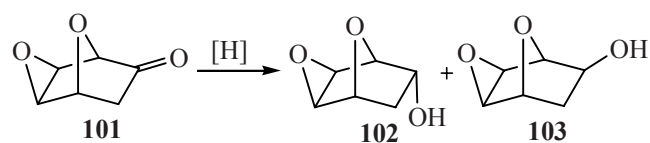


The thermodynamic instability of substituted *exo*-5,6-epoxy-2-azabicyclo[2.2.1]heptan-3-one **104** facilitated the rearrangement occurring in the course of the epoxide reduction with sodium borohydride [105] (Scheme 50).

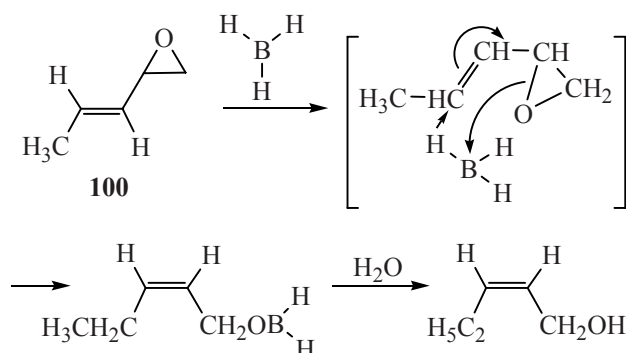
4. CATALYTIC HYDROGENATION OF EPOXY COMPOUNDS

Catalytic hydrogenolysis has been used for reduction of epoxides since the middle of the twentieth century,

Scheme 48.



Scheme 49.



Reduction products of epoxide **101**

Hydride	Quantity of H ⁻ , g-equiv	Solvent	Temperature, °C (time, h)	Yield, %			102:103
				101	102	103	
NaBH ₄	4	<i>i</i> -PrOH	0 (1.5)	4	63	30	2.1:1
NaBH ₄	2.7	MeOH	-78 (3)	14	53	31	1.7:1
NaBH ₄	2.7	THF	65 (24)	–	36	22	1.6:1
LiAlH ₄	8	Et ₂ O	36 (15)	6	41	28	1.45:1
AlH ₃	1.4	THF	25 (1.17)	–	31	49	1:1.35
AlH ₃	1.9	THF	-78 (1.17)	35	39	23	1.7:1

and it has a number of shortcomings, the most important among them are a relatively low selectivity and concurrent reaction of oxirane deoxygenation. Nonetheless the method is applied to the production of available and practically important compounds, for instance, cyclodecanol from epoxycyclodecene on both Raney nickel [106] and nickel-chromium-aluminum catalyst [107].

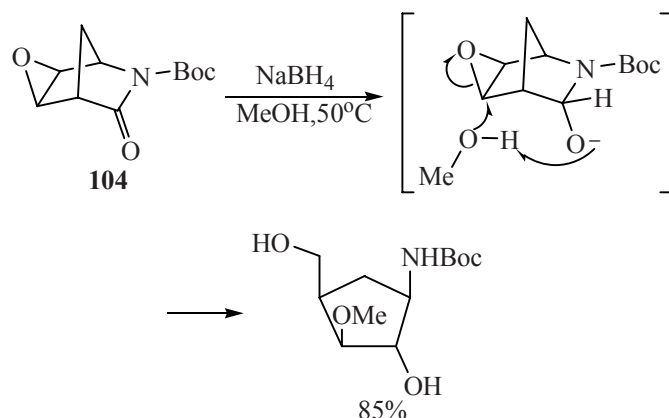
Epoxy compounds with the strained rings, in particular, 1-methyl-1,2-epoxycyclobutane in the course of hydrogenolysis on palladium catalyst first suffered the rupture of C–C and not C–O bonds. The abnormal reaction course was explained by better adsorption on this catalyst of carbon atoms compared to oxygen. As a result of this considerable deviation from the general rules of oxiranes opening the hydrogenolysis products were 2-methyltetrahydrofuran and pentan-2-one [13].

The specific features of regiochemistry of the catalytic reduction of the simplest epoxides, e.g., propylene oxide, on nickel and platinum catalysts were discussed in [108]. The prevailing formation of secondary alcohols on platinum catalyst and primary alcohols on nickel catalyst was established by kinetic methods. Bartok et al. believed

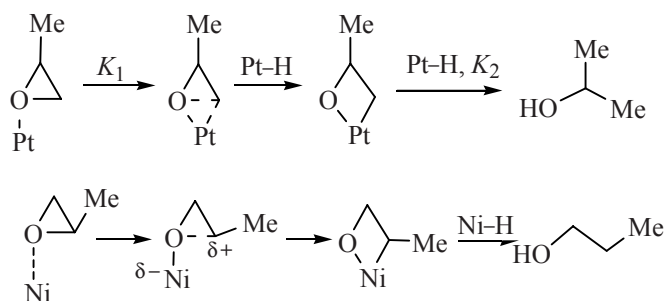
that the difference in regiochemistry originated from dissimilar reaction mechanisms that are presented in Scheme 51 for propylene oxide.

The regioselectivity mentioned in [108] is fundamentally important, but practically insufficient when mixtures formed of different reaction products. Some results evidence the regiospecificity in the hydrogenolysis of complex epoxides. The reduction of 2,5:3,4-dianhydro-*D*-yl-tritol **105** with hydrogen (on catalyst palladium hydroxide on carbon) gave isomer **106** (99%); at the use of lithium aluminum hydride equal amounts formed of regioisomers **106** and **107** [109] (Scheme 52).

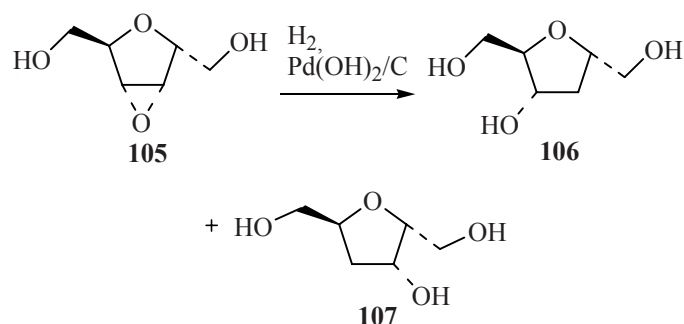
Scheme 50.



Scheme 51.



Scheme 52.



Stereochemical aspects of the epoxy ring opening in catalytic hydrogenolysis were studied by an example of *cis*- and *trans*-1,2-epoxy-4-*tert*-butylcyclohexane **108**, **109**. The analysis of the deuterated reduction products by ^2H NMR spectroscopy established that the cleavage of the C–O bond in the epoxide occurred with a high stereospecificity with configuration inversion at the use as catalysts rhodium, palladium, iridium, and platinum, and with retention of the configuration at the catalytic action of cobalt. Both stereochemical processes proceeded in hydrogenation on nickel, ruthenium, and osmium [110] (Scheme 53). The different stereochemistry of hydrogenation was attributed to variations in the metal affinity to the oxirane oxygen atom.

Formerly [111] the inversion of configuration characteristic of the reduction with lithium aluminum hydride was discovered in hydrogenation of the studied epoxides on 10% Pd/C. The formation of saturated hydrocarbons via deoxygenation products is especially typical for catalysts of cobalt (28–30%), and also of ruthenium and palladium.

As early as 1974 [112] comparison was performed of hydrogenolysis of 1-phenyl-7-oxabicyclo[4.1.0]heptane **110**, the corresponding aziridine, and cyclopropane in the presence of Raney nickel, Pd/C, Pd(OH) $_2$, PtO $_2$, and platinum black. The presence of a substituent at the epoxide ring facilitates the study of the reaction stereochemistry, but essentially affects the substrate sorption and therefore the course of the hydrogenolysis. The

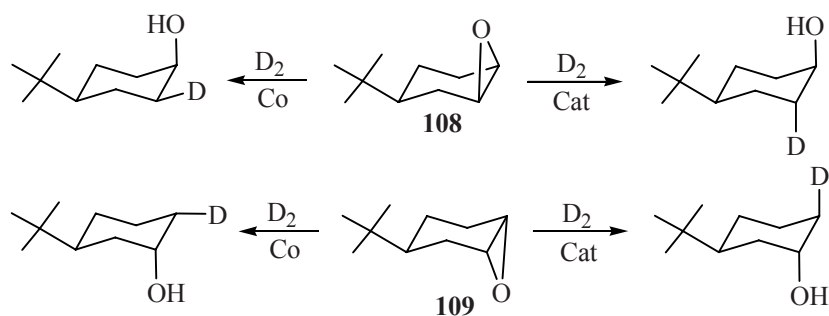
oxirane is strongly sorbed on nickel both through the oxygen and the phenyl ring the hydrogenolysis occurs by S_Ni -mechanism with the conservation of the configuration. In the presence of alkali the sorption of the oxygen decreased, and *cis*-2-phenylcyclohexanol formed by S_N2 -mechanism (Scheme 54).

The inversion of configuration (path *b*) is also characteristic of epoxide reduction on palladium catalysts both in the absence and presence of alkali. Here the hydrogenolysis proceeds through a benzyl π -complex formed at chemisorption of solely the phenyl group. Stereoselectivity of hydrogenolysis decreases from cyclopropane to oxirane, and it was attributed to the difference in the electronegativity of carbon, nitrogen, and oxygen atoms and to their unlike affinity to the catalyst [112].

The presence of a phenyl substituent at the carbon atom of the epoxide ring in the presence of an electrophilic catalyst often leads to the rupture of the oxygen bond with just this carbon for the electron deficiency arising on the carbon atom can be efficiently compensated by the electron-donor effect of the phenyl group [41–44]. A similar situation is observed in the case of 1-naphthyl-1,2-epoxycyclohexane. The matter changes crucially in the presence of alkyl substituents in the molecules of carvomenthene and limonene [113] **19** and **111**, apparently due to the steric control of the reaction site (Scheme 55).

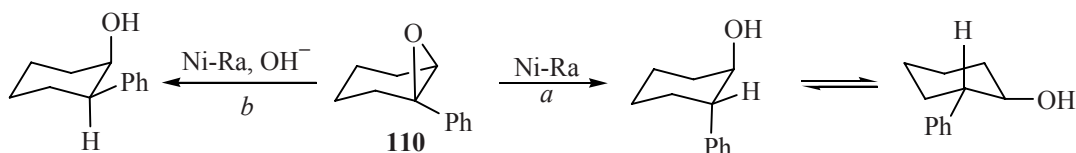
The examples of asymmetric hydrogenolysis are very rare. It was shown in [114] that disodium epoxysuccinate **112** was hydrogenated on norbornadiene rhodium catalyst

Scheme 53.

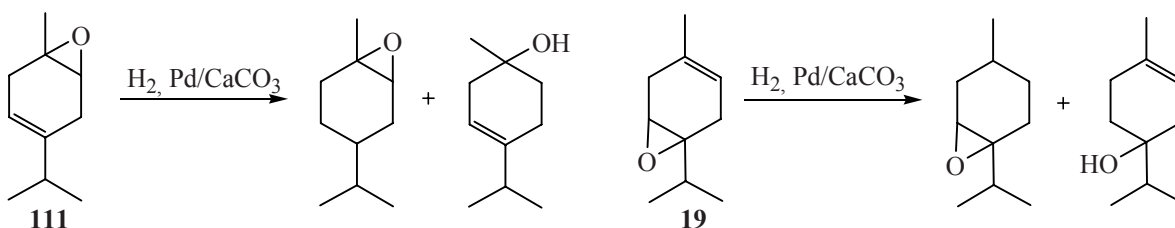


Cat = Rh, Pd, Ir, Pt.

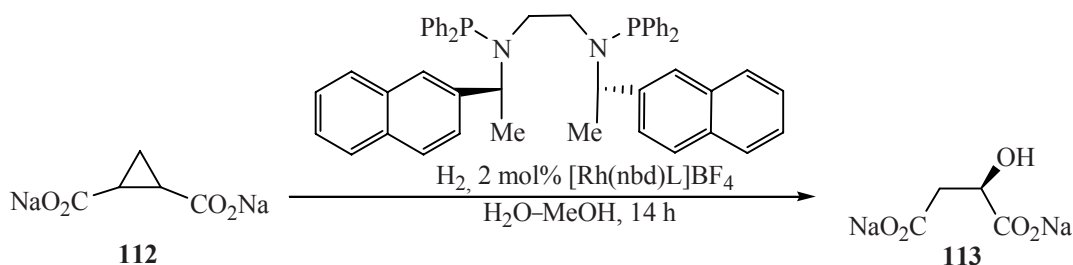
Scheme 54.



Scheme 55.



Scheme 56.

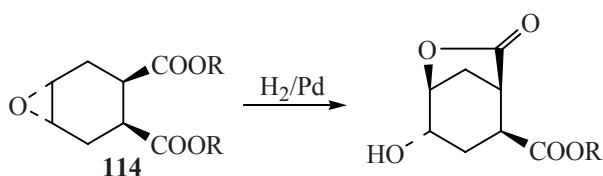


[Rh(nbd)L]BF₄ at room temperature to get optically active secondary alcohol **113** (62% *e.e.*) (Scheme 56).

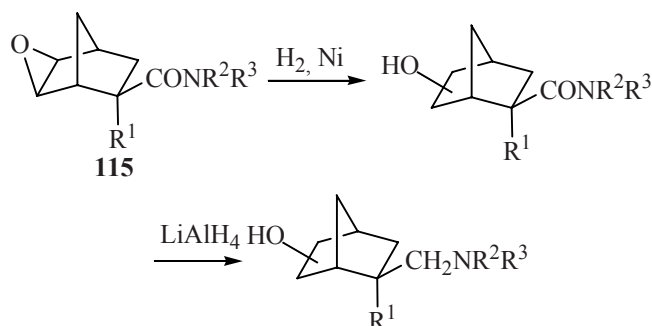
Intramolecular cyclizations occurred in some cases in the course of hydrogenolysis of epoxides **114** [115] (Scheme 57).

Epoxybornanes **115** were readily reduced by hydrogen on Raney nickel with conservation of the amide group. The mixture of regioisomers was further converted with lithium aluminum hydride into a mixture of aminoalcohols [13] (Scheme 58).

Scheme 57.



Scheme 58.



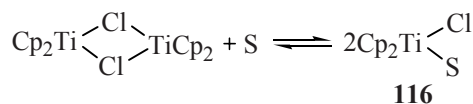
5. EPOXIDES REDUCTION THROUGH FORMATION OF RADICAL AND ION RADICAL INTERMEDIATES

Among radical reactions of epoxides exist two kinds of processes: those with application of tributyltin hydride, and the other utilizing titanium complexes; in the latter case the reagent reacting with epoxides with a preliminary homolysis of the C–O bond is the bis(cyclopentadienyl)titanium(III) dichloride (titanocene dichloride) known since nineteen seventies [18, 22]. It is dimeric in the solid state but in the presence of donor solvents it dissociates into monomer **116** (Scheme 59).

The regiochemistry of the homolytic opening of the epoxide ring is governed by the stability of the formed free radicals that can react with H-donors leading as a result to the reduction of the epoxide. In the absence of H-donors the radical under the action of Ti(III) transforms into an olefin. In all cases the reaction proceeds under sufficiently mild conditions that can be used for converting fairly sensible substrates [18, 22].

As hydrogen donor 1,4-cyclohexadiene was introduced that transformed into benzene under the

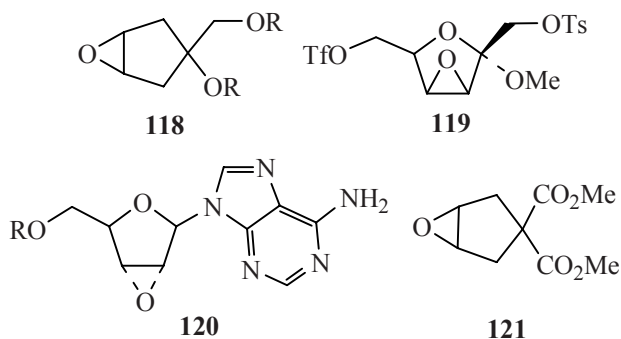
Scheme 59.



conditions of the radical catalytic process [18]. Substituted pyridine hydrochlorides and phenols of pK_a 5.25–12.5 were used as catalysts (Scheme 60).

Scheme 60 demonstrates the abnormal (contrary to Krasusky rule) regiochemistry of epoxide **117** reduction.

Alongside the trivial epoxides more complex substrates **118–121** [18, 22] were brought into the reaction.



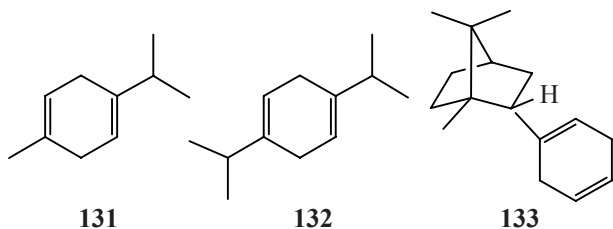
The reduction regiochemistry is commonly opposite to that observed in the classic S_N2 -mechanism whose occurrence is governed by steric hindrances to the approach of the nucleophilic reagent to the reaction site, but sometimes formation of two isomers **122** and **123** is observed, and for a number of reactions the regiochemical trends have not been studied completely (Scheme 61).

Strictly regioselective reduction process using titanocene was recently developed by an example of α,β -epoxyketones **124**, **125** etc. [21]; in all cases the reduction occurred at the carbon atom of the epoxy ring adjacent to the carbonyl group, even when this atom is linked to substituents (Scheme 62).

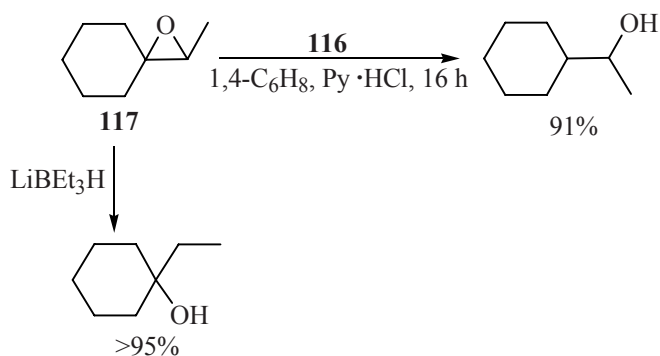
The strict regioselectivity of the reduction suggests the involvement of the carbonyl in the delocalization of the electron density in the intermediate molecule [21] (Scheme 62a).

Gansdner et al. [7] extended the catalyst group for epoxides reduction by the titanium derivatives **127–130**. Beside titanocenes complexes of other elements (strontium, niobium) were also used in the reactions [116] (Scheme 63).

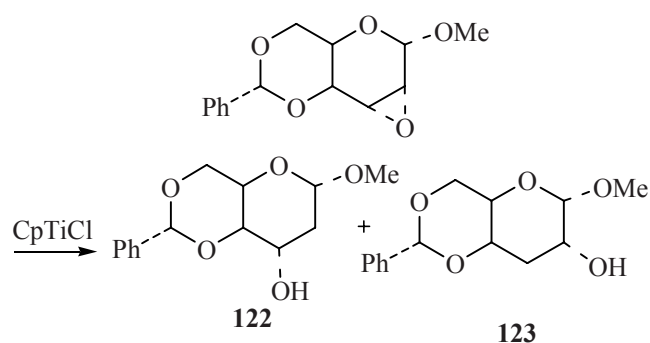
In [7] new opportunities were considered for hydrogen donors in epoxy compounds reduction, and into the series of donors compounds **131–133** etc. were included.



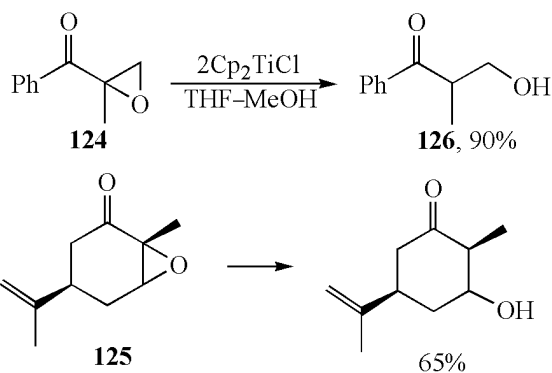
Scheme 60.



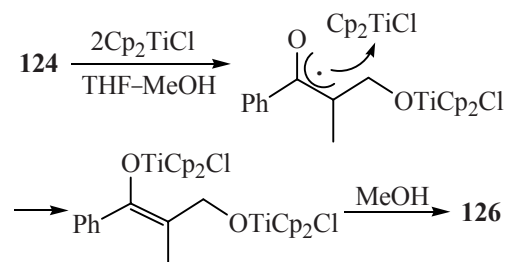
Scheme 61.



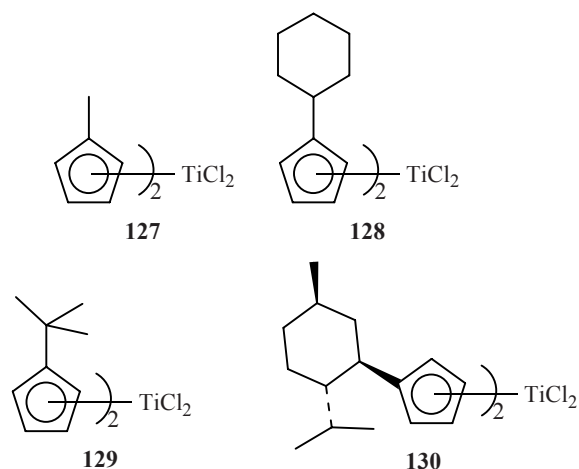
Scheme 62.



Scheme 62a.



Scheme 63.



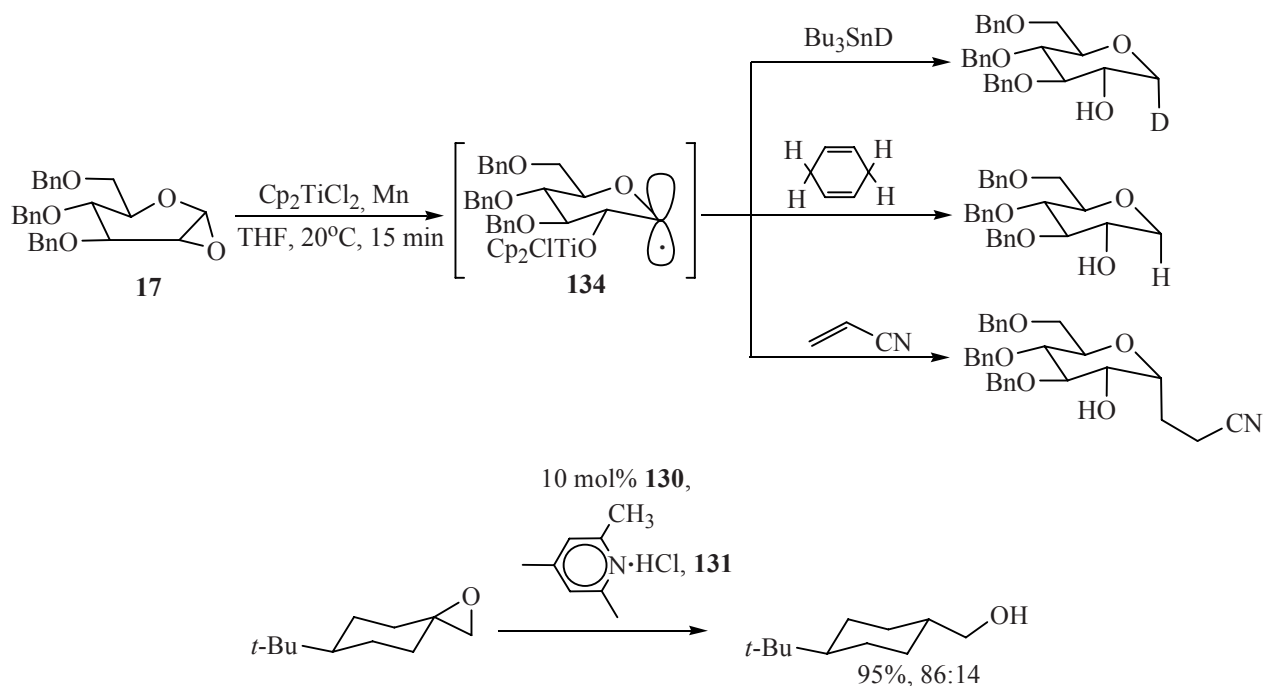
Parrish et al. [117] introduced various reagents to bind the radicals of intermediates **134** obtained from 1,2-anhydrosugars (Scheme 64).

The extended series of catalysts and hydrogen donors made it possible to prepare products with excessive amount of one of enantiomers [7].

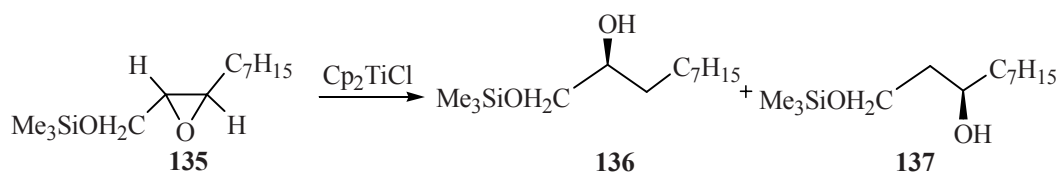
The reduction of silyl epoxide **135** led to the formation of compounds **136** and **137**, and the removal of the protection gave a mixture of enantiomerically pure 1,2- and 1,3-diols in a ratio 10:1 (Scheme 65). This result is especially important since the alternative way of diols preparation (asymmetric dihydroxylation of terminal alkenes) resulted in only slight enantiomeric excess [116].

Beside the reduction products it is possible to obtain from the radical intermediates olefins (deoxygenation of epoxides [116]) and various cyclization products involving contiguous functional groups [118]. It was shown that radical **116** was exclusively mild and selective reagent of deoxygenation by adding it to the solution of methylfuranoside **138** in THF at room temperature [18, 22] (Scheme 66).

Scheme 64.



Scheme 65.



In Scheme 67 are given examples of reactions resulting in the products of intramolecular cyclization **139** and **140** [119, 120].

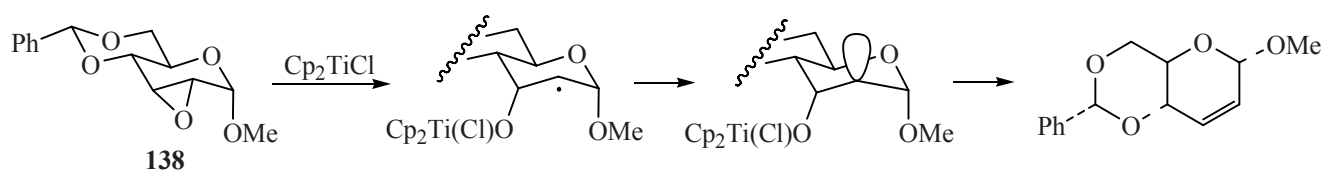
A review on application of tributyltin hydride was published in 1987 [121]. Although in the most cases the C–O bond suffered homolysis, in certain studies homolytic rupture of C–C bond was proved and this was even suggested as a test on the formation of radical intermediates [122, 123]. In [123] vinyl ether **141** was obtained by this procedure (Scheme 68).

In the majority of homolytic reactions the carbon-oxygen bond suffered the rupture [124]. The reduction,

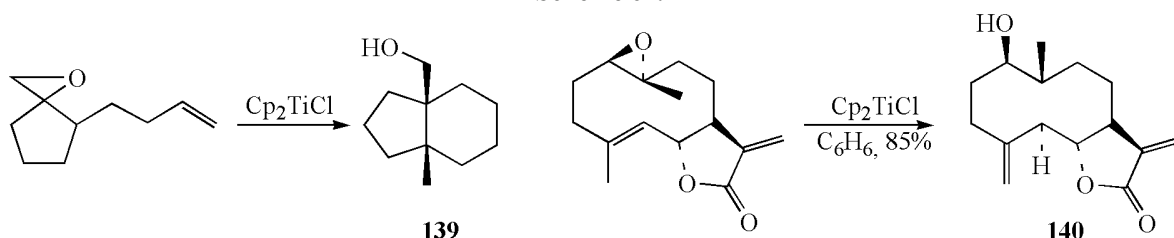
in particular, of epoxides **142** and **143** was among first instances of application of tributyltin hydride [125, 126] (Scheme 69).

The brightest prospects of development of this method were due to the formation of new cyclic systems [126–131]. In 2001 a review was published [132] on reactions of radical translocation of groups in organic syntheses where the first results of free radical transformations were summarized. In this type reactions the key stage consists in the transfer of the radical electron density by intramolecular translocation (**144** → **145**) of a hydrogen atom or a group (phenyl, cyano, trialkylsilyl); the

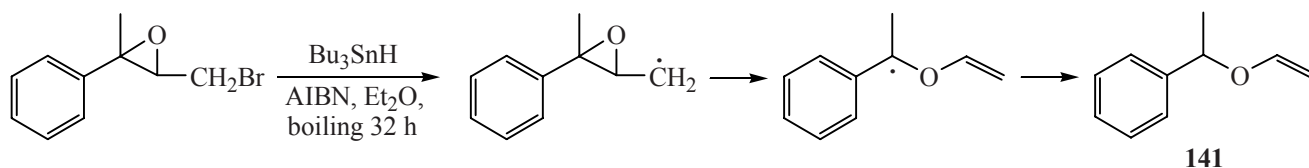
Scheme 66.



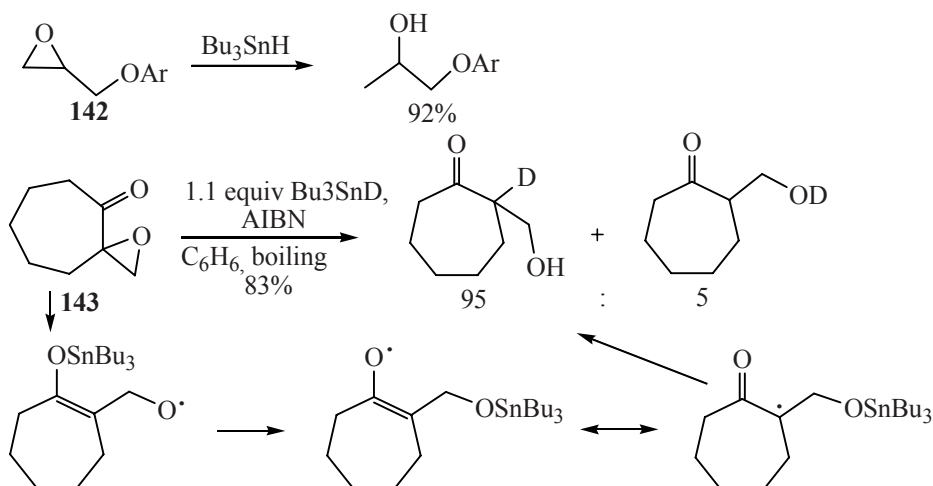
Scheme 67.



Scheme 68.



Scheme 69.



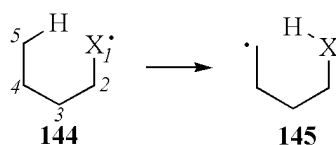
translocation rate of 1,5-hydrogen shift is very high ($k 10^6\text{--}10^7 \text{ s}^{-1}$) (Scheme 70).

The formation of new bicyclic systems **146** was described proceeding from vinyl- [128, 129] and ketoepoxides [126]. Compounds **146–148** ($R = \text{Ph}$, OCH_2Ph , $\text{CH}_2\text{CH}=\text{CH}_2$) were obtained at considerable prevalence of ketol **146** (51–67%) (Scheme 71).

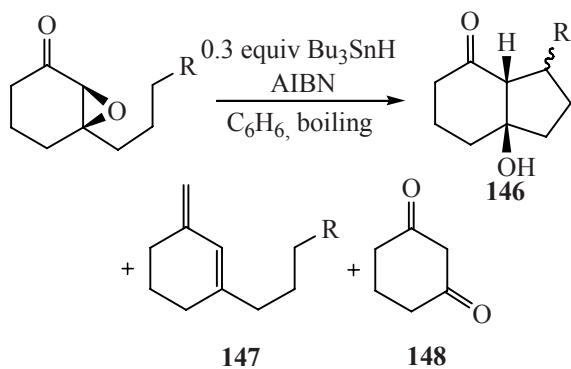
Sometimes the tributyltin hydride was replaced by triphenyltin hydride [127], $(\text{PhS})_2$ [132], Ph_3GeH , $(\text{Me}_3\text{Si})_3\text{SiH}$ [133].

Compared to nucleophilic substitution and radical processes the ion-radical opening of the epoxide ring

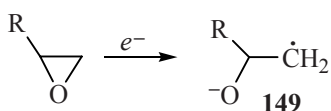
Scheme 70.



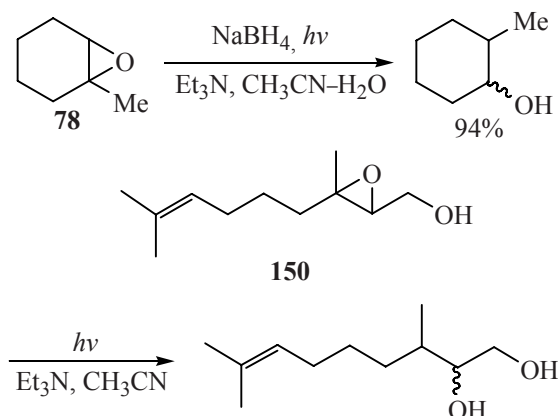
Scheme 71.



Scheme 72.



Scheme 73.



occurred relatively seldom [18, 134]. This type reactions have strong limitations compared to the nucleophilic opening of the epoxides due to the instability of carbanions with respect to elimination, to the narrow range of electrophiles fit for application, and also to the unsuitability of the reduction conditions for usual organic functional groups.

The electron transfer to an epoxide molecule was mentioned in the study of epoxides reaction with sodium in an argon matrix; the reaction resulted in the opening of the epoxy ring and the formation of a radical anion **149** [135]. This process was studied theoretically and by spectral methods; its possibility was governed first of all by the level of E_{LUMO} of the epoxide substrate (Scheme 72).

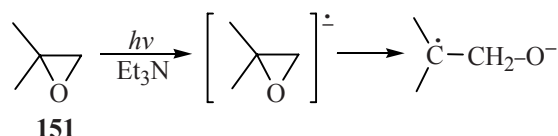
The radical-anion reactions of epoxides proceeding through a photochemically induced electron transfer can be cited [136, 137]. By an example of 1-methyl-1,2-epoxycyclohexane and other epoxides a regioselective reduction was carried out occurring by electron transfer, a new efficient photochemical method of epoxides reduction under UV irradiation ($\lambda 254 \text{ nm}$) in the presence of triethylamine and sodium borohydride under a nitrogen atmosphere [136]. The composition of reduction products of epoxides **78** and **150** was investigated by chromatography and NMR spectroscopy, the degree of regioselectivity reached 93% (Scheme 73).

Epling et al. believed that the key stage of the photochemical process was the electron transfer from triethylamine to epoxide **151**, and then the latter underwent the ring opening with the formation of a more stable radical. The reaction proceeded also without sodium borohydride, but with lower yield [136] (Scheme 74).

The reduction takes a similar route when the epoxy ring of the molecule is conjugated with a carbonyl group in substrate **152** [137] (Scheme 75).

The formation of radical anions as intermediates was proved for the epoxides reduction by lithium naphthalenide and also by metals dissolved in liquid ammonia or amines [138]; therewith a more substituted carbinol formed from the unsymmetrical alkyl-

Scheme 74.



substituted epoxides by cleavage of the C–O bond with the less substituted carbon of the ring. The regiochemistry of the reaction was subjected to *ab initio* calculations, and Dorigo et al. suggest that it was governed by the stability of carbinols obtained and was not related to the stability of intermediates [138].

In [79] lithium in ethylenediamine was used for reduction of terminal epoxides to alcohols. This method was applied when the lithium aluminum hydride either reacted slowly or gave rearranged products [139]. Lithium in ethylenediamine proved to be a fairly convenient reducer in the series of epoxysteroids; $7\alpha,8\alpha$ - and $9\alpha,11\alpha$ -epoxysteroids that were reluctant to react with lithium aluminum hydride were easily converted by this procedure into axial 8α - and 9α -alcohols. It was shown in [140] that this reducing system is advantageous for reactions with sterically hampered tri- and tetra-substituted oxiranes. The key stage in the cleavage of the carbon-oxygen bond in epoxide **1** by the reaction with lithium was the formation of a stable radical anion [141] (Scheme 76).

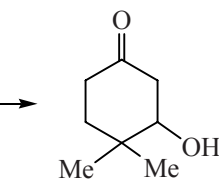
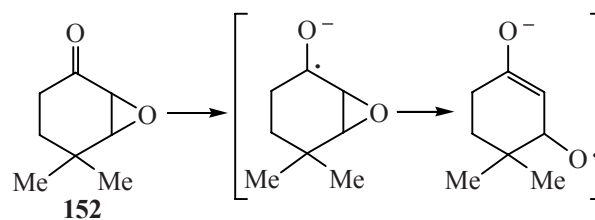
A similar in structure dilithium intermediate was obtained by the reaction of the metal with spirooxirane **153** [12] (Scheme 77).

Epoxides of the norbornane series also were subjected to reduction by metals. Lithium in ethylamine was used to reduce *exo*-epoxynorbornanes [11]. The low reduction rate of the majority of this group substrates with metals and also their ability to suffer deoxygenation made these processes unsuitable for synthetic purposes.

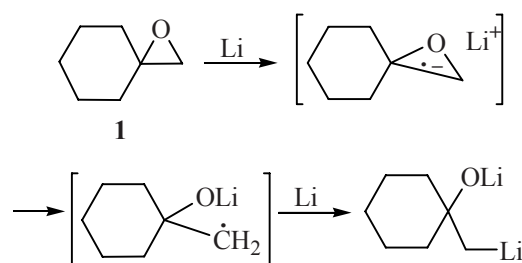
In certain cases the reduction was accompanied by rearrangements. For instance, one of the reduction products of caryophyllene α -oxide **154** with lithium in liquid ammonia was a tricyclic alcohol with a carbon skeleton of 5,8-cyclocaryophyllane **155** [142] (Scheme 78).

It was shown in [143] that calcium was worthy of competing with lithium. Both metals reduce regioselectively alongside the terminal oxiranes also epoxy

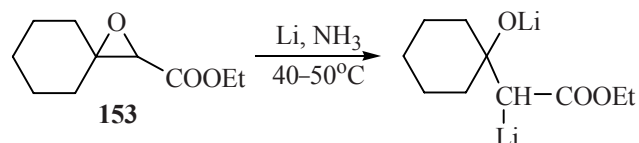
Scheme 75.



Scheme 76.

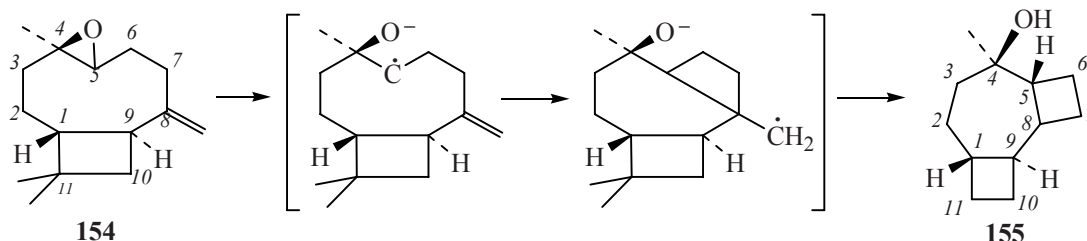


Scheme 77.



derivatives of methylcyclohexene, 9,10-epoxyoctahydronaphthalene, and 8,9-epoxytetrahydroindan. The regiochemistry of the reduction of the phenyl-substituted epoxides was spectacular: styrene oxide **5** was converted into 2-phenylethanol, 1,1-diphenylethylene oxide, into 2,2-diphenylethanol. This direction of the ring opening was ascribed to the greater stability of 1,3-dianions whose formation in this reaction was assumed [17] (Scheme 79).

Scheme 78.



preparation of valuable natural compounds kumausyne and kumausallene [150].

Examples of application of tellurium-containing reagents in the oxirane chemistry are given in the review [14]. Although these compounds are mostly used for deoxygenation of epoxides, in particular, compound **166** (Scheme 85), the cases of application of tellurium-containing intermediates for chemoselective reduction are also known.

In 2003 a conversion was described of α,β -epoxyesters **167** into 2,3-dideuteroesters where samarium diiodide was successfully used as catalyst [151] (Scheme 86).

A modified procedure was applied to preparation of hydroxyesters **168**. The reaction mechanism through an enolate intermediate that in the presence of the deuterium oxide converts into hydroxy ester **168** is presented in Scheme 87.

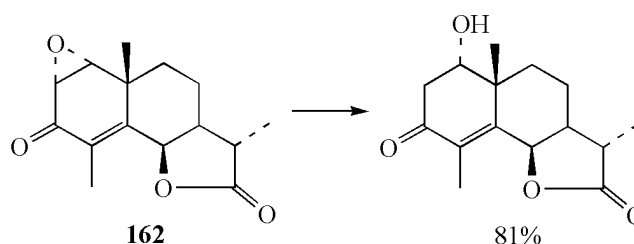
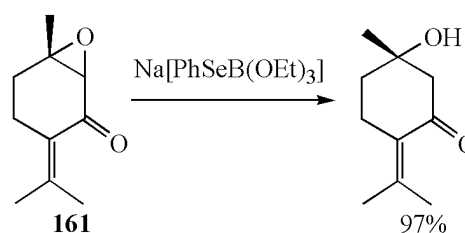
An electrochemical reduction procedure was developed for α,β -epoxycarbonyl compounds using diphenyl diselenide or diphenyl ditelluride as electroreducing mediators in a system $\text{CH}_3\text{OH}-\text{NaClO}_4-\text{Pt}$. α,β -Epoxyketones were converted into the corresponding aldols in the presence of malonic acid with conservation of the carbomethoxy and cyano groups. The use of other cathodes than platinum and other electrolytes (LiClO_4 , Bu_4NClO_4) and solvents (DMF, $\text{THF}-\text{H}_2\text{O}$, EtOH) considerably decreased the efficiency of the process [152].

Inokuschi et al. believe that the reduction of pulegone oxide **169** is sterically hindered by substituents at the epoxy ring, but the adjustment of the procedure led to the preparation of diol **170** [152] (Scheme 88).

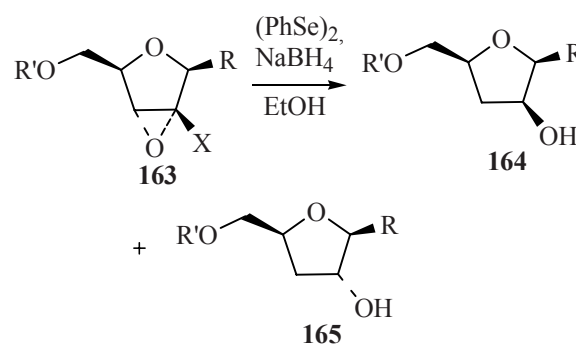
An electrochemical method was also developed for another reaction of epoxides: alkylation with triorganoboranes [153]; this method is no worse in the regioselectivity and in the yield that the known procedure with the Grignard reagent. The ratio of reaction products **171**, **172** equals from 100:0 to 77:23 (Scheme 89).

For reduction of α,β -epoxyketones and esters into aldols a reducing system was developed containing palladium, formic acid, and triethylamine. The system is fairly convenient for ketones containing phenyl groups and is inapplicable to sterically hindered substrates [154]. It was established that bulky cyclic (**173**) and steroid epoxyketones were reduced in a plausible yield (55–80%) by hydrogen (Pd/C), although sometimes with violated chemoselectivity of the process (Scheme 90).

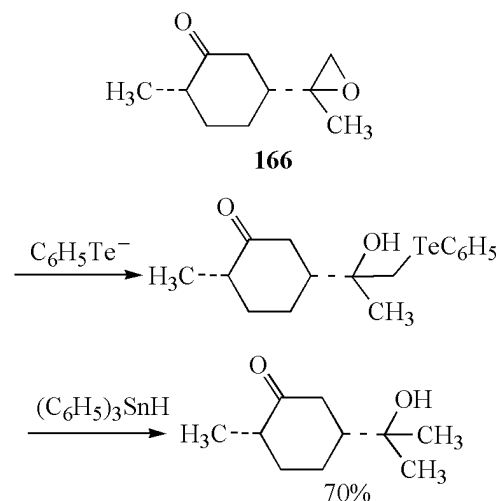
Scheme 83.



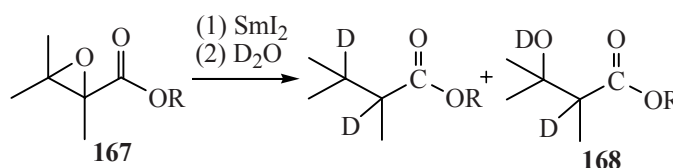
Scheme 84.



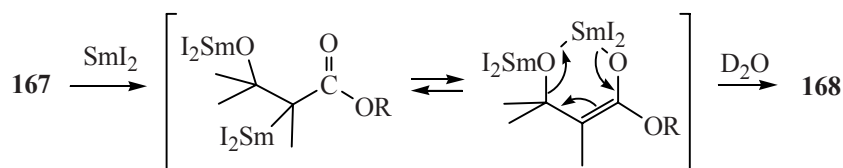
Scheme 85.



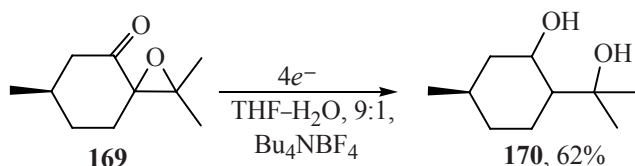
Scheme 86.



Scheme 87.



Scheme 88.



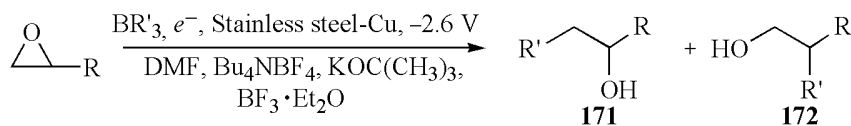
$\text{Pd}(0)$ -Catalyzed hydrogenolysis of vinyloxyepoxides is characterized by excellent regio- and diastereoselectivity [155–160]. Actually, the hydrogenolysis of *E*-epoxide **174** gave the *syn*-isomer of homoallyl alcohol with the inversion of configuration at the allyl carbon, whereas

Z-isomer **175** under the same conditions provided the *anti*-stereoisomer (Scheme 91).

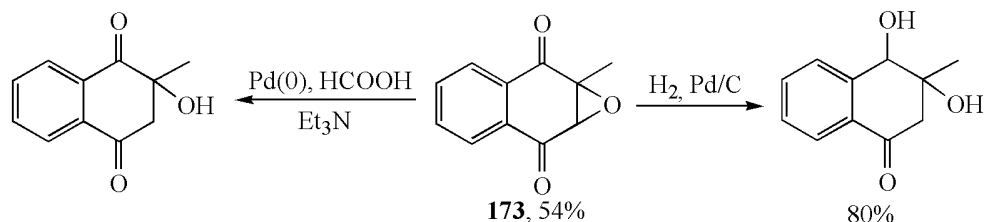
A transformation of epoxy group into alcohol occurred in the course of unusual rearrangement involving highly stereocontrolled migration of groups resulting in building up new quaternary centers [161, 162]. The key stage is a semipinacol-pinacolone rearrangement of epoxide **176** ($\text{R}, \text{R}' = \text{Alk}, \text{Ar}$) (Scheme 92).

The quaternary carbon atom was for a long time regarded as a difficultly accessible structural element, especially in the chemistry of naturally occurring

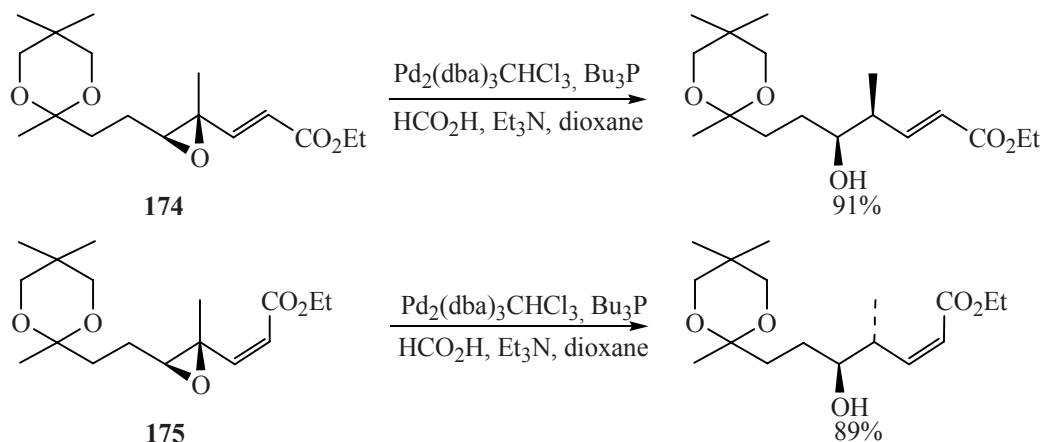
Scheme 89.



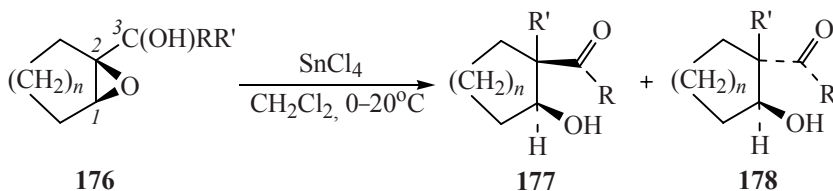
Scheme 90.



Scheme 91.



Scheme 92.



compounds, even when its formation was not diastereoselective. A group of valuable products was extended in [163] by introducing into reactions bicyclic compounds. It was found that the optimum catalyst was zinc bromide. As objects of the reactions α -hydroxyepoxides **179** were chosen containing five-membered and six-membered rings; these compounds provided better results than others. The high stereoselectivity of the reaction did not depend on the configuration of the carbon atom of the substituent. Tu et al. built up a series of rare spiro structures with various size of the ring (C_4 – C_8) (Scheme 93).

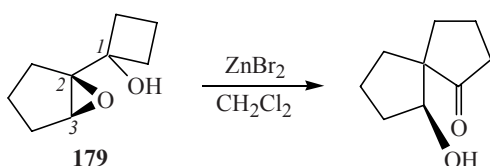
In neither case bromine-containing products or allyl alcohols were isolated. A mechanism of reaction was suggested [162] involving activation of the C^3 – O bond of epoxide **176** by coordination to the Lewis acid followed by *anti*-migration of substituent R' . The formation of minor amounts of compound **178** may result from the faster cleavage of the C^2 – O bond than the 1,2-migration and the formation of carbocation transition state ensuring the *syn*-1,2-migration of the substituent. A similar shift of a methyl group was observed in acid medium in an epoxide of nortriterpenoid structure [164].

Another (reductive) version of the rearrangement was developed with the use of aluminum isopropoxide [165]. The reaction is a new method of 1,3-diols synthesis and involves 1,2-alkyl and successive stereoselective hydride shift. The main reaction product **181** is characterized by the *syn*-location of the migrating and the hydroxy groups [166] (Scheme 94).

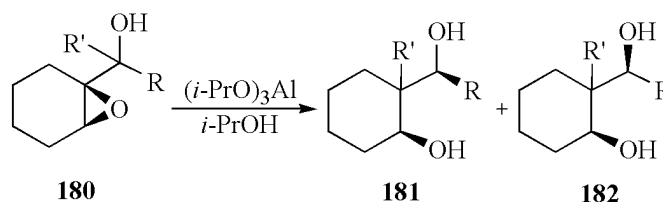
The reaction mechanism is presented in Scheme 95.

Cyclic carbinols were transformed into bicyclic spiro systems [165, 167] (Scheme 96).

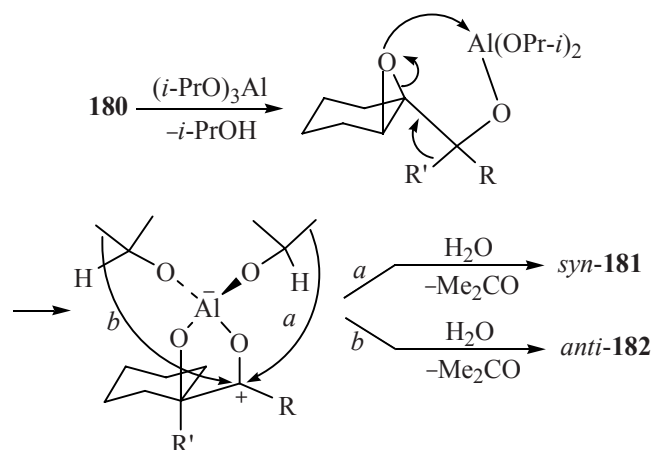
Scheme 93.



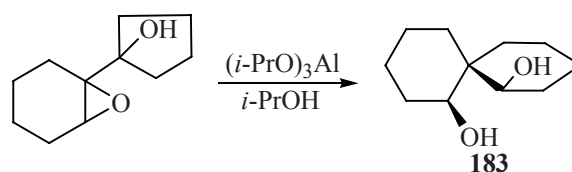
Scheme 94.



Scheme 95.



Scheme 96.



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