Russian Journal of Organic Chemistry, Vol. 37, No. 10, 2001, pp. 1361–1404. Translated from Zhurnal Organicheskoi Khimii, Vol. 37, No. 10, 2001, pp. 1431–1473.

Chemical Reactions of Spirooxiranes

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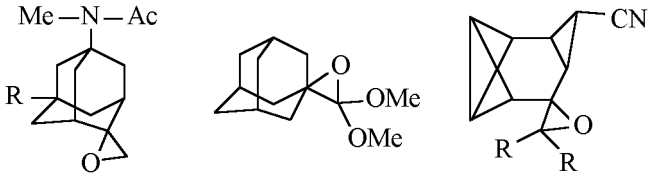
Received July 12, 2000

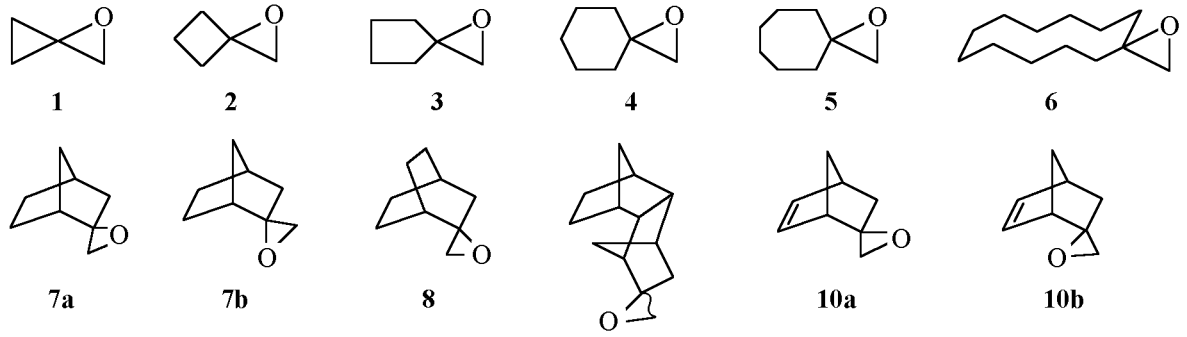
Abstract—The review covers the reactivity of spirooxiranes. The characteristic distinction of chemical behavior of this type epoxides from that of epoxycycloalkanes is discussed. In the spirooxiranes unlike epoxycycloalkanes the oxirane and alicyclic fragments are joined by one and not by two common atoms. The spirooxiranes are characterized by enhanced reactivity in the neutral and alkaline media, and also by versatile isomerizations and rearrangements in the presence of acidic catalysts. The relation between the chemical properties of spirooxiranes and the features of their electronic structure was considered. The main reactions of spirooxiranes with reductants, reactants with nucleophilic centers on oxygen, sulfur, carbon, nitrogen, and phosphorus, and with hydrogen halides are analyzed. The isomerization of spirooxiranes into carbonyl compounds and allyl alcohols is discussed. The possibility was considered of formation of the other cyclic systems proceeding from spirooxiranes.

INTRODUCTION

Spirooxiranes are compounds with a three-membered oxygen-containing heterocycle joined to an alicyclic fragment by a common carbon atom. To this large group belong 1-oxaspiro[2.*a*]alkanes, in particular epoxides (**1–6**) [1–3], and also spiro-oxiranes with bicyclic (**7a, b, 8**) [4–7] and tetracyclic (**9**) fragments [4], unsaturated spirooxiranes (**10a, b**) [6], and bicyclospirooxiranes with more intricate structures [8–13].

Several spirooxiranes were synthesized with adamantane and other complicated carbon skeletons [14, 15].





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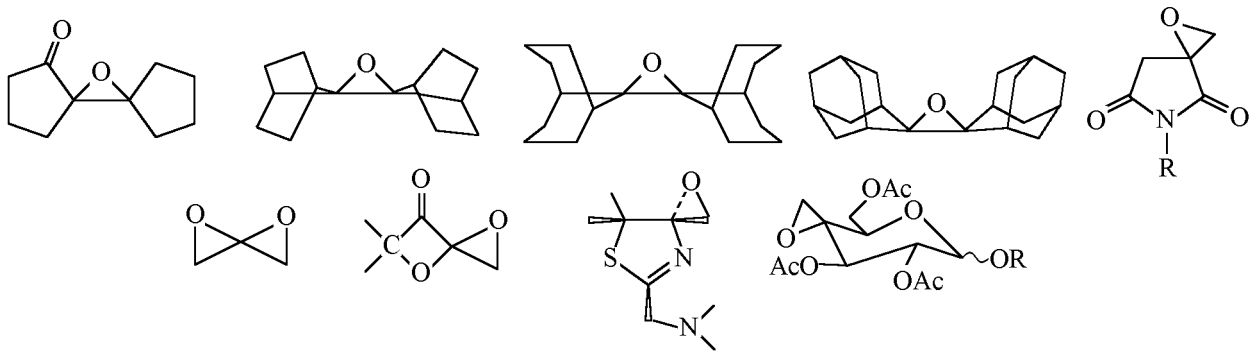
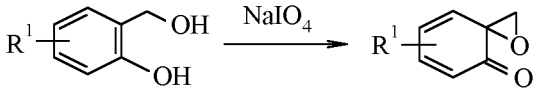


Also bispiroepoxides [16–21] and epoxides of this group with various heterocyclic fragments [22–24] were prepared. In some cases the spirooxiranes were isolated as individual spatial structures and optically active compounds [8, 25, 26].

The methods of synthesis for this group epoxides were described in a book [27], and before that in [28] and as some examples in reviews of general character [29, 30]. Besides the most often used peroxy acids also dioxiranes are now applied to the preparation of spirooxiranes [31]. An attempt to oxidize methylenecycloalkanes in the presence of enzymes is known [32]. Since the double bond in methylenecycloalkanes is less shielded by substituents than in cycloalkenes their epoxidation with peroxy acids and dioxiranes is of low stereoselectivity [29, 31, 33]. Therefore even in the modern procedures the synthesis of spirooxiranes with the desired stereostructure is carried out along the classical halohydrin method, e.g, in the synthesis of epicoryoline [33], in preparation of synthons for potential glycosyl transferase inhibitors [23] etc.

A group of new spirooxiranes (**13**) was recently obtained by [4+2]-cycloaddition of various dienophiles (enol ethers, susbstituted styrenes, *N*-methylvinylacetamide) to spirodienes (**12**) prepared by oxidation of substituted hydroxymethylphenols (**11**) by Adler–Beker procedure [34].



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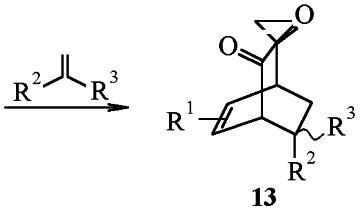

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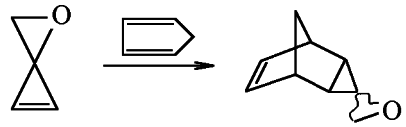
Under special conditions of diene synthesis was obtained spiroepoxide (**15**). The original strained oxaspiropentene (**14**) was first described in the same publication [35]. The structure of compound **14** was proved by comparison of parameters of its ^{1}H and ^{13}C NMR spectra with spectral parameters calculated by ab initio methods.



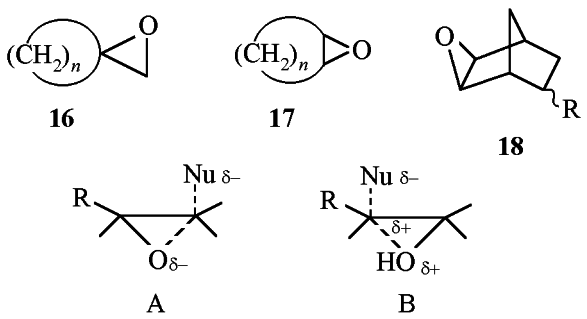
14 **15**

Epoxy ring is a structural moiety contained in quite a number of biologically active compounds, both natural and synthetic [30]. Among the biologically active epoxides are known numerous spirooxiranes prepared from natural terpenoids and the other natural substances of related structures. It is presumable that their active biological function is due to versatile transformations of the epoxides from this series. For instance, the alkylation of nucleophilic centers of polypeptide chains is known to be capable to alter the genetic code of a cell [36]. Therefore some epoxides are carcinogenous, and some others are used as antitumor pharmaceuticals. Some spirooxirane reactions serve as models for decoding of biological processes mechanism, and others are applied to development of syntheses of biologically active compounds or important synthons. These problems are treated in reviews [30] and in numerous special publications. Among spirooxanes are known antibiotics [30, 37–39], efficient growth inhibitors of artheries [40]. The derivatives of a sesquiterpene pentalenolactone among which quite a number was prepared by asymmetrical synthesis show versatile antibacterial and antiviral properties [37, 41, 42]. Fumagillin derivatives are successfully used in treatment of rheumatism, psoriasis, diabetes, and as antitumor agents [43].

A special place among the biologically active compounds belongs to trichodecenes [30, 44–49] applied to anticancer therapy [50] and also possessing fungicidal, phytotoxic, insecticidal, and cytotoxic activity [30, 51].

II. GENERAL ESTIMATION OF REACTIVITY. EFFECT OF THE STRAIN IN ALICYCLIC FRAGMENT

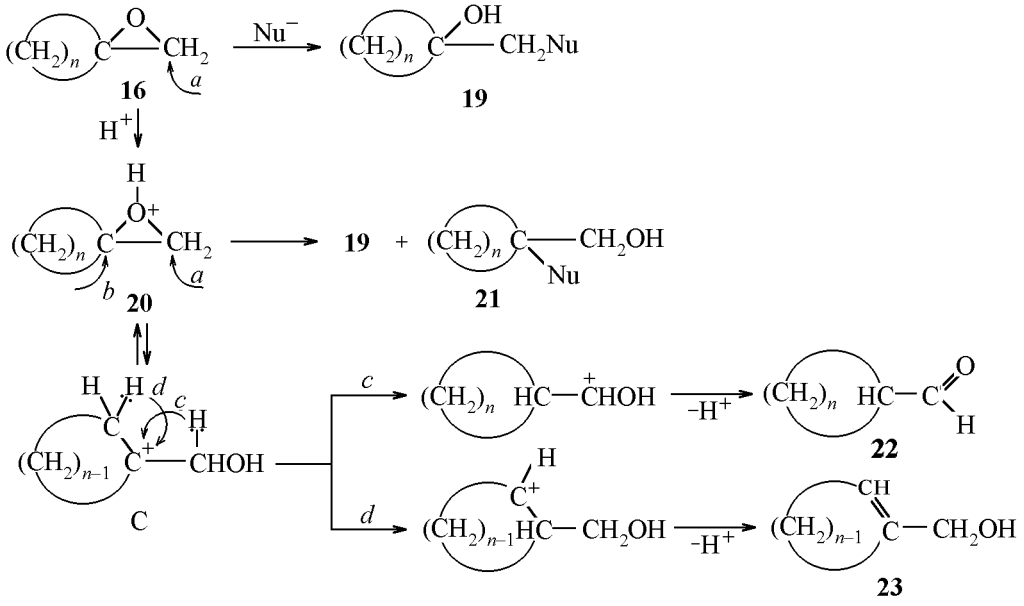
The reactivity of epoxides of spirooxiranes group (**16**) was not previously specially treated although important data thereof appeared in reviews and particular communications [27–29, 52–59]. A special review thereof is required since the spirooxiranes take a particular place among epoxy compounds and considerably differ in chemical properties from the related epoxides of the alicyclic series, from epoxycycloalkanes (**17**) and epoxynorbornanes (**18**) [52, 57].



Specific features of spirooxiranes do not prevent the principal possibility of describing their reactions with nucleophilic reagents with the classical models of Parker and Isaacs for transition states in neutral and basic (A) and acidic (B) media [60]. The reactivity features of spirooxiranes (**16**) are determined by the structure of the compounds and are above all expressed in their high activity in reactions with nucleophilic reagents in any media (from basic to acidic) and also in fabulous versatility of their transformations. The activity of terminal epoxides from this series in the neutral and basic media depends first of all on the spatial accessibility of the electrophilic carbon center to the attack of a nucleophilic reagent. This attack occurs usually regioselectively according to Krasusky rule [61] along (*a*) pathway resulting in compound **19**.

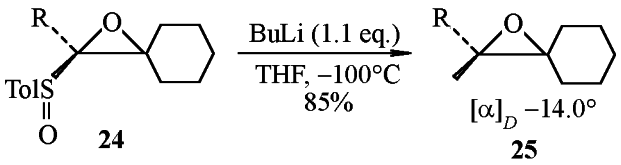
In the acidic medium the opening of the heterocyclic ring is complicated by molecular rearrangements [29, 57, 62]. Protonated epoxide (**20**) in conformity to the known models of Parker and Isaacs [60] and Dewar [63] is prone to form a reaction product **21** counter Krasusky rule (pathway *b*) and to transform into aldehyde **22** (in the general case, into a carbonyl compound) (pathway *c*) and into allyl alcohol **23** (pathway *d*). The rearrangements are facilitated by the stability of intermediate tertiary carbocation (C) [27, 29, 57].

The above diversity of spirooxiranes transformations illustrates the difficulties that meet the chemist in the course of their synthesis with the use of peroxy acids. In a series of papers [64, 65] was described epoxides preparation alongside a great number of



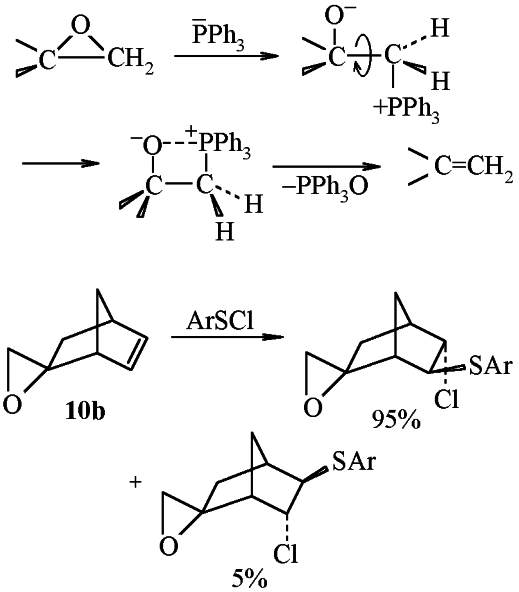
rearrangement and acidolysis products. Thus in [66] reporting on preparation of a group of the simplest 1-oxaspiro[2.*n*]alkanes the synthesis was performed along halohydrin method.

Although the spirooxiranes are more reactive than epoxycycloalkanes still in some reactions the three-membered heterocycle is conserved. In some cases the optical activity of epoxides is retained [26], e.g., in reduction of sulfone (**24**) the arising spirooxirane (**25**) has the same configuration.



24 **25**

In the known cases of addition reactions with unsaturated spirooxiranes (**10a, b**) the configuration of the latter significantly affects the regiochemistry of electrophilic addition of 2-nitrophenylsulfenyl chloride under conditions of kinetic control [9].

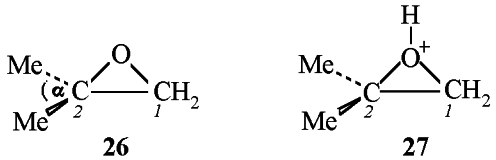


10b

Ar = 2-$NO_2C_6H_4$.

Spiroepoxy systems were extensively studied by theoretical methods [7, 67, 68]. The molecular mechanics procedure MM2 was used to calculate the structural parameters, formation heats, strain energies, and conformational characteristics of epoxy derivatives obtained from methylenecyclo- and methylenebicycloalkanes (**2–4, 7, 8**) [67]. The folding parameters of molecules were studied to characterize the form of rings. In this series epoxides the formation heat and strain energy grow with the size of the alicyclic fragment in the order: cyclohexane < cyclopentane < bicyclo[2.2.2]octane < norbornane < cyclobutane. Note the small difference in the strain energy of stereoisomeric spirooxiranes (**7a, b**) (172.8 and 174.7 kJ mol^{-1}) as compared to the large difference for *exo*- and *endo*-epoxynorbornanes where the epoxy fragment shares two atoms with the bicyclic norbornane system (185.2 and 194.1 kJ mol^{-1}) [7]. Epoxides are distinguished by the contribution of individual kinds of strain and interactions into the total sterical energy of molecules. With epoxides of methylenenorbornane and methylenecyclobutane the most important are the distortions of bond angles, with epoxymethylenecyclopentane (**3**) these are the torsional strains, and for epoxides with six-membered rings (**4, 8**) these are the van der Waals interactions. In this series was observed a linear dependence of the bond lengths in the epoxy ring on the strain energy: $R(C–C) = 1.482 - E_n \times 10^4$ (r 0.95), $R(C–O) = -7.33 \times 10^{-5} - E_n + 1.525$ (r 0.92) [67].

In [68] was carried out the quantum-chemical calculation of reactivity of this series epoxides, and the dependence thereof was established on the character of the alicyclic fragment. The contribution of angle strain into the chemical behavior of molecules was studied by quantum-chemical method SCF LCAO MO in the valence approximation MINDO/3. In simulation of strain increase with decrease in bond angles compared with the standard value was used a molecule of nonsymmetrical 1,1-dimethyloxirane (**26**) and its protonated form (**27**). The bond angle α (MeCMe) at the epoxy ring was varied within 90–120° range. The choice of the model provides a possibility to discuss the structure and behavior of 1-oxaspiro[2.*n*]alkanes (n = 3–5) for the variation of similar angles thereof lie in the same range [68].



26 **27**

The electronic structure and behavior of the electrophilic centers in the molecules were characterized by charges on C^1 and C^2 atoms and by values of LUMO energy (Table 1). Within the epoxides series under consideration the alteration of the calculated parameters is insignificant. Stronger changes were observed for protonated forms of

Table 1. Characteristics of 1,1-dimethyloxirane (**26**) and its protonated form (**27**) by charges and energy

α, deg.	**26**					**27**				
	$q(C^1)$	$q(C^2)$	q(O)	E_{LUMO}, eV	ΔE, kJ mol^{-1}	$q(C^1)$	$q(C^2)$	E_{LUMO}, eV	ΔE, kJ mol^{-1}	PA, kJ mol^{-1}
120	0.206	0.275	–0.398	1.59	–144.2663	0.331	0.335	–5.31	–145.3960	–709.1
115	0.211	0.273	–0.395	1.56	–144.2701	0.328	0.339	–5.31	–145.3964	–707.1
110	0.214	0.274	–0.394	1.52	–144.2655	0.323	0.344	–5.34	–145.3884	–704.8
105	0.215	0.275	–0.392	1.48	–144.2516	0.317	0.349	–5.34	–145.3716	–703.1
100	0.213	0.276	–0.389	1.44	–144.2282	0.308	0.356	–5.36	–145.3452	–701.0
95	0.209	0.278	–0.387	1.44	–144.1930	0.296	0.363	–5.36	–145.3067	–699.3
90	0.205	0.280	–0.383	1.35	–144.1440	0.280	0.371	–5.38	–145.2551	–697.6

[a] ΔE is the total energy of a molecule, PA is the proton affinity value.

Table 2. Basicity and chemical shifts of ^{17}O nuclei in the series of 1-oxaspiro[2.*n*]alkanes (2–8) [69]

Parameter	**2**	**3**	**4**	**5**	**6**	**7a, b**	**8**
$\Delta\nu$, cm^{-1}	243	237	256	235	248	241	233
pK_b	6.03	6.20	5.65	6.21	5.87	6.07	6.29
Chemical shift from cyclohexane, $\Delta\delta$, Hz	300	–	315	315	320	–	–
^{17}O NMR spectrum, δ_O, ppm	–14.1	–17.2	× 10.0	–17.4	–11.9	–22.6	–19.8

epoxides: the growth of the angle strain (decrease of angle α) resulted in enhanced electron density on C^2 atom and increased electronegativity of C^1 atom; the shift of the electron density was the greater with the higher angle strain [68]. It was presumed that in reactions occurring by activation of the oxygen in the epoxy ring the growing strain and accordingly the growing electrophilicity of the carbon suffering attack should favor higher activity of spirooxirane. This is also evidenced by the decreasing LUMO energy at smaller α angles in both models under consideration; it is the most characteristic for unprotonated form of 1,1-dimethyloxirane (Table 1).

As indices of the epoxide basicity were taken the values q(O) of the negative charge on oxygen atom, and the proton affinity (PA) calculated as a difference of total energy of protonated and unprotonated forms of the epoxide. The calculation showed that diminishing of α angle (increase in strain) is accompanied by small decrease in the negative charge on the oxygen atom and in the estimated values of proton affinity (Table 1) [69].

Experimental data were published on evaluation of the epoxymethylenecycloalkanes basicity with the use of two spectral methods [69]. By IR spectroscopy was measured the shift ($\Delta\nu$) of the stretching vibrations band of O–H in phenol on addition of epoxide (Table 2). Using the relation between the $\Delta\nu$ value and basicity indices for a number of acyclic epoxides [70, 71] were graphically derived pK_b values. The strength of the hydrogen bonds was also studied by ^{1}H NMR spectroscopy. The strength of hydrogen bonds and consequently basicity was evaluated by the change in the chemical shift ($\Delta\delta$) of the proton from the phenol hydroxy group in the presence of epoxide as compared with the proton signals of a reference (cyclohexane). Both methods showed the same place of the epoxides in the basicity series. ($\Delta\nu$ = 2.876–$\Delta\delta$ – 484.9, r 0.9877).

The chemical shifts of ^{17}O nuclei are regarded as significant criteria of basicity [69]. It was found that pK_b values and ^{17}O NMR spectral parameters change in parallel (pK_b = –0.060 – δ_O + 5.11, r 0.9551). In the epoxides series under consideration the basicity range is narrower than that of epoxycycloalkanes (**21**) where the chemical shifts of ^{17}O vary within 25 ppm. This conclusion is consistent also with the other experimental data and calculated parameters, in particular, with the values of strain energy in the molecules. In general, the growth of the strain in the alicyclic fragment results in more active involvement of the lone electron pairs of oxygen into the reverse

Table 3. Hydrogenolysis of epoxides **28a, b** in cyclohexane

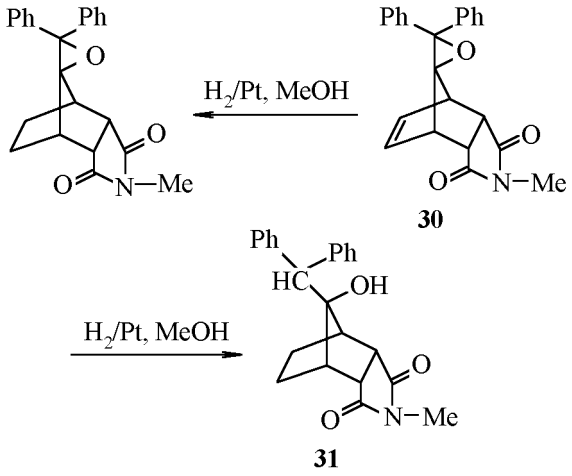
Catalyst	Epoxide	Reaction products						
		29c	**29d**	**29e**	**29f**	**29g**	**29h**	**29i**
Pb	**28a**	18	7	26	34	11	4	–
	28b	21	–	34	16	24	3	2
Pt	**28a**	23	5	2	7	33	30	–
	28b	18	–	5	–	41	32	4
Rh	**28a**	3	–	18	64	8	7	–
	28b	5	–	60	21	9	5	–
Ni	**28a**	10	–	–	–	48	42	–
	28b	6	–	–	–	50	44	–

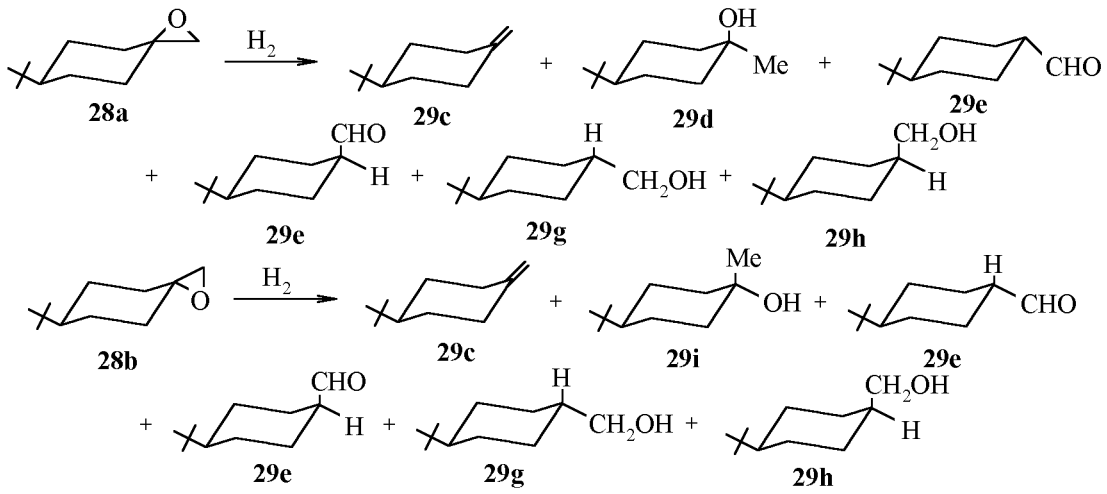
coordination with two-carbon (basal) fragment [63]; consequently the epoxide basicity is decreased. Such effect in methylenecycloalkane epoxides that is transferred through a single atom of the spirane system should obviously be less pronounced than in the series of epoxycycloalkanes (**17**), as actually is observed.

III. REDUCTION OF SPIROOXIRANES

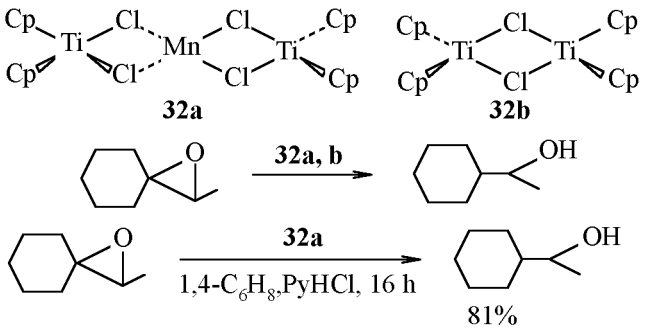
A review [72] was published in 1989 treating the methods of epoxides reduction. Regretfully, no data was mentioned on reactions with epoxides containing cyclic fragments, also with spirooxiranes. As regards the spirooxiranes reduction, the publications on this topic show that the reductants used are common to the other oxirane groups (epoxyalkanes, epoxycycloalkanes, etc.). Alongside hydrides used for reduction already since around 60 years [73], and complex hydrides, the most well-known modern reductant for epoxides, are also applied other reagents and other methods, in particular, liquid-phase hydrogenation in the presence of various metal catalysts [74]. The latter method, the least studied one, is on the one hand versatile, and on the other hand is very sensitive to the character of the catalyst. A complex mixture of substances was obtained at hydrogenation of *cis*- and *trans*-epoxides of 4-(*tert*-butyl)methylenecyclohexane (**28a, b**) in 2-propanol and cyclohexane on palladium, platinum, or rhenium on activated carbon, and also on Raney nickel. Proper selection of solvent and catalyst resulted in considerable selectivity of the process. The hydrogenation of epoxides on nickel afforded mostly primary alcohols (**29g, 29h**), on rhodium arose aldehydes (**29e, 29f**). Tertiary alcohols (**29d, 29i**) are virtually absent evidencing violation of the principal regiochemical law of epoxide reactions, the Krasusky rule.

On the contrary, the reduction of epoxyimide of norbornene series (**30**) with hydrogen on palladium catalyst afforded tertiary alcohol (**31**), but the process was nonselective [75]. As at the use of a platinum catalyst a double bond is easily hydrogenated.

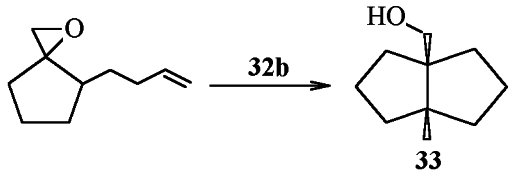




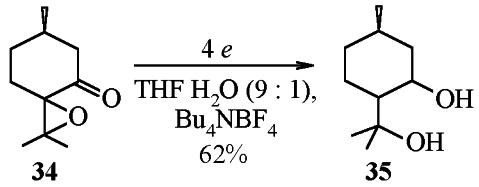
In 1998 was reported on application to reduction of epoxides of various structures into alcohols of new catalysts, titanocene chlorides (**32a, b**). As electron donor was successfully used cyclohexa-1,4-diene that under conditions of the radical catalytic process was transformed into benzene.



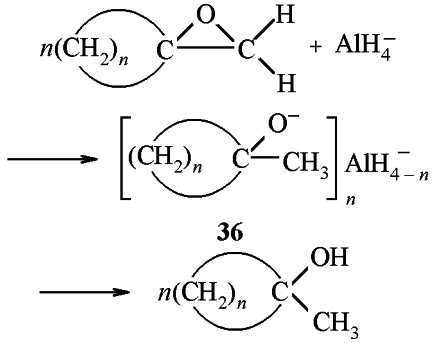
The substituent sometimes also takes part in reaction that furnishes a cyclization product (**33**) [76].



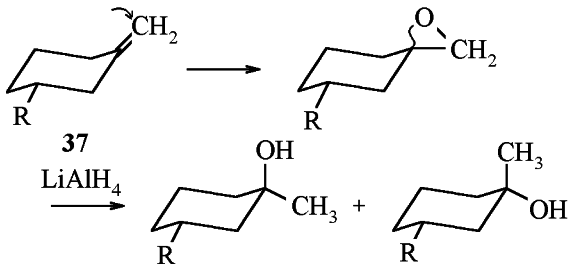
A new approach to the synthesis of β-hydroxycarbonyl compounds from the corresponding epoxides was developed with the use of diphenyldiselenide or diphenylditelluride in the electrochemical reduction in a system methanol–sodium perchlorate–platinum. The reduction of pulegone oxide (**34**) under these conditions was presumed [77] to be sterically hindered by substituents at the epoxy ring. However at electrochemical reduction was obtained the corresponding diol (**35**).



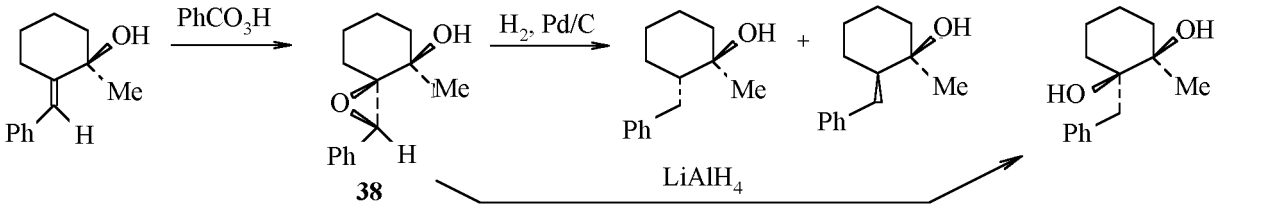
As with other groups of epoxides the most common reduction agents are complex metal hydrides, especially lithium aluminum hydride. The reduction with this reagent of epoxymethylenecyclohexane afforded the more substituted alcohol resulting from the attack of a nucleophile on the primary carbon of the terminal epoxy group [78, 79]. In the course of oxirane reduction arises a complex hydride (**36**) that further transforms into an alcohol molecule.



In reduction of epoxy derivatives of 3-substituted methylenecyclohexanes was confirmed the prevailing π-face (axial) stereoselectivity in epoxidation of spiroolefins effected by *m*-chloroperbenzoic acid. Actually, for olefins possessing trimethylsilyl, *tert*-butyl, phenyl, and trifluoromethylphenyl groups in position 3 of the cyclohexane fragment the fraction of the axial attack amounted to 52, 60, 70, and 75%; with no substituent it is 69% [80].

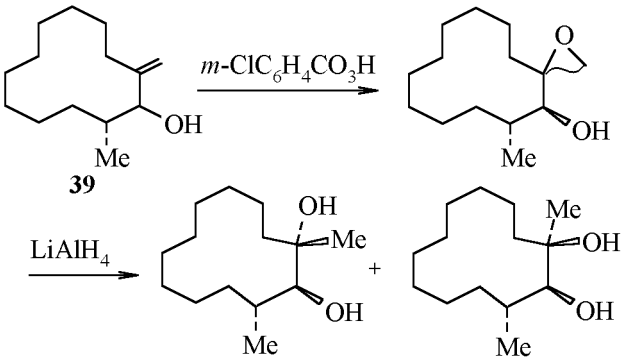


The reduction of epoxide **38** with lithium aluminum hydride was used as a proof of *cis*-epoxidation with respect to hydroxy group of (±)-1-methyl-2-*trans*-benzalcyclohexanol with perbenzoic acid [81]. The hydrogenolysis of the epoxide carried out for the

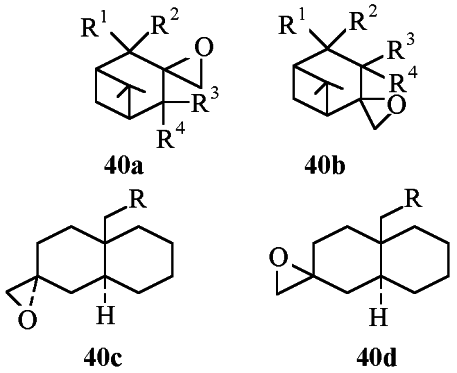


sake of comparison was shown to proceed in another fashion, namely, through elimination of the heteroatom followed by hydrogenation of the olefin [81].

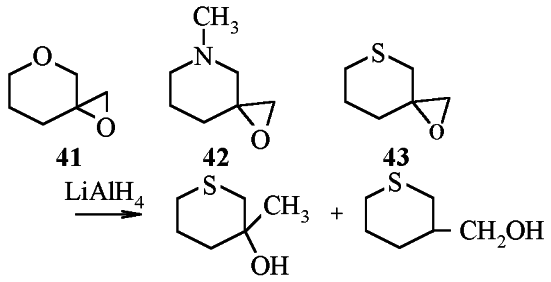
The same procedure was used in [82] for deriving the effect of allyl hydroxy group on the stereochemistry of peracid attack on methylenecycloalkanol (**39**) with a medium cycle.



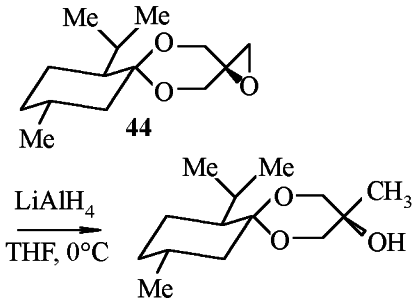
Tertiary alcohols were obtained by reduction of various spirooxiranes (**40a–d**) [83, 84].



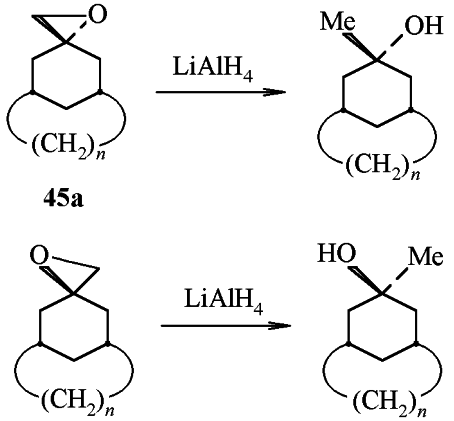
The regiochemistry of reduction in the presence of a heteroatom in the six-membered ring changed only in the presence in this ring of sulfur (**43**); the reduction of epoxides (**41, 42**) with lithium aluminum hydride follows the Krasusky rule [85].



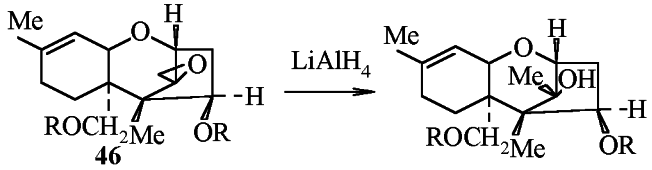
Lithium aluminum hydride is a convenient reduction agent for spiroepoxide (**44**) that has been obtained with the use of 1-menthone as chiral matrix [86].



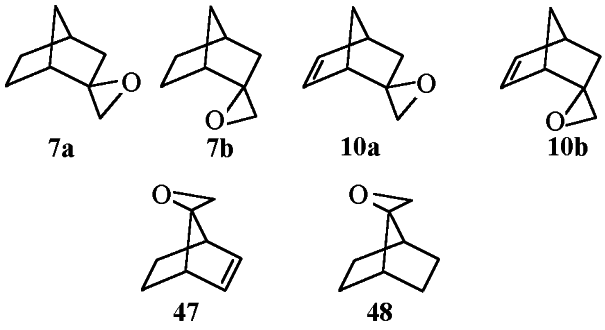
The reduction of epoxycyclohexanes included into a *cis*-[*n*.3.1]bicyclic system (**45a, b**) was described in [87].



The traditional regio- and stereochemistry of the process is retained in the reduction of compounds from verrucarol group [88], in particular, of epoxide (**46**).

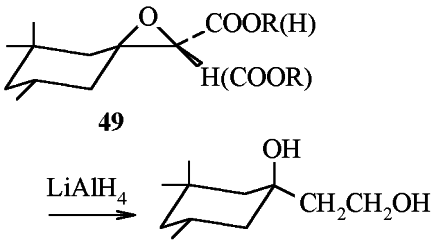


The spirooxiranes with bicyclic carbon skeleton (**7a, b, 10a, b, 47, 48**) with spiroepoxy group attached to different atoms of the skeleton on reduction always afforded tertiary alcohols [6].

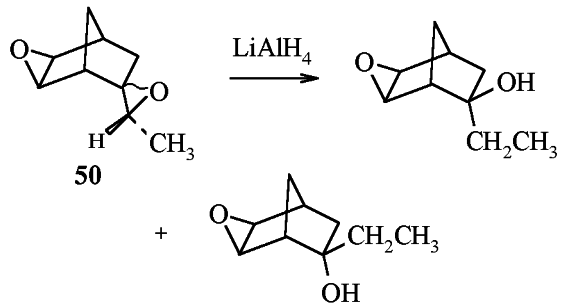


The reaction of 1-methyl-substituted epoxy derivatives of norcamphene with lithium aluminum hydride was described in [89].

Alongside the reduction of the epoxy ring in compound **49** undergo reduction also the other reactive groups [90].

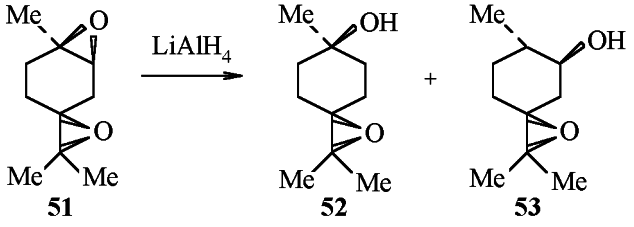


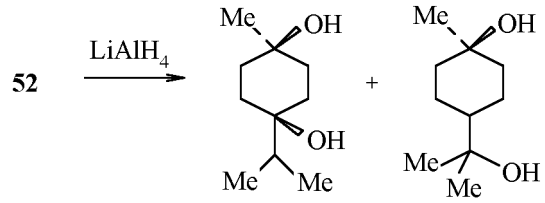
The presence in the molecule of several epoxy fragments provides a possibility of chemoselective reduction depending primarily on the structural features of the substrate. For instance, in [91] was performed a stereoselective reduction of a mixture of stereoisomeric 3-oxatricyclo[3.2.1.$0^{2,4}$]octane-6-spiro(3-methyl)oxiranes (**50**).



The course of reaction suggests the presence of significant steric hindrance arising at the attack of the nucleophilic reagent on the electrophilic centers of the epoxynorbornane fragment. The more favorable turned out to be the rupture of C–O bond neighboring to the methyl group; the latter determined the strict chemo- and regioselectivity of the process.

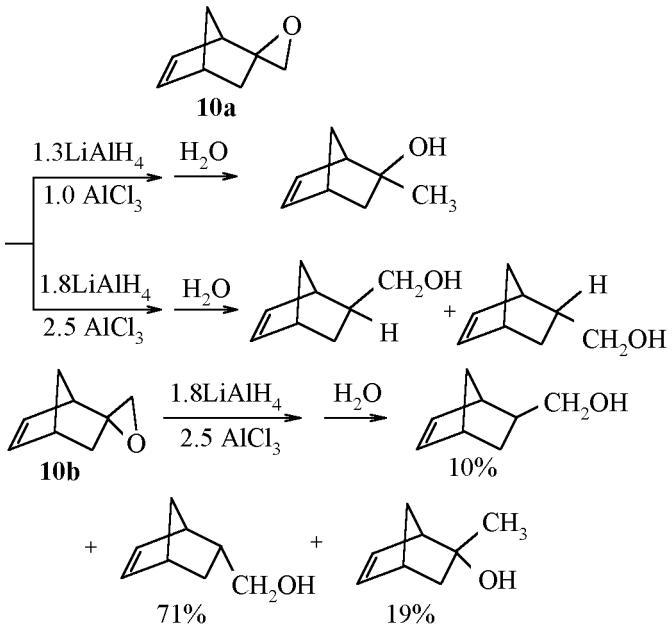
A strict chemoselectivity was also found in reduction with lithium aluminum hydride of stereoisomeric terpinolene diepoxides [92]. Both in the *cis*- and *trans*-isomer the reduction occurs not at the spiroepoxy moiety but at epoxycyclohexane fragment yielding equal amounts of regioisomers (**52, 53**).



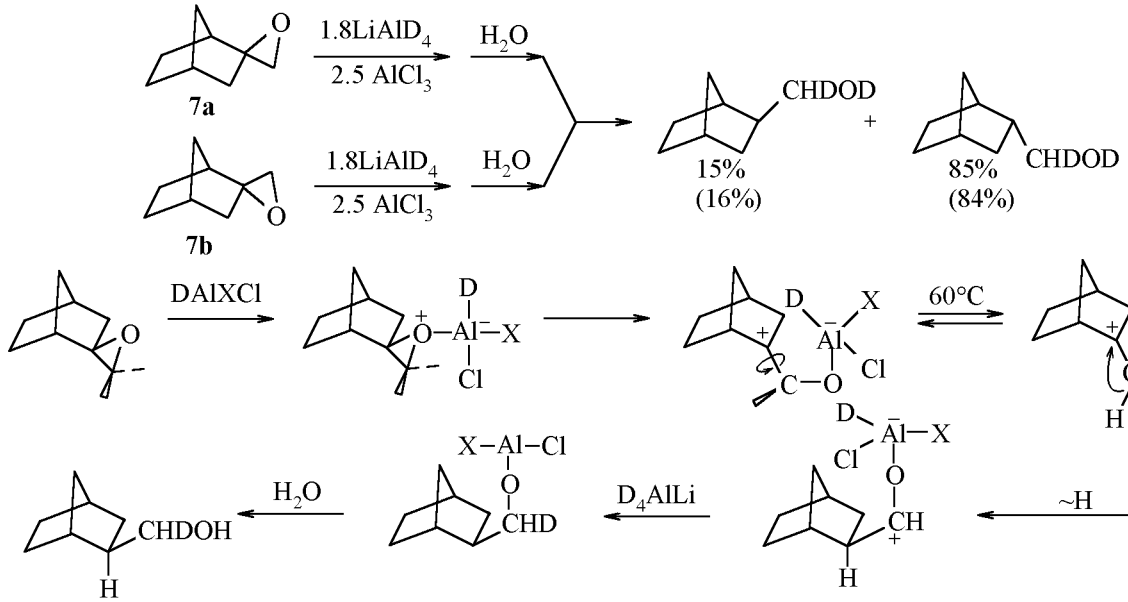


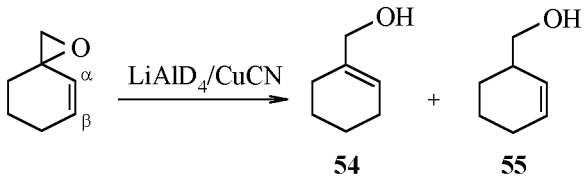
Further reduction of spiroepoxide (**52**) with lithium aluminum hydride in boiling ether afforded a mixture of equal amounts of regioisomeric diols [92]. Here the passive behavior of the spiroepoxy moiety in compound **51** also is due to a steric factor since in the fragment in question are neither primary nor secondary carbons in the epoxy ring that are spatially accessible for a nucleophilic attack.

To achieve reduction of sterically hindered epoxides sometimes was used activation with aluminum chloride addition [6]. Therewith the reduction with the reagent $LiAlH_4$–$AlCl_3$ often provided "abnormal" reaction products. As active reagents operated alane (AlH_3) and chloroalanes that to a significant extent possessed properties of Lewis acids, therefore the hydride added to the more substituted carbon of the epoxy ring. Depending on the strength of the Lewis acid (alane < chloroalane < dichloroalane) were obtained individual "normal" or "abnormal" products of the ring opening, or a mixture thereof. For instance, the reaction with epoxymethylenenorbornenes (**10a, b**) gave rise either to tertiary alcohol or its mixture with a primary alcohol [6]. At larger amount of catalyst prevailed the "abnormal" product.

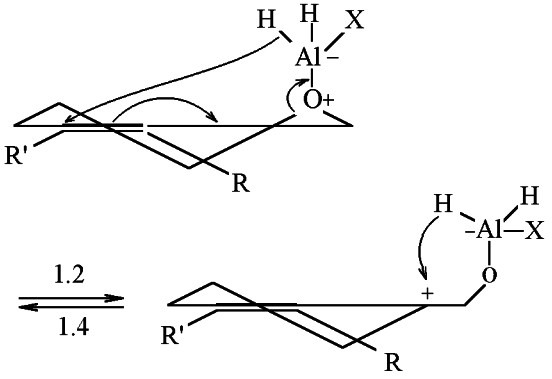


Epoxides of methylenenorbornane (**7a, b**) are reduced by this system to primary alcohols with equal amount of *endo*- and *exo*-isomers [6]. The assumed reduction mechanism is presented on the following scheme:



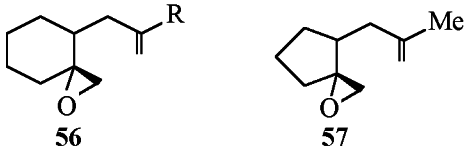


The reaction mechanism may be represented by a scheme below. The direction of the reaction depends on the character of substituents R and R'. With alkyl groups in α- and β-positions the ratio of compounds 54 and 55 equals to 19 : 1; on the contrary, with α-methyl and β-aromatic substituents this ratio is 1 : 2, and the overall yield decreases from 90 to 60%.



In the other study [93] the lithium aluminum hydride was modified by addition of copper cyanide; this reagent was suitable for a regioselective 1,4-reduction of 1-oxaspiro[2.5]oct-6-enes (yield 93%, [54] : [55] = 2 : 1).

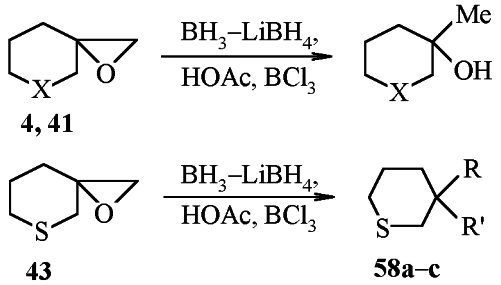
A selective reduction of epoxy derivatives of methylenecycloalkanes was carried out using 4-R-substituted diisobutylaluminum 2,6-di-*tert*-butylphenoxides (R = Me, *T*-Bu, Br) [94]. The epoxides used were epoxymethylenecyclohexanes (**56**, R = H, Me) and the corresponding cyclopentane analog (**57**).



Among complex borohydrides are well known reductants lithium, sodium, and zinc borohydrides [95, 96]. The lithium borohydride is a weaker reduction agent than lithium aluminum hydride. It was applied to reduction of epoxymethylenecyclohexane and its heteroanalogs in combination with boron derivatives that activated the epoxy ring as Lewis acids [95]. It turned out that epoxides (**4, 41**, X = CH_2, O) react differently under conditions mentioned. Unlike the other epoxides the sulfur-containing compound **43** suffered rearrangement and ring contraction (**58a–c**, R = Me, R' = CH_2OH; R = CH_2OAc, R' = CH_2OH; R = R' = CH_2Cl) [95].

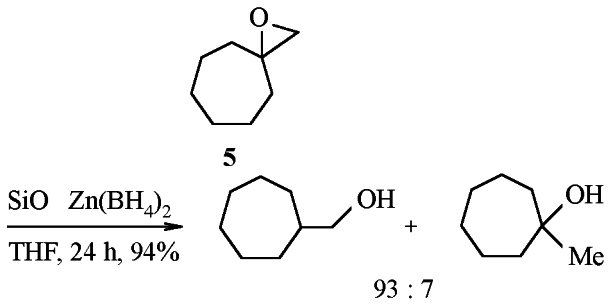
Table 4. Reductive opening of the epoxy ring in compound **59**

Reagent	Solvent	Temperature, °C	Yield, %	Isomers ratio			
				cis-**60**	*trans*-**60**	**61**	**62**
$LiAl(i\text{-}Bu)_2H$ (1.1)	CH_2Cl_2	–78	60	40	50	–	10
$LiAl(i\text{-}Bu)_2H$ (1.1)	Hexane	–78	85	87	5	–	8
$LiBEt_3H$ (1.1)	THF	–78	93	–	–	>99	–
$NaBH_4$ (5.0)	CH_3OH	0→20	83	23	1	3	73
$LiBH_4$	THF	0→20	68	49	4	47	–



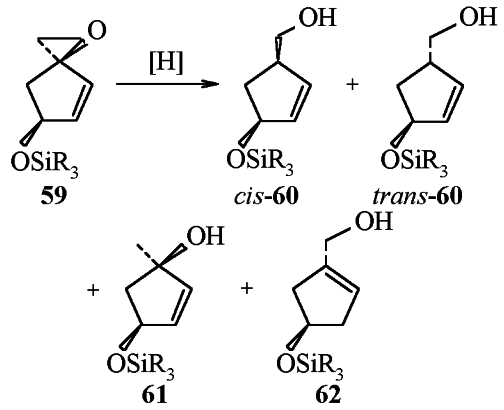
The results obtained by epoxymethylenecyclohexane reduction under similar conditions were confirmed in [97].

In 1992 was observed that epoxy derivatives of epoxymethylenecycloalkanes were transformed into less substituted alcohols when for reduction was used zinc borohydride on silica gel carrier [98]. In the investigation were used epoxides with five-, six-, and seven-membered rings, with alkyls and the other groups in various positions of the alicyclic fragment.

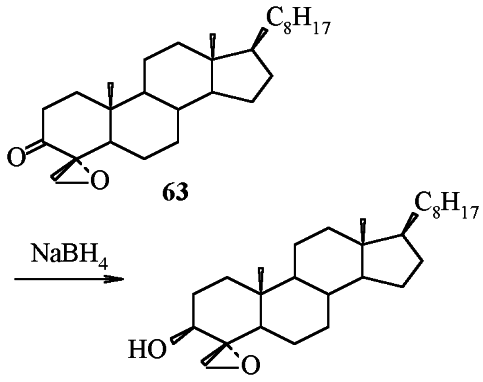


This regioselectivity of epoxides reduction by this reagent was stressed in [99] since with the majority of the other reagents had been observed previously the opposite trend: formation of the more substituted alcohols.

By an example of spirocyclic epoxides containing 4-siloxycyclopent-2-ene fragment (**59**) were compared reductions by lithium diisobutyldihydroaluminate, sodium borohydride, lithium triethylborohydride, and lithium borohydride [100] (Table 4).

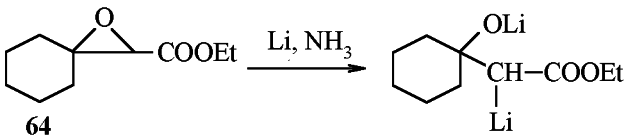


The high regio- and stereoselectivity was observed in the synthesis of (*cis*-**60**) compound effected by lithium diisobutyldihydroaluminate in hexane, and in reduction of epoxide (**59**) along Krasusky rule by the action of lithium triethylborohydride (>99%). Similar effect of this reductant was also observed with the other substrates [96]. The data in the table show that sodium borohydride serves rather as isomerization catalyst than as reducting agent. The passive behavior of this reagent in reduction of spirooxiranes was additionally confirmed later [101]. It was shown that optically active epoxy derivatives of cholestanones (**63**) were reduced by sodium borohydride into biologically active alcohols with conservation of the oxirane fragment.



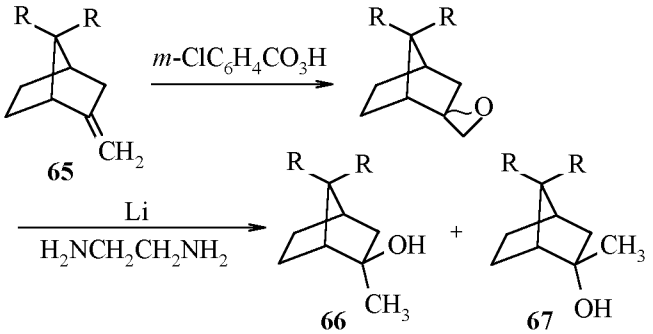
Interestingly the reduction of epoxide (**59**) with lithium diisobutyldihydroaluminate in different solvents occurred in dissimilar way. In the nonpolar hexane the reaction follows predominantly the S_N2 mechanism, and in the relatively polar dichloromethane a contribution of the S_N1 mechanism is also possible with participation of carbocation-like intermediate that further affords a mixture of isomeric alcohols (*cis*- and *trans*-**60**) [100].

The last method of spirooxiranes reduction we are going to consider is the treatment with alkali metals. This method is well known since nineteen seventies and is presumed to include intermediate formation of carboanions [102]. Lithium in liquid ammonia transforms spirooxirane (**64**) in intermediate dilithium derivative. The other metals (K, Na) react in a similar way.

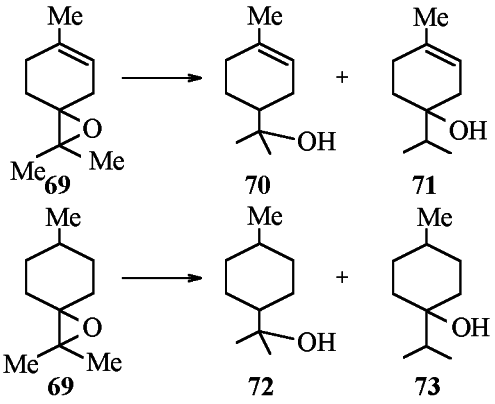


64

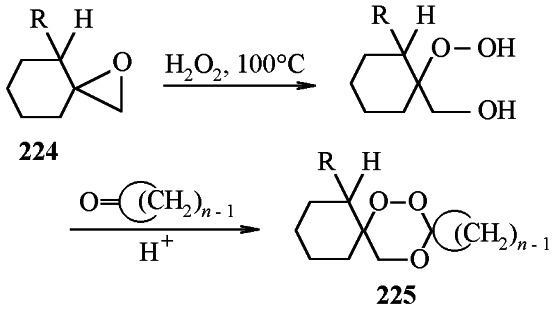
A kind of this method was applied by Brown to analysis of the stereochemical features of epoxidation with *m*-chloroperbenzoic acid of a group of compounds with norbornene and norbornane fragments. Stereoisomeric epoxides (**65**, R = H, Me) were reduced into alcohols, and the ratio of the latter was determined by GLC [103].



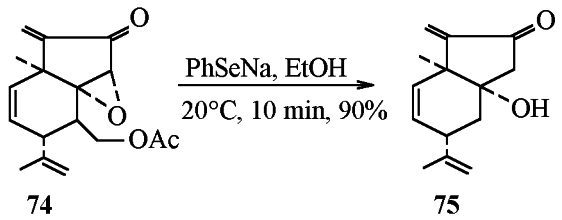
Methylenenorbornane (**65**, R = H) afforded 86% of *exo*-alcohol (**66**), and 2-methylene-7,7-dimethylnorbornane (**65**, R = Me) yielded 84% of *endo*-alcohol (**67**). It was recently demonstrated that this method is very convenient for reduction of the sterically hindered tetrasubstituted spirooxiranes (**68, 69**) [104]. The ratio of regioisomers prepared from two analogous epoxides are quite different: [**70**] : [**71**] = 60 : 40, and [**72**] : [**73**] = 95 : 5.



It is possible also to use lithium β-alkoxides, the reaction products of epoxides with aromatic anion radicals, in particular, with lithium 4,4'-di-*tert*-butylbiphenylide [105]. The key stage in the rupture of the carbon-oxygen bond in epoxide **4** in reaction with lithium is the formation of a stable anion radical.

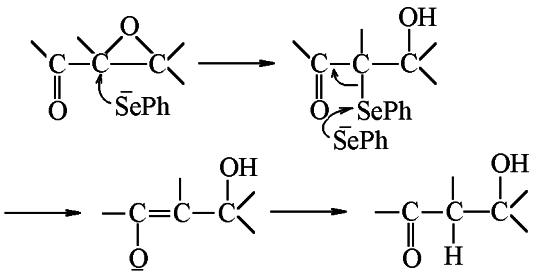


In [106] was proposed the use of organoselenium reagents for reduction of α,β-epoxyketones to β-hydroxyketones. The neutral medium favors the retention of the double bonds in the highly unsaturated structure of oxirane (**74**) and the formation of β-hydroxyketone (**75**).

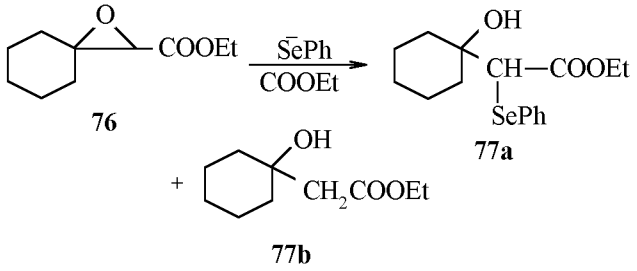


74 **75**

The transformation mechanism of ketoepoxides includes primary regioselective nucleophilic substitution with the phenylseleno group followed by nucleophilic attack of the second molecule of the reagent on the selenium atom [106].



The reduction of glycidyl ether (**76**) under the same conditions afforded a mixture of substitution and reduction products [hydroxyesters (**77a, b**)].



IV. REACTIONS WITH AGENTS CONTAINING NUCLEOPHILIC CENTERS ON OXYGEN, SULFUR, AND CARBON ATOMS

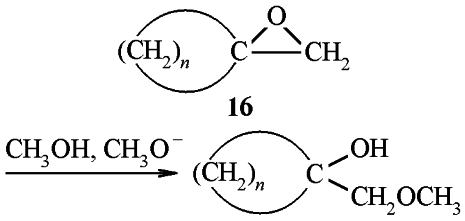
A steadily growing interest attracts alcoholysis of epoxides for the reaction simulates the process occurring between epoxy binders with oxygen-containing hardeners. The alcohols have a definite advantage before the other nucleophilic reagents since it is possible to vary in alcoholysis reactions the character of medium as one of the decisive factors for reactivity of epoxides.

The existing reviews [29, 55, 60, 107, 108] contain very scanty data on the reactivity of spirooxiranes although the reactions of epoxycycloalkanes are treated comprehensively. The reactions between spirooxiranes and alcohols are poorly studied although are known examples of such reactions in basic [3, 68], acidic [109] media, and even under UV irradiation [110].

The cleavage of the epoxy ring in reaction of epoxymethylenecycloalkanes (**16**) with methanol under basic catalysis proceedes regiospecifically: The single product of methanolysis of epoxymethylenecycloalkanes (n = 3–6, 10) arises in accordance with Krasusky rule in conformity with the decisive role of the steric factor at the weak activation by methanol of the oxygen in the epoxy ring [3, 68].

Table 5. Kinetic and activation parameters of epoxycyclopentane and spiroepoxides methanolysis [7, 68]

	Temperature, °C	$k \times 10^6$, l mol^{-1} deg^{-1}	E_A, kJ mol^{-1}	$-\Delta S^{\neq}$, J mol^{-1} deg^{-1}	k_{rel}, 40°C
2	12	1.2 ± 0.1	67 ± 7	133 ± 13	5.25
	15	1.5 ± 0.1			
	20	2.7 ± 0.1			
	25	4.0 ± 0.2			
	40	14.7 ± 0.7			
4	25	1.7 ± 0.1	88 ± 9	70 ± 7	3.14
	30	2.7 ± 0.1			
	37	6.4 ± 0.3			
	40	8.8 ± 0.5			
5	30	2.1 ± 0.1	77 ± 7	109 ± 11	1.79
	35	3.3 ± 0.2			
	40	5.0 ± 0.3			
	45	8.9 ± 0.5			
6	40	1.6 ± 0.1	79 ± 8	113 ± 11	0.57
	45	2.4 ± 0.1			
	50	4.3 ± 0.2			
	55	6.2 ± 0.3			
7a, b	30	3.5 ± 0.3	69 ± 7	132 ± 13	3.29
	35	4.6 ± 0.2			
	40	9.2 ± 0.5			
	45	11.5 ± 0.6			
8	30	1.6 ± 0.1	76 ± 8	122 ± 12	1.51
	35	2.6 ± 0.1			
	40	4.2 ± 0.2			
	45	6.9 ± 0.3			
78	35	2.1 ± 0.1	73 ± 7	126 ± 13	1.00
	40	2.8 ± 0.1			
	45	4.9 ± 0.2			
	50	4.7 ± 0.4			

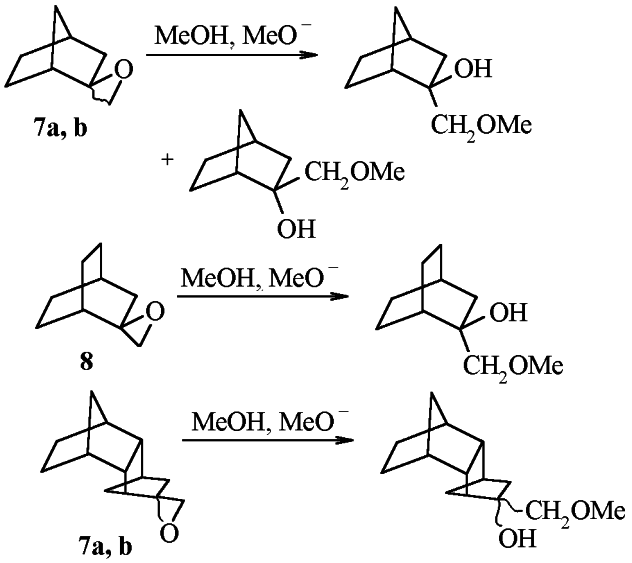


The enhanced reactivity of 1-oxaspiro[2.n]alkanes as compared with isomeric epoxycycloalkanes (**17**) is due to the accessibility of the primary carbon to the nucleophilic attack: For instance, with the former compounds the heating is required for methanolysis completion only with epoxymethylenecyclododecane [68].

Table 6. Strain energy, energy of frontier orbitals, bond order, and bond strength in epoxy ring of spiroepoxides [7, 111]

Epoxide no.	E^{str}, kJ mol^{-1}	Bond order		Bond strength, a.u.		E_{LUMO}, eV	E_{HOMO}, eV
		CH_2–O	C–O	CH_2–O	C–O		
2	236.86	0.9421	0.8766	–0.5311	–0.4793	1.87	–9.94
3	129.85	0.9456	0.8759	–0.5355	–0.4744	1.89	–9.98
4	101.61	0.9467	0.8724	–0.5374	–0.4700	1.81	–9.81
7a	172.80	0.9424	0.8818	–0.5313	–0.4791	1.83	–8.89
7b	174.72	0.9432	0.8789	–0.5350	–0.4751	1.73	–9.70
8	145.60	0.9451	0.8790	–0.5350	–0.4751	1.90	–9.70
26	–	0.9487	0.8669	–0.5385	–0.4700	1.90	× 10.01

In [7] was described the methanolysis of spiroepoxides with bi- and tetracyclic carbon skeletons (**7a, b, 8, 9a, b**). A kinetic investigation was carried out in the presence of sodium methylate [68] in comparison with analogous reaction of epoxycyclohexane (**78**) (Table 5). The kinetic data confirm that spiroepoxides possess higher reactivity than epoxycyclohexane under conditions of the basic catalysis.

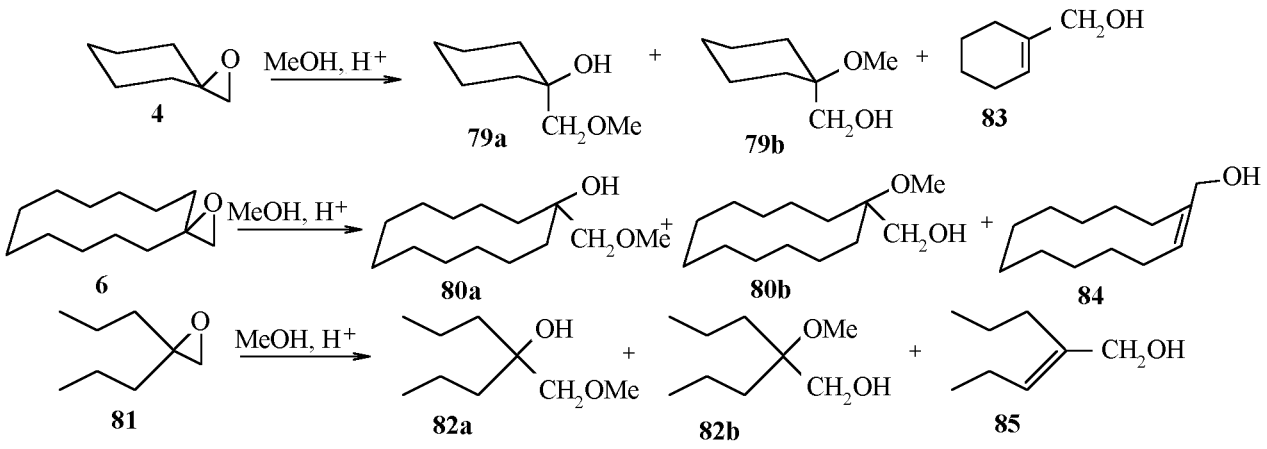


The most reactive was the strained epoxymethylenecyclobutane (**2**) (k_{rel} 5.25). With growing alicyclic fragment epoxides (**4, 5, 6**) that do not significantly differ in strain become less active (k_{rel} 3.14, 1.79, 0.57 respectively). This fact may be due to growing steric hindrances or to the conformational characteristics of the molecules. The negative value of activation entropy also increases in this series, and $\Delta S^{\neq}$ values are respectively –70, –109, –113 J mol^{-1} deg^{-1}. Similarly alter the parameters in going from epoxymethylenenorbornane (**7a, b**) to its bicyclo[2.2.2]-octane analog (**8**). The low activity and high negative value of the activation entropy for epoxycyclohexane as compared to those of epoxymethylenecyclohexane may be due both to lower electrophilicity of the center suffering the attack and to lesser sterical accessibility of the secondary carbon atoms in the epoxide for the attack of electrophilic reagent.

Very illustrative are the data of the quantum-chemical calculations of bond characteristics carried out by SCF LCAO MO method in the valence approximation MINDO/3 (Table 6) [7] for the key epoxides of the series under consideration. For comparison in Table 6 are given the calculation data for 1,1-dimethyloxirane (**26**) performed by the same procedure [111].

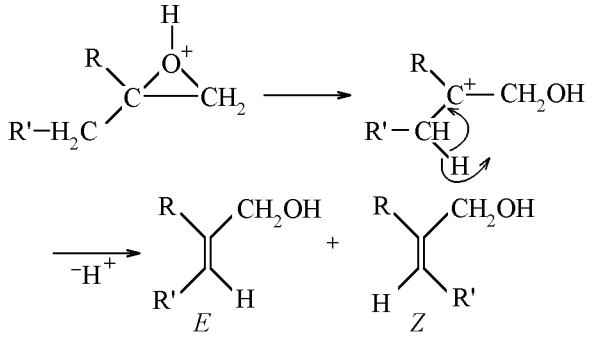
From the calculation results of characteristics of oxygen bonds with extracyclic carbon follows primarily their enhanced activity as compared to 1,1-dimethyloxirane (**26**). The order and strength of the cleaving bond CH_2–O decrease with the growing strain. Although the CH_2–O bond everywhere is the stronger one the nucleophile attacks this bond because of steric reasons [7].

The methanolysis of epoxymethylenecycloalkanes in acidic media was studied on less compounds [68, 109]. Epoxy derivatives of methylenecyclohexane (**4**) and methylenecyclododecane (**6**) in acidified methanol (0.1% solution of sulfuric acid) in the cold afford complicated mixtures of products generated by epoxy cycle opening in two directions, according to Krasusky rule (**79a, 80a**) (up to 15%), and against this rule (**79b, 80b**) (60–80%) [109]. In a similar way reacted dipropyloxirane (**81**) studied for the sake of comparison: It gave rise to hydroxyethers (**82a, b**). Besides the products mentioned all cases by the chromatography were in detected and identified the corresponding allyl alcohols (**83–85**) (8–20%).



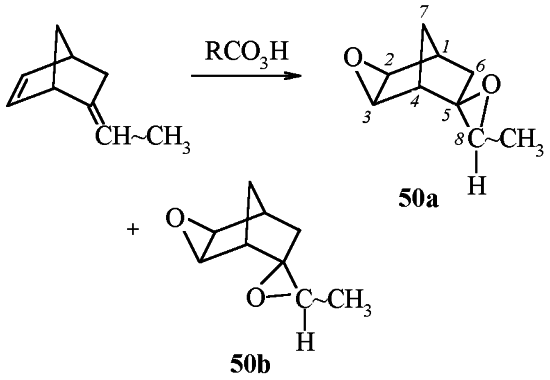
The observed change in regioselectivity of methanolysis reaction in going from basic to acidic medium were rationalized [109] with the use of a known Dewar's model [63]. The efficient epoxide oxygen activation in the acidic medium according to the model is accompanied with more planar structure of the two-carbon fragment due to increased π-complex character of the three-membered ring. This change in geometry enhances accessibility for an attacking nucleophile of the more shielded and more electrophilic (according to the quantum-chemical calculations) spiro carbon of the ring; the main product in the acidic medium is a primary (less substituted) alcohol, abnormal product of the ring opening in the spirooxirane.

In macrocyclic and acyclic alcohols (**84, 85**) were established by ^{1}H NMR spectra the ratios of *E*- and *Z*-isomers (50 : 50 and 56 : 44 respectively). The allyl alcohols arise apparently via a tertiary carbocation with subsequent proton elimination.



Since the formation of the *Z*-isomer requires a rotation around a carbon-carbon bond in the cation, it is sterically hindered in compounds with small and common rings. It is apparently the reason of formation of 1-hydroxymethylcyclohex-1-ene (83) as a pure stereoisomer as evidences the ^{1}H NMR spectrum of the compound.

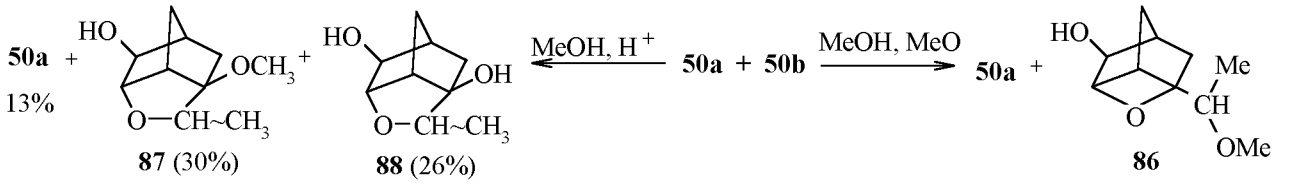
The character of the reaction medium governs the direction of methanolysis of the mixture of stereoisomeric spiroepoxides (**50a, b**) prepared from



ethylidenenorbornene, the known component of polymer (rubber) compounds [112, 113].

In the basic medium methanolysis of epoxides occurred chemoselectively at the external epoxy ring under more rigid conditions than the reaction with 1-oxaspiro[2.*n*]alkanes described above, namely, at 60°C for 16 h [112].

The structure of unreacted epoxide (**50a**) was established from ^{1}H NMR spectrum. These data indicated the sterical hindrances arising at the attack of a nucleophile from the internal (endo) cavity of the bicyclic norbornane skeleton; just this factor provides a higher inertness of epoxides (**50a, b**) in S_N2-process [52] as compared with 1-oxaspiro[2.*n*]alkanes.



The regioselective methanolysis of isomer (**50b**) (along Krasusky rule) was accompanied with intramolecular cyclization to form oxetane (**86**) by attack of a nucleophilic alkoxide anion on one of carbon atoms of the substituted epoxynorbornane [112]. Such oxetane structure was produced formerly only under action of potassium tert-butylate [114].

In the reaction mixture after methanolysis in acidic medium of stereoisomers (**50a, b**) mixture [113] alongside the unreactive isomer (**50a**) were found two compounds of similar structure (**87, 88**). The first one originated from the chemoselective opening of the external epoxy ring of diepoxide (**50b**) against Krasusky rule; its formation is favored both by substitution at C^8 atom and by acidic character of the reaction mixture. Diol (**88**) was obtained presumably through regioselective "normal" attack of methanol on epoxide (**50a**) followed by elimination of a methyl group in the course of intramolecular cyclization. The presence of both compounds **87, 88** evidences the wide range of transformation products forming from epoxides under acid catalysis, and comparison thereof with oxetane **86** demonstrates the decisive role of epoxy ring activation in chemo-, regio-, and stereoselectivity of oxiranes reactions.

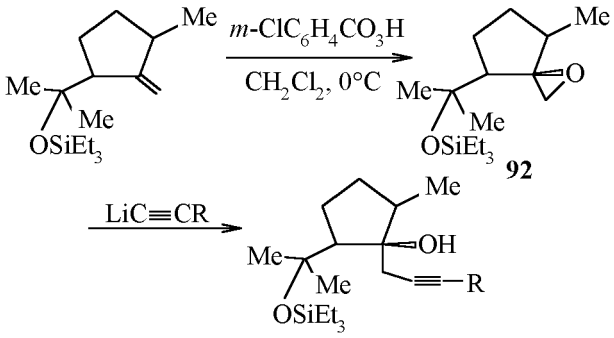
An interesting case of formation of two isomeric alcoholysis products (along and against Krasusky rule in 0.4 : 1 ratio) from epoxymethylenecyclohexane was observed [110] with no acid catalyst but under UV irradiation of the reaction medium or of methanol (ethanol) prior to reaction. The reaction proceeded also after irradiation and was stopped only on quenching the reaction mixture with alkali.

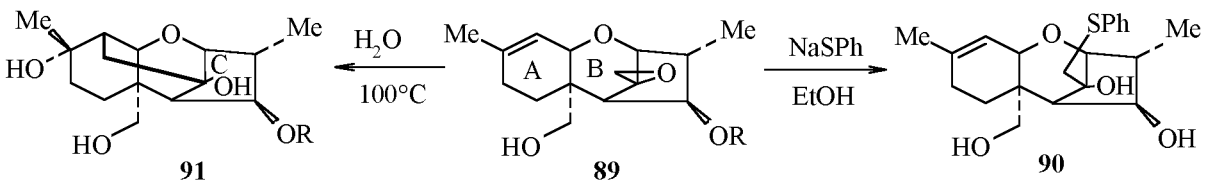
The reactions of spirooxiranes with sulfur-containing nucleophiles are poorly investigated [115–117]. An interesting case is degradation of trichotecene (**89**, R = H), a representative of an extensively studied group of biologically active spirooxiranes [116]. The reaction with sodium thiophenolate occurs at boiling and it ends by regioselective opening of the epoxy ring to furnish compound **90**.

The initial stage of trichotecene (**89**, R = Ac) hydrolysis proceeds in a similar way, but this reaction is accompanied by intramolecular cyclization with participation of a double bond that is located in the A ring of the polycyclic spirooxirane, and as a result forms ether **91**. The hydrolysis of spirooxiranes was also studied in [118, 119], and reaction with toluenesulfonic acid in [120].

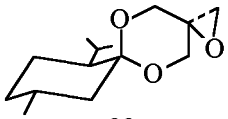
Among reactions of spirooxiranes with nucleophilic reagents that lead to epoxy ring opening are now extensively studied reactions with C-nucleophiles. The transformations described are effected by metal acetylides [95], organocuprates [86], trimethylsilyl cyanide [121], and dimethyloxosulfonium methylide [122].

A reaction proceeding from epoxide (**92**) is a part of an enantiospecific synthesis of sesquiterpene curculeanolide A containing a spirolactone bicyclic fragment [123].





In a reaction of spiroepoxide **93** prepared from natural menthone with organocuprate was formed an equatorial alcohol isolated as trimethylsilyl ether **94**.



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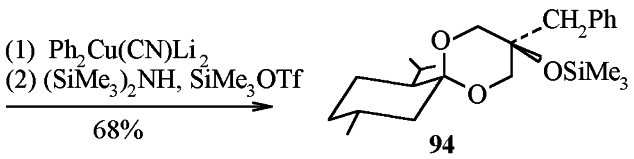
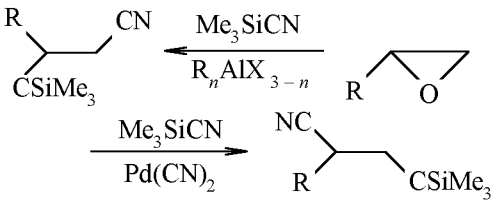
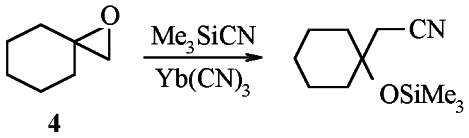


94

The regiochemical potential of cyanotrimethylsilane in reactions with epoxy compounds is versatile [121], from the "normal" addition under the action of aluminum complexes to "abnormal" reaction in the presence of palladium cyanide.

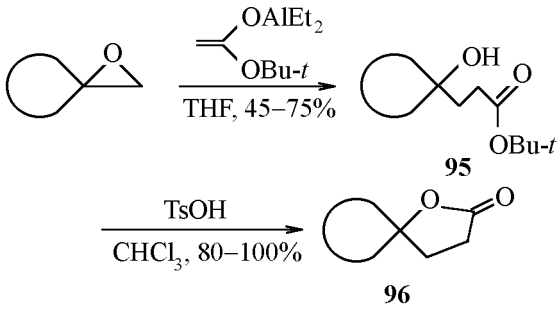


A new catalyst was developed for performing the cyanosilylation in strict conformity to Krasusky rule [121].



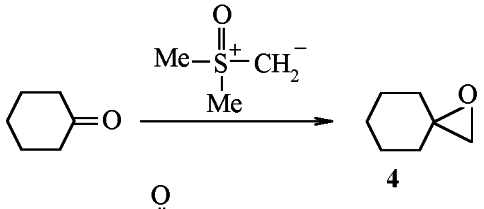
4

Among the natural and synthetic 1-oxaspiro[4.*n*]-alkan-2-ones was found a large group of biologically active compounds with antibiotic and antitumor properties. Some synthetic γ-lactones (**96**) are used as templates for construction of conformationally rigid systems for fixing protein kinase C. A wide series of lactones including spirolactones with cyclobutane, cyclopentane, cyclohexane, and cycloheptane fragments was described in [124]. These lactones were prepared from spiroepoxides with the use as nucleophilic reagents of aluminates of hydroxyenol ethers [124]. The isolated γ-hydroxyethers were further cyclized into the corresponding spirolactones (**96**). The spirolactones were also obtained without purification of the intermediates.



96

The dimethylsulfoxonium methylide is known to successfully act as epoxidizing reagent for ketones. It was shown later that the excess ylide reacted with oxirane (**4**) and with the others to yield spirooxetane systems (97) [122].



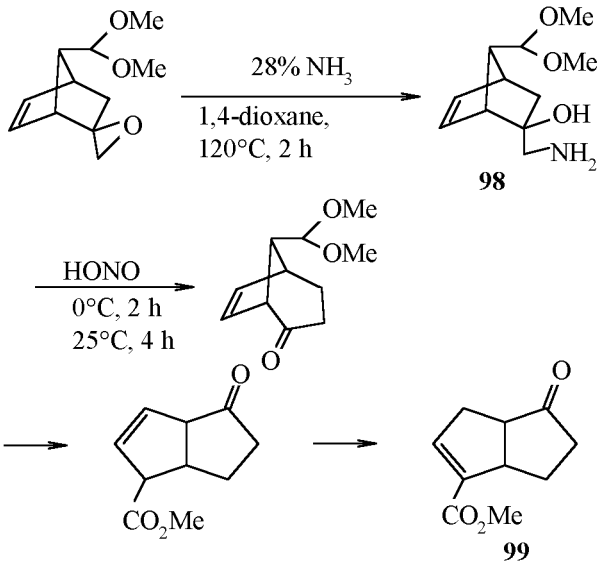
97

Unfortunately no enantioselective transformations effected by oxygen-containing nucleophiles that are known with epoxyalkanes and epoxycycloalkanes [125, 126] were performed with spiroepoxides. The mentioned enantioselective ring opening in these epoxides was performed by carboxylic acids [125] in the presence of the chiral cobalt complexes. A new method of catalytic methoxycarbonylation of aliphatic racemic epoxides was developed resulting in enantiomerically pure β-hydroxyethers. Similar advances in the chemistry of the less studied spirooxiranes may be expected.

V. REACTIONS WITH NUCLEOPHILIC AGENTS CONTAINING NITROGEN AND PHOSPHORUS

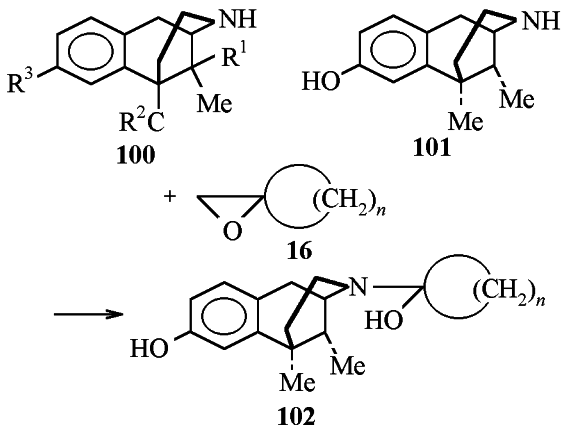
β-Aminoalcohols are an important class of organic compounds of great interest for pharmacology and medical chemistry [127–129]. In particular, aminoalcohols from the norbornene series, e.g., alcohol (**98**), served as initial compounds for preparation of important biologically active products of natural and synthetic origin. It was recently shown that therefrom could be prepared numerous series of interesting

compounds with bi- and tricyclopentanoid skeletons. In [130] are described syntheses of aglycones (±)-missaenoside and (±)-8-epiloganine using ketone (**99**).

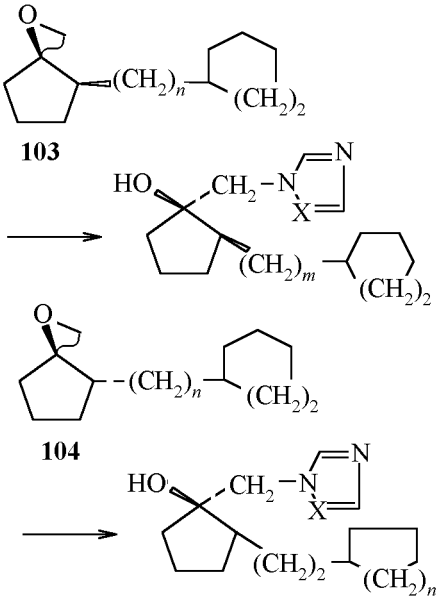


The success of such syntheses depends first of all on stereoselective preparation of the initial epoxide and on its regioselective opening in reaction with aqueous solution of ammonia.

In reaction of secondary amines (**100, 101**, R^1 = H, Me, R^2 = R^3 = H, OH, OR etc.) with oxides (**16**) of various methylenecycloalkanes (n = 2–5) were obtained promising analgetics, anticonvulsants, morphine antagonists [131–133].

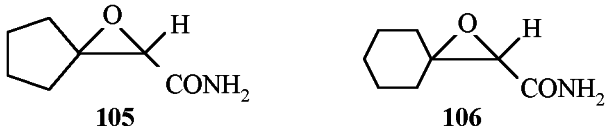


Fungicides for agriculture and gardens were obtained by reaction of epoxides (**103, 104**) with azoles or their salts with alkali metals (X = N, CH, m = 0, 1, n = 1, 2) [134].

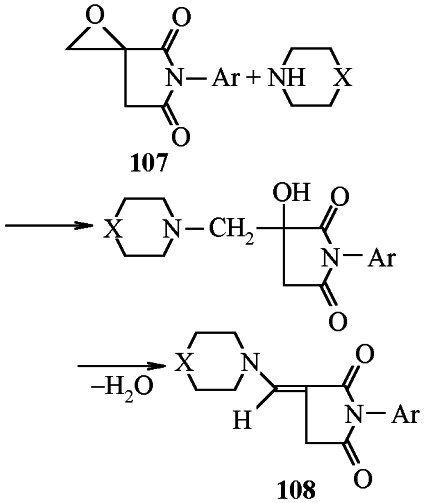


Although the preparation of β-aminoalcohols from epoxides is widely used in organic synthesis [135, 136], this reaction has certain disadvantages. For instance, this method requires that amine be in excess in the reaction medium, and it sometimes results in bis-alkylation. The choice of conditions for regioselective opening of the epoxy ring is also a difficult problem and in certain cases it depends on the substrate structure [136]. The low nucleophilicity of amines requires that the reaction should be performed under stringent conditions and at elevated temperature. Finally, the sterically hindered amines show very low reactivity in this reaction. Still the specific structure of spirooxirane where the epoxide fragment often contains an unsubstituted methylene group facilitates aminolysis due to lower level of sterical hindrances in the transition state of the reaction. The sterical accessibility of the electrophilic carbon center subjected to attack favors aminolysis of 1-oxaspiro[2.n]-alkanes (**16**) as compared to reactions of the other alicyclic epoxides (**17, 18**).

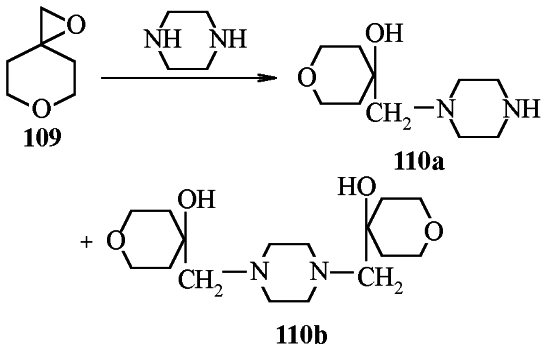
The study of spirooxirane aminolysis started a lot later than similar reactions with the other groups of epoxy compounds. However already to the end of nineteen fifties was described [65] reaction of spiroepoxides (**105, 106**) with benzylamine.



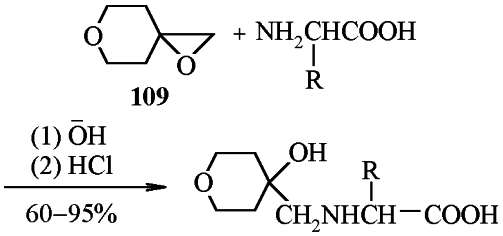
The first examples of direct transformation of spirooxiranes (**107**) into enamines (**108**, X = O, CH_2; Ar = C_6H_5, 4-ClC_6H_4, 3-ClC_6H_4, 3-$NO_2C_6H_4$) by boiling a suspension of oxirane and amine in ethanol were described in [137].



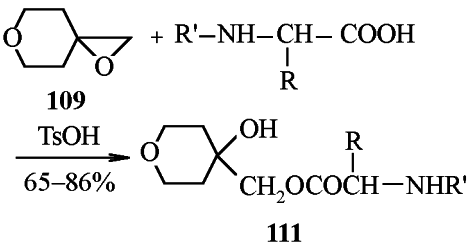
An available epoxide of 4-methylenetetrahydropyran (**109**) (the alkene is a side product of industrial isoprene synthesis from isobutylene and formaldehyde) is a convenient synthon for introduction into molecules of tetrahydropyran ring [138–140]. Under treatment with aqueous amines or ammonia the epoxy ring is opened according to Krasusky rule (product **110a**). With piperazine forms also a bis-adduct **110b**.



α-Aminoacids depending on reaction conditions react with epoxide (109) by amino or carboxy group [138, 140]. At the use of sodium salts of D,L-α-aminoacids in the presence of 10% excess sodium hydroxide that favors transition of a zwitterion into conjugate base form the reaction in water solution at 80°C afforded *N*-(4-hydroxy-4-tetrahydropyranylmethyl)aminoacids.

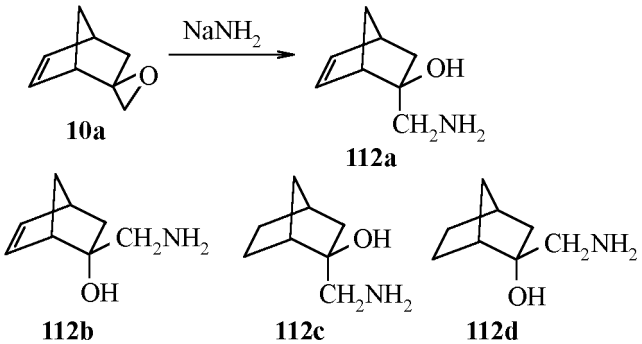


The heating with epoxide (**109**) of N-substituted aminoacids (R' = Ts, Ac) in chloroform in the presence of catalysts gave rise to esters (111) [140].

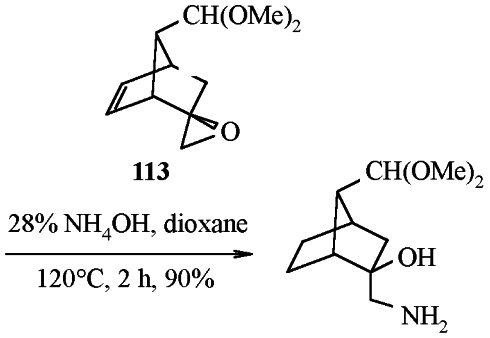


Although in this reaction was expected formation of isomer mixture, the TLC data and ^{1}H NMR spectra evidence that the single reaction product originated from the nucleophile reaction on the less substituted carbon atom.

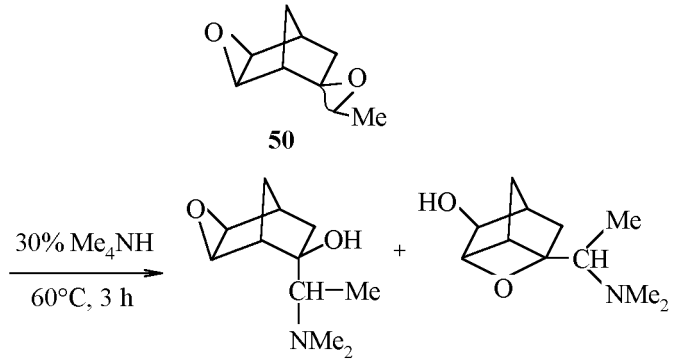
Unlike the above described spirooxiranes the epoxides possessing rigid skeleton of norbornene and norbornane react under more stringent conditions, apparently because of additional sterical hindrances from bicyclic fragments. Aminoalcohols (**112a–d**) from the corresponding epoxides (**27a, b, 10a, b**) were obtained by treating with sodium amide [64].



The other studies [130, 141, 142] also confirmed that aminolysis of epoxides at the lack of protons occurred only under rigid conditions. The ammonolysis of epoxide (**113**) was performed by heating the reagents solution in a sealed ampule [130].

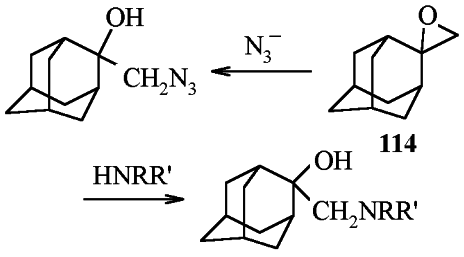


The reaction between dimethylamine and the stereoisomer mixture of ethylidenenorbornene diepoxides (**50**) also was carried out in a sealed ampule [142].

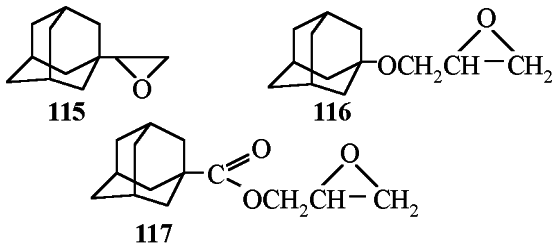


The composition and structure of reaction products show that each of the isomeric epoxides undergoes individual chemo- and regioselective transformation retaining the epoxynorbornane fragment. In one of diepoxides in the rear (endo) side of epoxynorbornane is generated a nucleophilic hydroxy group; it is followed by an attack on an electrophilic carbon atom of the epoxy group. The strain in the oxetane ring does not prevent cyclization [142].

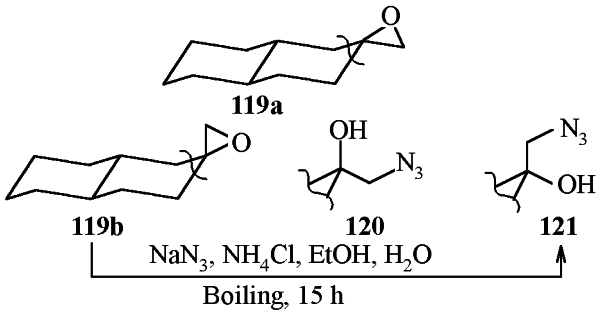
Aiming at the preparation of new antiviral pharmaceuticals various reactions of adamantylspirooxirane (**114**) were performed, among them also those with amines and sodium azide [143].



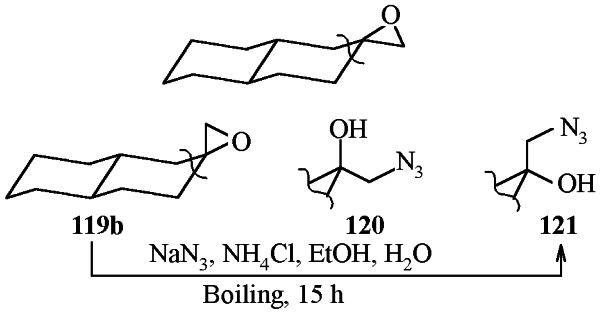
The reactivity of spirooxirane (**114**) was compared with that of three other oxiranes containing an adamantane structural fragments (**115–117**).



The initial reaction rates of oxiranes **114–117** with piperidine are respectively 0.0058, 0.018, 0.30, and 0.29 mmol l^{-1} s^{-1}. The low reactivity of oxiranes (**114, 115**), especially of the first one Shiryaev et al. [143] ascribe to the spatial effect of the carbon skeleton. However spirooxirane **114** is capable to give a relatively stable carbocation that under Ritter's reaction conditions is easily transformed into diacetylamino derivative (**118**).



The reaction of spirooxiranes with sodium azide was studied in [144–147]. The reaction of stereoisomeric epoxides (**119a, b**) afforded the expected products **120, 121** respectively [144].



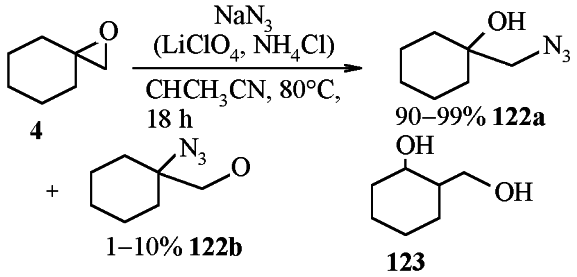
Reaction of methylenecyclohexane oxide (**24**) with sodium azide in water solution was carried out at different pH values [148].

The acidity of the medium turned out to be decisive for the rate, composition of reaction products (azidoalcohol **122** and glycol **123**), and regioselectivity of the process. Actually, the epoxide protonation (at pH 4.2) sharply changes the regiochemistry

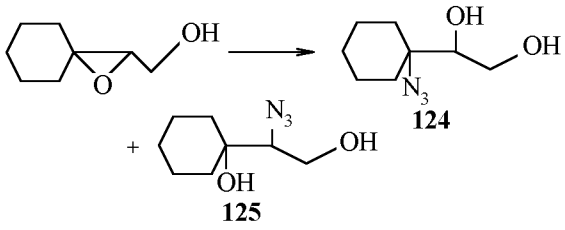
of the process that occurs as prevailing attack on the α-position in conformity to the known models of Parker and Isaacs [60] and Dewar and Ford [63].

pH	Time, h	α- and β-attack	Reaction products (**122**/**123**)	Yield, %
9.5	20	3/97	88/12	77
4.2	1.5	70/30	94/6	58

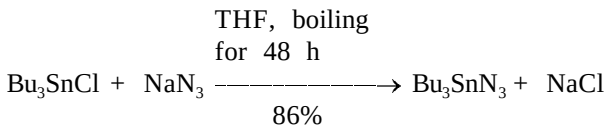
Later Chini *et al*. [145] developed a new simple regioselective azidation procedure for spirooxiranes performed in acetonitrile in the presence of metal salts. The use of aprotic solvent was advantageous as compared to previously applied methods. Simple salts (lithium and magnesium perchlorates) efficiently catalyze the process due to their pronounced properties of Lewis acids. Normal reaction product **122a** prevails.

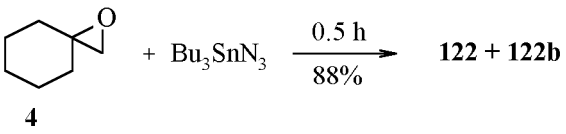


For epoxides sensitive to water solutions and relatively rigid reaction conditions an efficient method was developed with the use of zeolites [147]. As think Onaka *et al*. [147], the direction of reaction is governed by the cation in the zeolite carrier. It was shown that the ratio of isomeric compounds **124** and **125** amounted to: 94 : 6 (CaY), 66 : 34 (Al_2O_3), 78 : 22 (SiO_2), 76 : 24 (NH_4Cl).

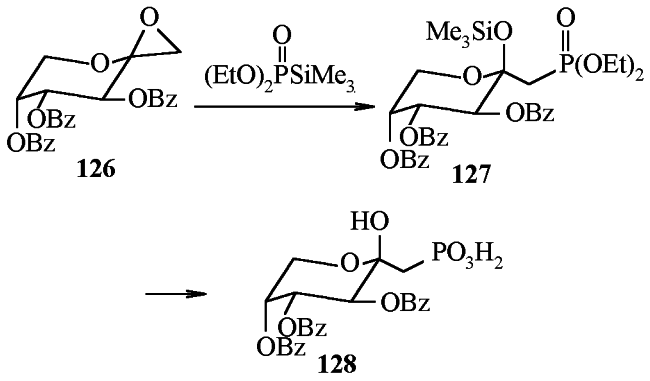


Further development of the process was due to the use of new reagents with azide group, in particular trimethylsilyl azide [149–153]. The latter found wide application in combination with Lewis acids and transition metal complexes. Saito *et al*. proposed for successful preparation of 1,2-azidoalcohols to use tributyltin azide [146] that cleaved the epoxy ring with no additional activation in the absence of solvent [**122a**] : [**122b**] = 1.7 : 1).

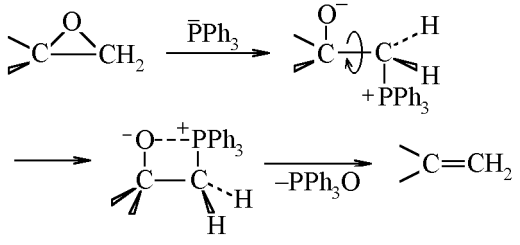




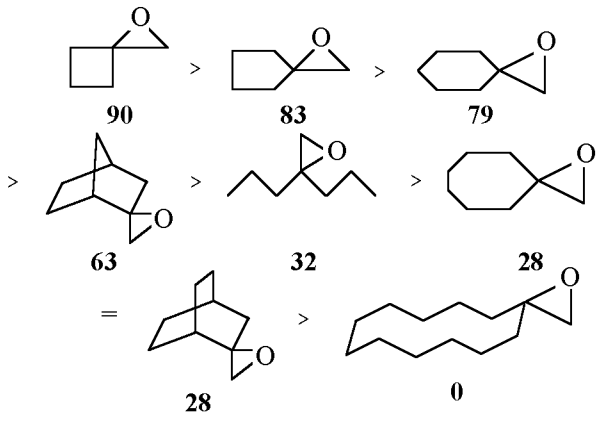
The reactions of spirooxiranes with phosphorus-containing reagents are poorly known. Several studies carried out are important both as syntheses of new analogs of natural compounds and as a valuable contribution to the investigation of structural factors governing the reactivity of spiroepoxides. A synthesis was described of *D*-1-deoxyfructoso-1-phosphonic acid (**128**) proceeding from a new spiroanomeric epoxide, derivative of natural fructose (**126**) [154].



The reaction of a number of epoxymethylenecycloalkanes with triphenylphosphine was shown to afford the corresponding methylenecycloalkanes [155]. The corresponding reactions were also carried out with epoxymethylenebicyclo[2.2.1]heptane and epoxymethylenebicyclo[2.2.2]octane [113].



In the main stage of reaction (attack of nucleophilic triphenylphosphine on electrophilic carbon center of epoxide) electrophilic activation of the oxygen atom is totally absent. The probability of reaction occurrence and its rate may depend on the conformational flexibility of the arising zwitterion; however, in the epoxides group in question this factor is hardly significant. The reaction was carried out in a sealed ampule at 200°C, and the subsequent analysis of the reaction mixture after its treatment with anhydrous ether was performed by GLC. The degree of epoxide conversion into olefin is shown below as an activity series of epoxymethylenecyclo- and -bicycloalkanes [113, 155].



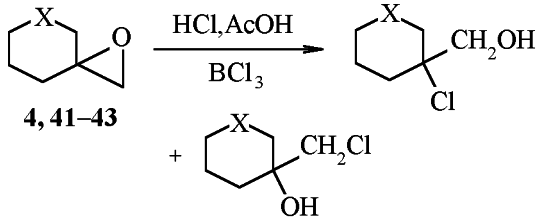
It is presumable that the course of reaction is affected by two main factors: strain and steric hindrance. The former can be the most important with the strained epoxides possessing mono- and bicyclic carbon skeleton. Apparently in the transition state of the limiting stage of the reaction the strain in the system is decreased due to transition of carbon atoms into sp^3-hybridized state, and this factor is more favorable with the most strained epoxides. With growing volume of epoxide molecules in the series under consideration increase the sterical requirements of the bulky attacking nucleophile (triphenylphosphine) to the performance of the primary attack on the epoxide. With epoxides at the end of the activity series the effect of the strain is not felt.

VI. REACTIONS WITH HYDROHALIC ACIDS AND THEIR ANALOGS

The products of hydrohalogenation of spirooxiranes same as spirooxiranes proper are applied as synthons in the chemistry of biologically active compounds. In some cases halohydrins per se possess biological activity. For instance, a considerable antiphlogistic and moderate antibiotic activity is characteristic of salinamide B that is obtained by hydrochlorination of salinamide A, a natural spiroepoxide from marine Streptomyces [39].

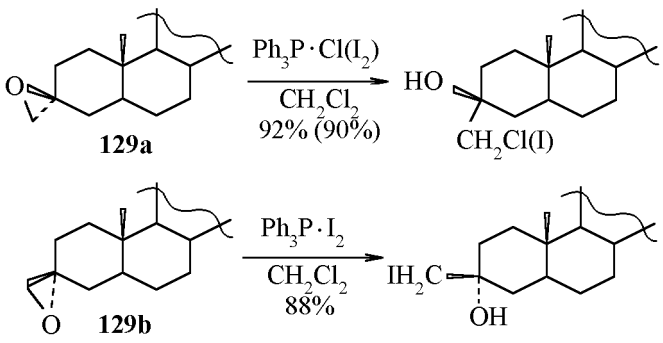
The recent research on chemo-, regio-, and stereoselective transformation of oxiranes resulted in preparation of valuable vicinal halohydrins. In their synthesis were used epoxyalkanes, quite a number of epoxycycloalkanes, some epoxyalcohols and the other oxiranes of the mentioned groups [156]. Besides hydrohalic acids in halohydrin syntheses were used metal halides. Unfortunately, only rare studies concerned syntheses of similar derivatives from spirooxiranes [85, 120, 157–163].

From the first reactions of the group should be mentioned the reaction of epoxides group with hydrogen chloride (**4, 41–43,** X = CH_2, O, NCH_3, S) [85].



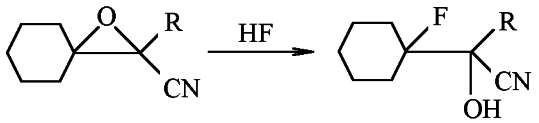
In glacial acetic acid in the absence of catalyst (boron chloride) epoxides **4, 41** do not react, but with the catalyst they afford in various ratio isomeric adducts and acetates.

In hydrochlorination in methanol solution of a spiroepoxide separated from spurge seeds containing an 11-membered fragment occurred only "normal" opening of the epoxy ring, and methanol also took part in the reaction. Ishiguro et al [161] stressed the importance of the sterical factor in the regiochemistry of the process. The same factor and also specific character of the reagent led to regiospecific transformation of stereoisomeric steroid epoxides **129a, b** into halohydrins; as reagents were applied halogen complexes with triphenylphosphine [160]. The process is free of side reactions and apparently proceeds via S_N2 mechanism [160].



The reactions were carried under totally anhydrous conditions. Caputo *et al*. suggested that nearly complete deoxygenation of the epoxides had been observed by Paryzer and Wydra [164] just due to neglect of this important condition. It is significant that hydrohalogenation of the epoxy derivative of 1-methylenecyclohexene along this procedure occurred in accordance with the frontier S_N2 mechanism and resulted in formation of isomeric products [165].

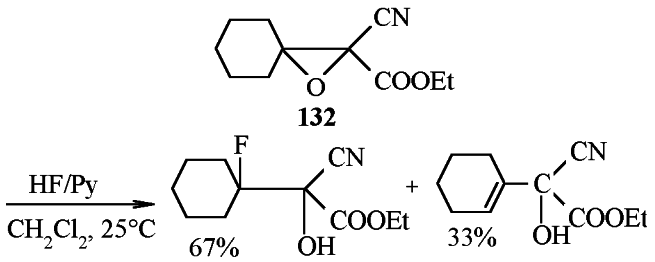
Although preparation of respective fluorohydrins by reaction of epoxysteroids with anhydrous hydrogen fluoride is well known [162], relatively simpler epoxides react in more complicated way: 1-oxaspiro-[2.5]octane-2-carbonitrile (**130a**, R = H) affords fluorohydrin only in 30% yield, analogous 2-methyl-derivative (**130b**) reacted with a higher yield [162, 166].



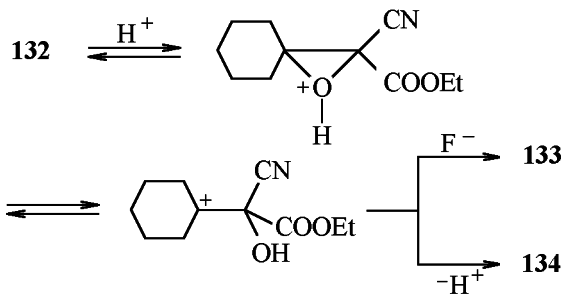
130a, b **131**

R = H (**a**), Me (**b**).

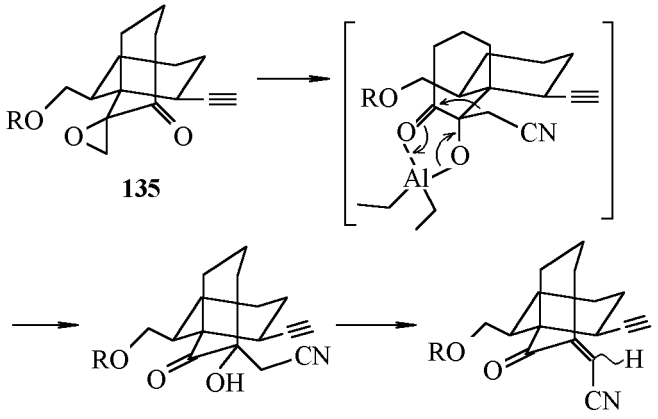
It was recently established that with pyridine polyhydrofluoride the reaction occurred regioselectively but was accompanied with dehydrofluorination to afford substituted cycloalkene (**134**) [158].



Obviously the reaction proceeds via intermediate formation of a tertiary carbocation:

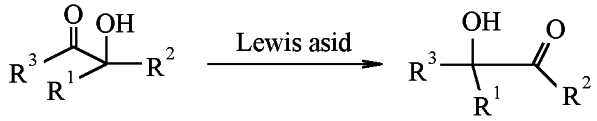


Recently in the study of a related reaction of spirooxirane (**135**) hydrocyanation was observed a 1,2-anionotropic rearrangement [167].



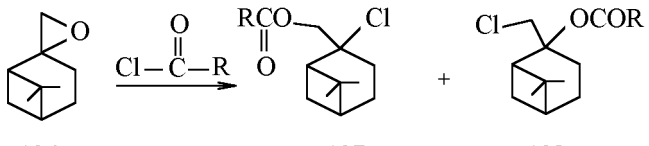
R = *t*-$BuPh_2Si$.

The rearrangement is related to the known ketols isomerization discovered to the end of the nineteenth century by Lobry de Bruyn and Alberda van Eckenstein. The isomerization results in accumulation of the more stable isomer.



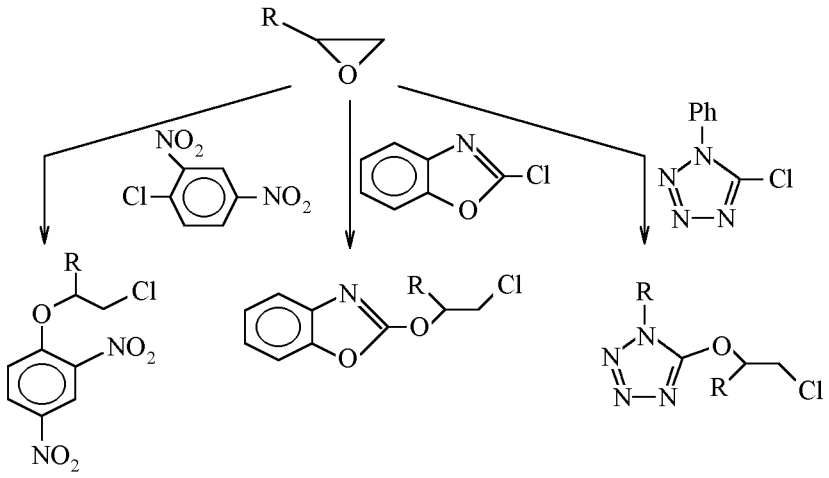
In [167] was observed the rearrangement of α-hydroxyketone in the moment of its formation in hydrocyanation of epoxide (**135**); here migrated the cyanomethyl group; the hydroxy group protection in epoxide (**135**) was performed by formation of *tert*-butyldiphenylsilyl ether [167].

The labile halogen atoms present in halides of carboxylic acids and the other compounds may be considered as possible reagents for opening of epoxy cycle. An interesting example of such reaction was described in 1994 [159] for β-pinene oxide (**136**).



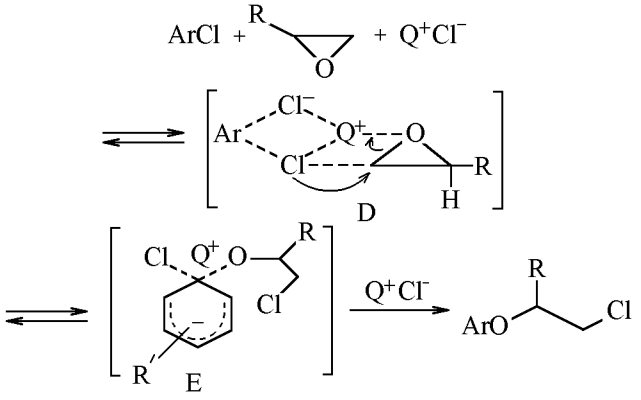
136 **137** **138**

R = Alk, Ar.



Unfortunately in the reactions with the epoxides group under considerations were not used the other reagents containing labile halogen atoms, in particular, very interesting and promising chloro-substituted aromatic and heteroaromatic compounds [163]. Hopefully, this reaction will be successfully applied to spirooxirane series.

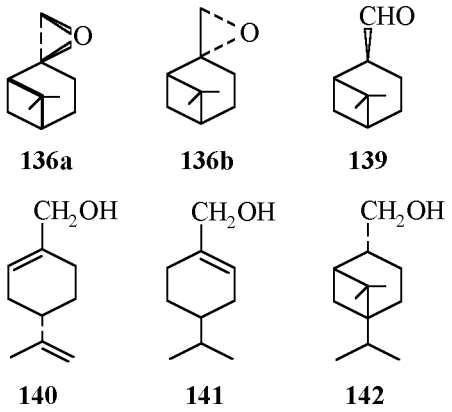
This reaction was carried out in the presence of a phase-transfer catalyst (dodecyltrimethylammonium chloride) in chlorobenzene or diglyme. The yield of target products amounted to 60–90%. The regioselective opening of the epoxy ring occurred apparently along the following mechanism.



The scheme contains two important points, namely, chlorine attack on the less substituted carbon of the oxirane providing complex D and capability of the latter to transform into a stable intermediate E (of Meisenheimer type intermediate). As a driving force is presumed the electronacceptor property of the aromatic ring [163].

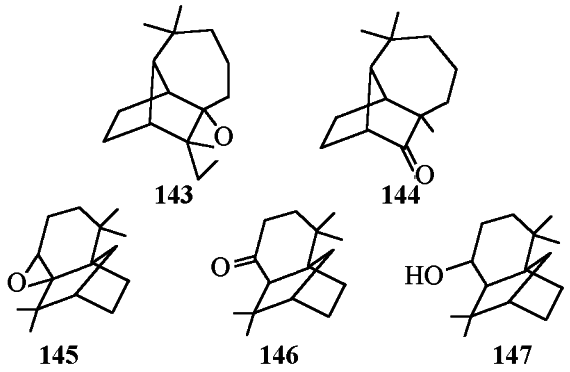
VII. ISOMERIZATION OF SPIROOXIRANES

These reactions attract special attention because of versatility of forming products, reagents, and catalysts. Isomerization results both in carbonyl compounds and allyl alcohols that in some cases may arise from regio- and stereoselective transformations. Recent trends in thermal and photochemical processes consists in fixing substrates by adsorption on solid catalysis or by complexing with cyclodextrines that significantly increase the selectivity of reactions [56]. Using zeolites of various types with salt additives permits preparation from one epoxide products of different classes of compounds, and the process can be performed with high selectivity. For instance, from β-pinene *cis*-epoxide (**136a**) can be obtained *cis*-myrtanal (**139**) [56, 168], perryl alcohol (**140**) [169, 170], phellandrol (**141**) [56]; from *trans*-isomer (**136b**) is prepared *trans*-myrtanol (**142**) [171].

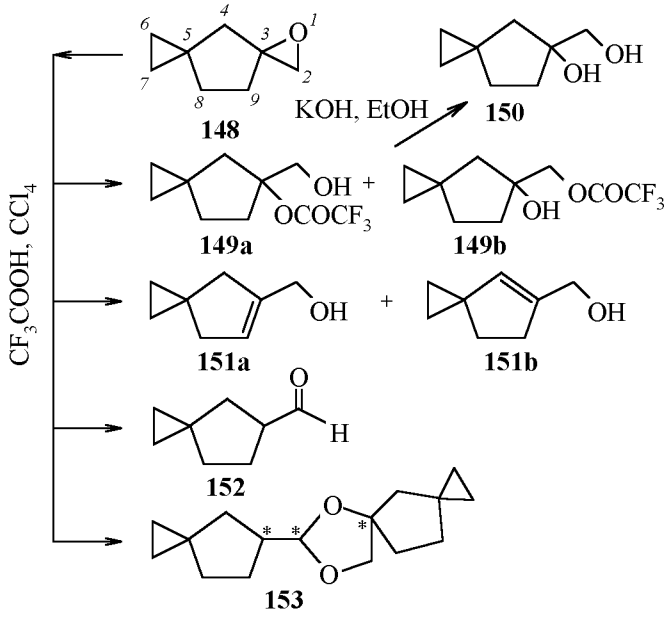


Longifolene epoxide (**143**) on zeolite A-4 is transformed into longicamphenilone (**144**), and epoxy

derivative of isolongifolene (**145**) on different zeolites affords isolongifolan-4-one (**146**) and isolongifolan-4-ol (**147**) [56].

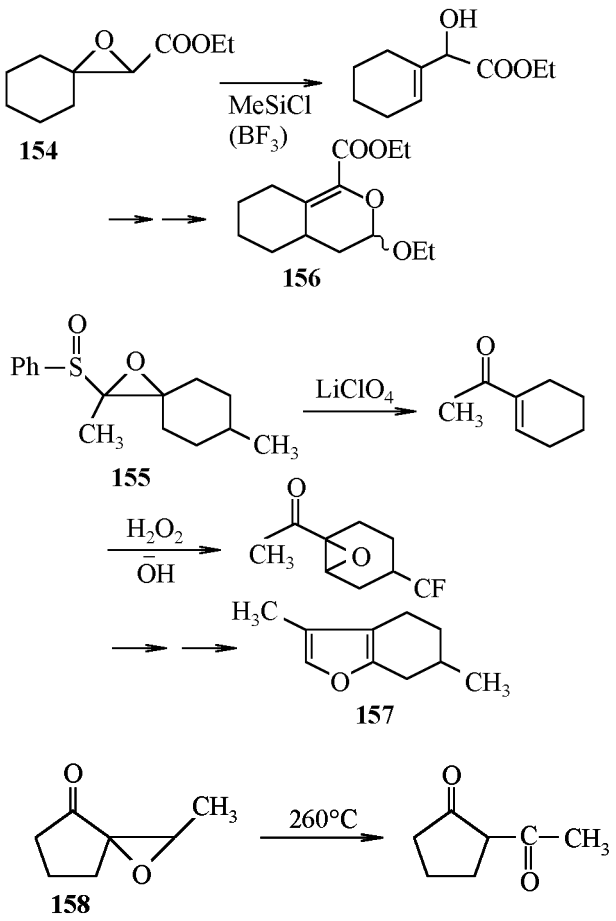


The ring opening in spirooxiranes carried out in acidic medium is often accompanied by isomerization, and frequently traditional products form in smaller amounts than isomerized compounds. This fact was confirmed in reaction of 1-oxadispiro-[2.1.2.2]nonane (**148**) with trifluoroacetic acid [172]. Alongside a mixture of hydroxytrifluoroacetates (**149a, b**) that afford glycol (**150**) on hydrolysis, arise also isomeric unsaturated alcohols (**151a, b**), aldehyde (**152**), and acetal (**153**).



The isomerization of spiroepoxides (**154, 155**) is the first stage of synthesis of valuable biologically active compounds **156, 157** [173, 174].

Under different conditions the epoxides can be transformed into carbonyl compounds, e.g., at thermal isomerization of epoxide **158** [175].



However the main catalysts of isomerization in such reactions are Lewis and proton acids. The most extensive studies were carried out with boron trifluoride and magnesium bromide [176–178]. The

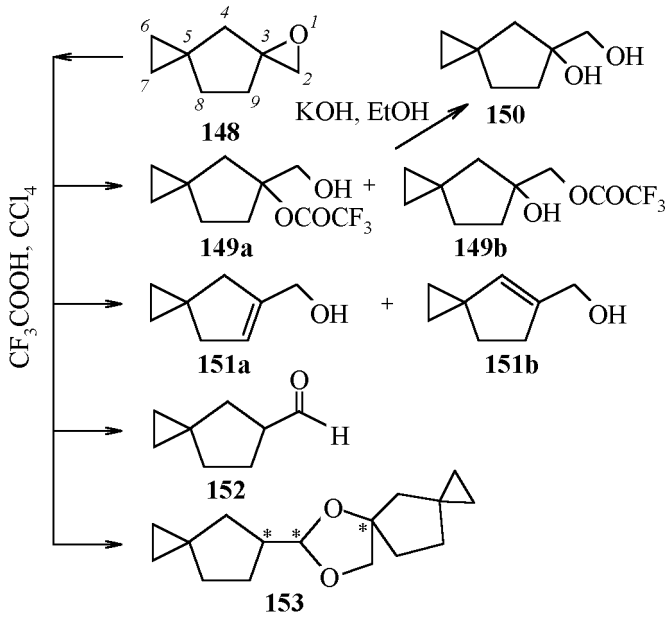
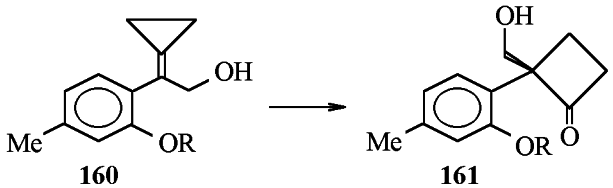


Table 7. Isomerization conditions and ratio of products obtained from 3,3-dimethyl-1-oxaspiro[2.2]pentane (**162**) [188]

Reaction medium (catalyst, solvent, 30°C)	Reaction time	Yield of compounds **163a** + **163b**, %	[**163a**]: [**163b**]
LiI, CH_2Cl_2	< 1 min	100	7.5
$LiClO_4$, CH_2Cl_2	24 h	83	10
LiBr, CH_2Cl_2	72 h	100	3.5
LiBr, CH_3NO_2	3 h	–	14
TsOLi, CH_3NO_2, 70°C	10 h	–	15
TsOH–H_2O, CH_2Cl_2	3 h	76	11
Decalin, 150°C	30 min	65	11

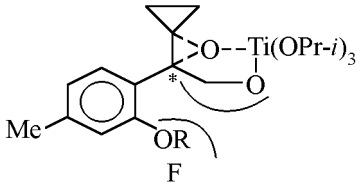
rearrangements were also observed in the presence of chlorides of zinc, titanium(IV), aluminum, of hydrochloric acid in ether, of hydrofluoric acid in acetonitrile, etc. Mono- and 1,1-disubstituted epoxides were mainly transformed into aldehydes; for 1,2-di- and trisubstituted epoxides was common formation of a mixture of carbonyl compounds [57]. The ease of epoxides isomerization in the course of epoxidation was many times described [27, 29. 179–182] for methylenecycloalkanes (**16**) and also for methylenecyclanes, e.g., camphene.

In [183] was described a tandem asymmetric epoxidation (according to Katzuki–Sharpless) followed by enantioselective opening of the epoxy ring affording finally chiral 1-alkyl(aryl)-1-(hydroxymethyl)cyclobutanes (**159**) in high yield and of high stereochemical purity. This group compounds turned out to be valuable initial substances for enantioselective synthesis of compounds with quaternary carbon centers. Proceeding therefrom were performed syntheses of both (+)- and (–)-α-cuparenones [183]. In [184] was analyzed the effect of a substituent in the *ortho*-position of benzene ring in compound (**160**) on the enantiomeric purity of the target product **161**.



160 **161**

The highest enantioselectivity (95%) at 98% yield was obtained in reaction of *tert*-butyl silyl ether as



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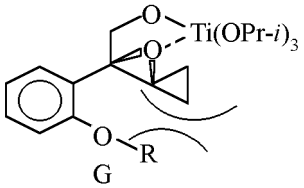

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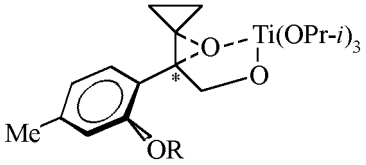

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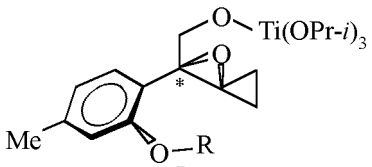


I

compared to the other ethers. The observed effect of substituents was attributed to steric hindrances arising between ether moiety (OR), hydroxymethyl and cyclopropyl groups in the assumed intermediates (F) or (G).

The minimal steric hindrances should apparently be expected in conformers (H, I).

An important factor of intermediate stability is the possible overlapping of π-electron system belonging to phenyl group with the positive charge of the chiral center; this stabilization is hampered in conformers (H, I); as a result a high enantioselectivity is observed in these reactions [184].

Individual epoxides of methylenecyclohexane and methylenecycloheptane isomerize into the corresponding aldehydes under the action of boron trifluoride and lithium perchlorate [176]. The isomerization of epoxymethylenecyclobutane (**2**) and epoxymethylenecyclopropane (**1**) was easily effected by lithium halides [185–188]; in the latter case was also used sodium methylate [189].

A similar behavior of 3,3-dimethyl-1-oxaspiro-[2.2]pentane (**162**) was shown in [188] where also

was demonstrated its isomerization at heating in decalin over 100°C. The ratio of isomeric reaction products (**163a, b**) obtained under different conditions is listed in Table 7.

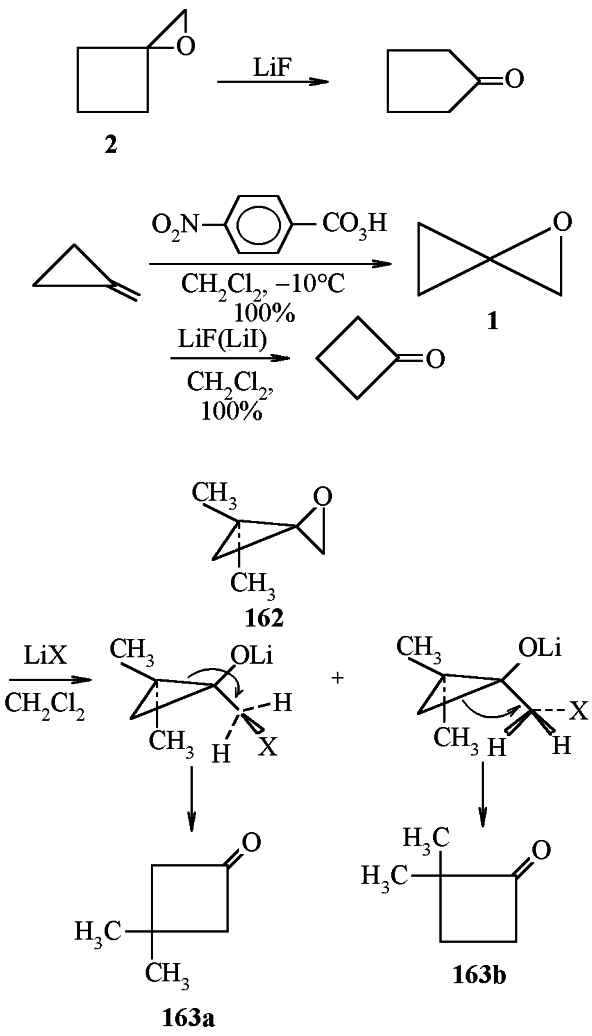


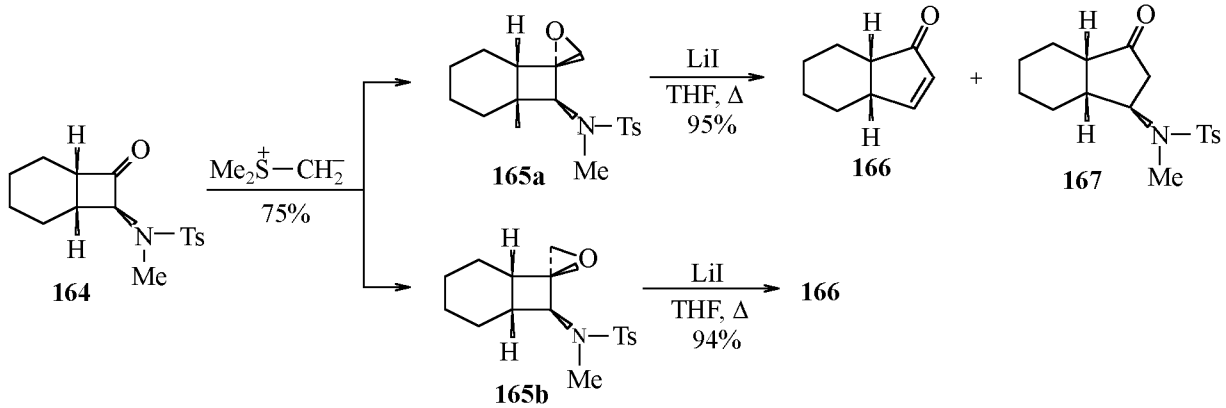
Table 8. Isomerization of epoxides **165`, b**) in boiling THF [190]

Catalyst	**165a**		**165b**	
	Yield, %	[**166**]: [**167**]	Yield, %	[**166**]: [**167**]
LiI	95	3 : 1	94	100:0
LiI, 12-Crown-4	0	–	0	–
$LiNTf_2$	0	–	0	–
LiBr	98	0:100	95	100:0

It is seen from Table 7 that predominantly occurred migration of quaternary center and not that of primary one. This fact may originate from many factors, among them from the value of positive charge on the migration center. The latter experiments show that the ratio of isomerization products remains constant disregarding dissimilar reaction conditions: in the presence of *p*-tolyenesulfonic acid, its lithium salt, and at thermolysis.

Note that in epoxide (**162**) isomerization the epoxide ring is cleaved prevailingly at the primary carbon atom even when the catalyst favors the S_N1-reaction. A similar regiospecificity is characteristic of reactions of oxaspiropentane (**1**) with lithium iodide, hydrogen chloride, methanol in the presence of perchloric acid [188].

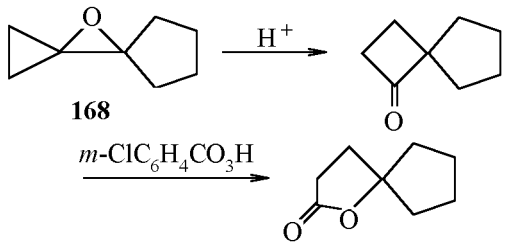
Recently was described [190] the isomerization of stereoisomeric spiroepoxides (**165a, b**) effected by lithium iodide.



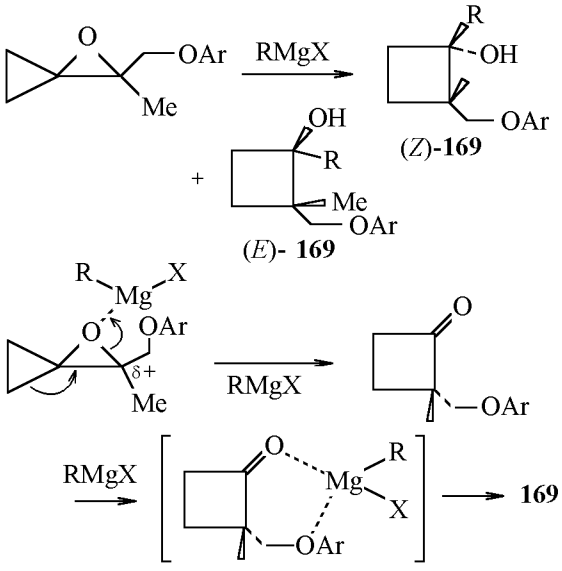
The expected isomerization product **167** of epoxide **165a** turned out to be the minor reaction product (the ratio [**166**]:[**167**] is 3:1); it was proved that compound **167** is not intermediate in formation of ketone **166**. The reaction of chiral initial cyclobutanone (**164**) gave rise of compounds 166 and 167 of 92% enantiomeric purity. The specific operation of catalysts is shown in Table 8.

The reaction mechanism was not studied; however, the reaction turned out to be characteristic of quite a number of epoxides **165** analogs [190].

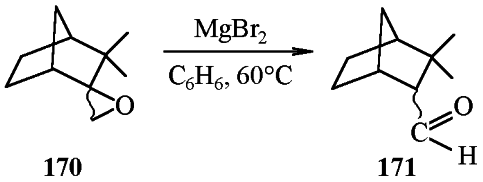
The presence in 9-oxadispiro[2.0.4.1]nonane (**168**) of a tertiary cyclopropyl fragment reduced its stability against acids; from the ketone arising in acidic media was easily obtained less strained butyrolactone [188].



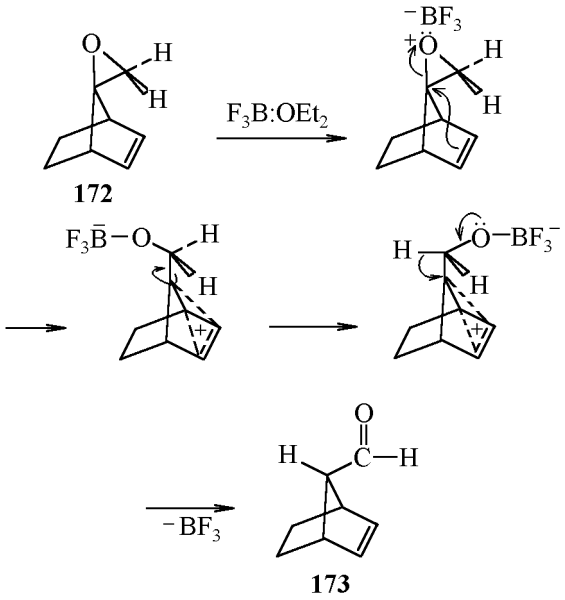
A similar isomerization apparently occurs in the first stage of reaction between oxaspiropentanes (Ar = *n*-$MeOC_6H_4$, C_6H_5) with Grignard reagents; the latter catalyze both key stages of the process [191].



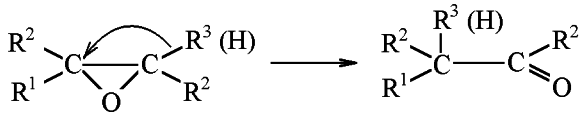
In some cases spirooxiranes treated with proton acids and Lewis acids transform into aldehydes: This kind of reaction is especially characteristic of various epoxymethylenenorbornanes. Thus the isomerization of camphene oxide (**17**) into 2-formyl-3,3-dimethylnorbornane (**171**) was successfully effected by magnesium bromide [192].



The reactions are significantly affected with a conformational factor. The rearrangement of epoxide of 7-methylenenorborn-2-ene (**172**) into 2-norbornene-7-*syn*-carbaldehyde (**173**) proceeds via an intermediate where the positive charge on a carbon atom is stabilized by delocalization of the π-electrons of the double bond followed by rotation of the migrating terminal group [6].



The key moment in the transformation of epoxides into carbonyl compounds (aldehydes and ketones) is the migration of a substituent in the molecule of the activated oxirane [57, 102, 193, 194].



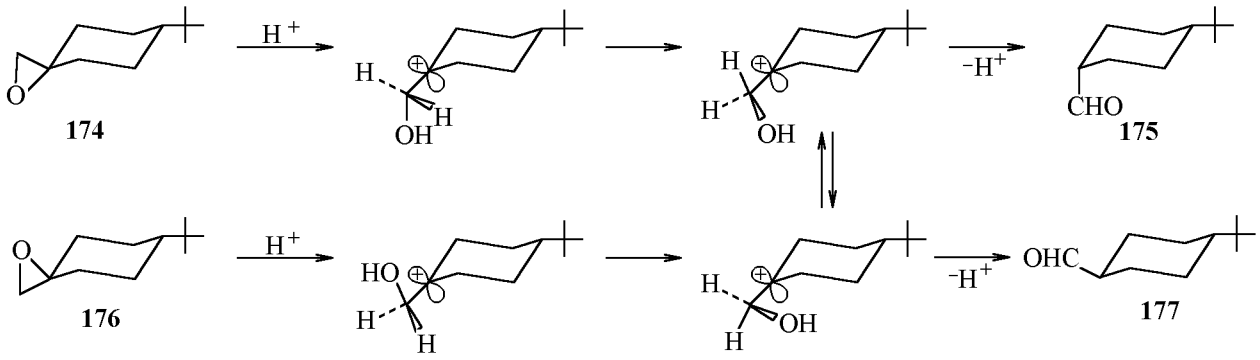
The shift ability of substituents decreases in the following order: aryl > acyl > H > ethyl > methyl. By an example of epoxides originating from several alkenes with no alicyclic fragments was established a

prochiral selection of hydrogen atoms in the course of spontaneous isomerization of epoxides into aldehydes [194].

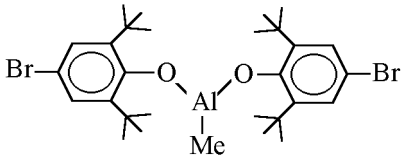
Although the epoxides rearrangements initiated by acids accompanied by hydride shift and alkyl and aryl groups migration were formerly regarded as concerted processes, the rearrangements of the spiroepoxides should be treated otherwise, as processes with stepwise mechanism having carbocations as intermediates.

Schematic representation of the rearrangement of epimeric spiroepoxides (**174, 176**) [195] shows that from epoxide (**174**) should preferably form aldehyde (**175**), and from epoxide (**176**) aldehyde (**177**). The conformation of molecules is fixed by introduction of a *tert*-butyl group as "conformational anchor". However since epoxide (**176**) affords alongside aldehyde (**177**) also compound **175** evidently exists a carbocation intermediate [196].

The asynchronous stages of propylene oxide rearrangement into propanal were confirmed by results of [195]. Quantum-chemical calculations ((MP 2/6-31G*//MP 2/6-31G*) revealed that after cleavage of the C–O bond in the protonated propylene oxide the shift underwent prevailingly the proton in *trans*-position with respect to the methyl group (20 : 1 as compared with the *cis*-proton).

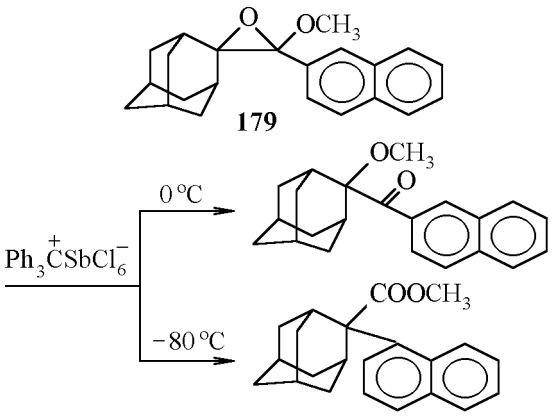


Alongside the common acids was developed an efficient catalytic system with an aluminum-containing reagent prepared in situ from trimethylaluminum and a bulky 4-bromo-2,6-di(*tert*-butyl)phenol [197].



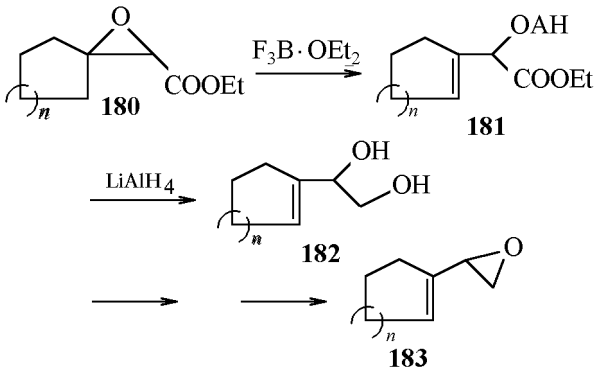
178

With the use of this catalyst the epoxycyclododecane was isomerized into cyclododecanecarbaldehyde in 58% yield. In some cases the epoxides isomerization is carried out as chain process initiated by one-electron oxidants. The reaction furnishes carbonyl compounds [198]. It was found that the isomerization direction of 3-methoxy-3-(naphthyl)spiro[oxiran-2,2'-adamantane] (**179**) is governed by the reaction temperature.

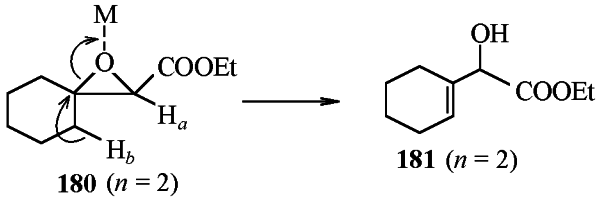


It is presumed that as a result of a one-electron transfer the epoxides give rise to cation-radicals that further suffer opening of the epoxide ring [198].

An alternative spiroepoxide isomerization affords allyl alcohols. This direction was observed as a side reaction in the hydrolysis [199] and methanolysis [68, 109] of epoxymethylenecyclohexane in the presence of sulfuric acid and at treating epoxymethylenecyclopentane with trifluoroacetic acid [172]. The apparent pathway of unsaturated alcohols formation consists in proton ejection from the α-position with respect to the reaction site in the intermediate stable tertiary carbocation [172]. Such reactions served as the starting point in the synthesis of vinylepoxides containing cyclopentane, cyclohexane, and cycloheptane fragments. The process included reduction of α-hydroxy-β,γ-unsaturated ethers (**181**) into vicinal diols (**182**) that were further transformed into epoxides (**183**) through tosilates [200].

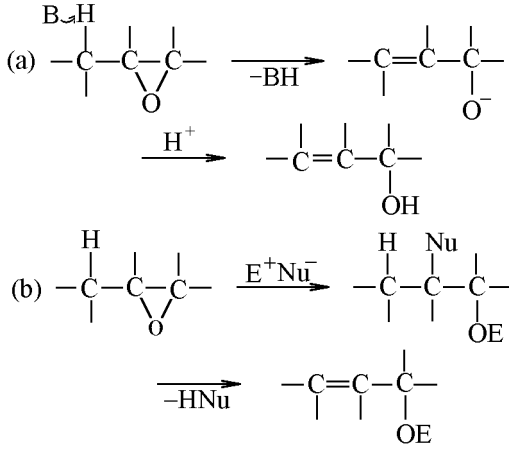


The isomerization of the mentioned glycide ethers (**180**) to afford α-hydroxy-β,γ-unsaturated ethers (**181**) succeeded with the use of naphthione-H, salt catalyst of acid type [201]. The isomerization occurs in dichloromethane at room temperature, although at slow rate; the optimum rate in this solvent is reached at boiling the reaction mixture. A similar regioselective isomerization is catalyzed by zeolite (H-ZSM5, Si/Al 35 : 1) [202].



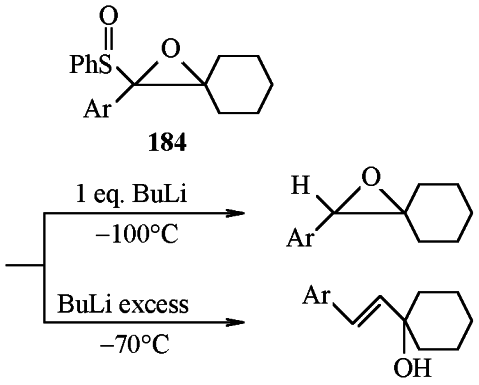
All described cases of glycidyl ethers isomerization were distinguished by lack of carbonyl compounds in the reaction products.

The epoxides rearrangements into allyl alcohols effected by strong bases were studied on epoxy derivatives of acyclic alkenes and epoxycycloalkanes [203–208]. The isomerization of epoxy compounds takes one of two possible routes: (a) Abstraction by bases of a proton in β-position with respect to epoxy ring

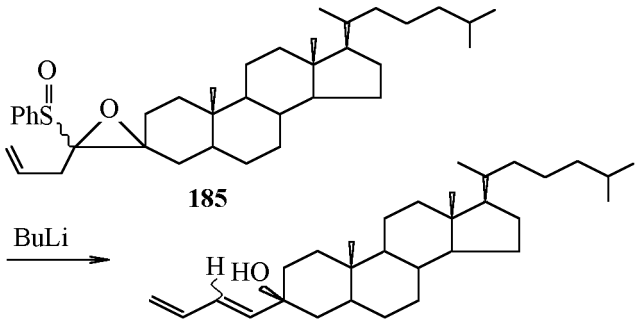


followed by the ring opening and transformation of the compound into allyl alkoxide; b) Opening of the epoxy ring by nucleophilic reagent to afford the addition product followed by elimination of HNu molecule, and hydrolysis of the olefin obtained yielding allyl alcohol [57].

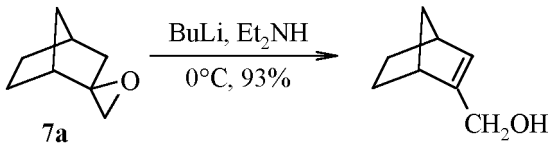
The transformation of spiroepoxides into allyl alcohols was performed with the use of various bases: butyllithium [209, 210], metal amides [58, 211, 212], diborane [213]. The reaction of butyllithium with α,β-epoxysulfoxides (**184**) proceeds in different way depending on the reaction conditions [209].



The reaction with one equiv of the base at −100°C results in the loss of sulfoxide moiety, with excess base at −70°C an isomerization of the intermediate epoxide into an allyl alcohol is observed. In a similar mode proceeds the reaction with a steroid epoxide (**185**).

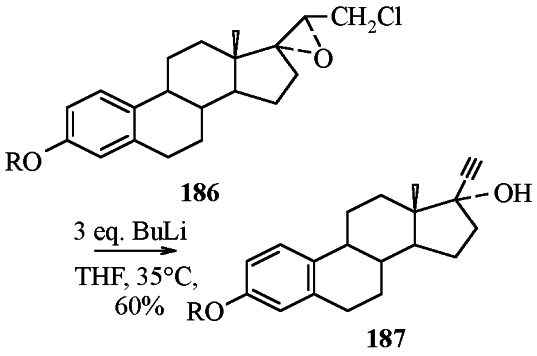


Alongside the above base were also tried methyllithium, *tert*-butyllithium, and ethylmagnesium bromide, and butyllithium was the most efficient isomerization reagent [209]. This base was used in an enantioselective synthesis of (1*S*,4*R*)-bicyclo[2.2.1]-

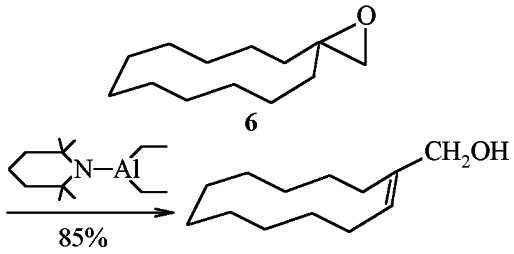


hept-2-enemethanol from an optically active spiroepoxide (**27a**) [210]

Recently by treating of halide (**186**) with excess butyllithium was prepared silylated 17-epiethynylestradiol (**187**) [214]. Double elimination afforded a triple bond.

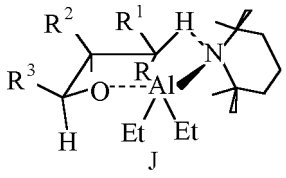


A reaction was described of epoxymethylenecyclododecane (**6**) with diethyl-2,2,6,6-tetramethylpiperidinodiethylaluminum and with the other organoaluminum amides [212, 215].

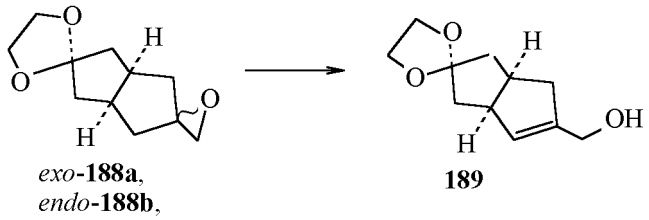


The investigation of bases action on isomerization of epoxide (6) revealed that the yield of allyl alcohols grew with basicity of the catalyst. The isomerizing efficiency of bases $RR'NAlEt_2$ increases in the following RR'N series: diethylamide (yield 5%) < dicyclohexylamide (36%) < diisopropylamide (45%) < tetramethylpiperidine (80%). The regioselectivity of isomerization effected by the above bases was studied by an example of nonsymmetrical epoxides. The ease of β-elimination of proton from epoxide decreases in the series: primary > secondary > tertiary.

The regioselectivity of isomerization depends also on the structure of catalyst. Very bulky bases, for instance, tetramethylpiperidinodiethylaluminum, play an important part in defining the stereospecific reaction path [212, 215]. It was established that preferably is eliminated the proton in *cis*-position with respect to epoxy ring when it is capable of considerable orbital overlapping with nitrogen of the base in the cyclic transition state (J) that occurs in the energetically favorable chair conformation.

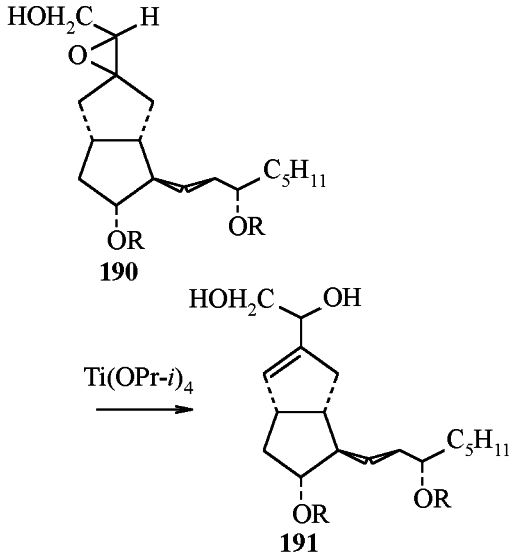


Enantioselective opening of epoxides (**188a, b**), derivatives of cis-bicyclo[3.3.0]octane-3,7-dione, is performed in the presence of chiral lithium amides [211].



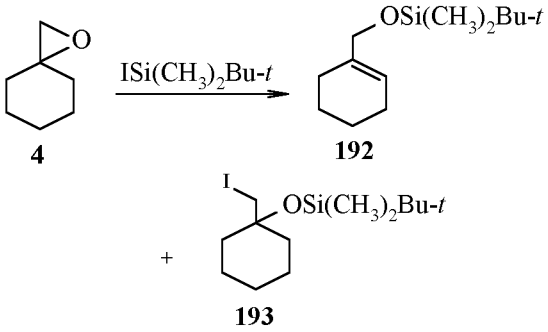
Chiral bases selectively react with exo-epoxide (**188a**), and the yield of the enantiomeric alcohol (**189**) amounts to 76%. At variation of solvent (THF, benzene, ether) was observed reversal of the enantioselectivity that was attributed to weakening of coordination bonds between lithium and nitrogen [211].

In the synthesis of 3-oxaisocarbacycline [216] was used the regioselective formation of allyl glycols (**191**) from spiroepoxyalcohols (**190**) under treatment with isopropyl orthotitanate.

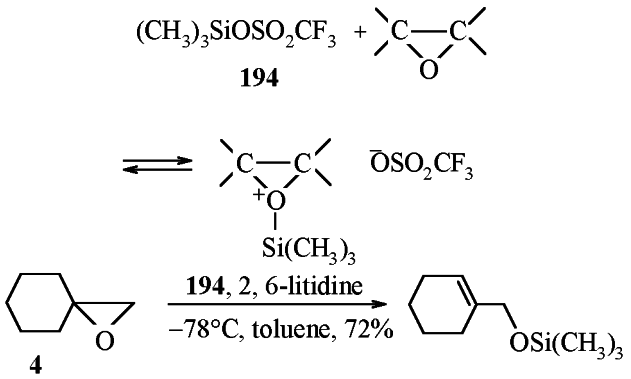


The ready isomerization was observed in the presence of organosilicon reagents [217–220]. This transformations were understood as *trans*-addition of the reagent to the epoxide followed by anti-elimination of the nucleophilic rest under the action of a base [220]. Among organosilicons were used trimethylsilyl chloride [219], silyl bromides, and silyl iodides [217]. The treatment of epoxide (**4**) with *tert*-butyldimethylsilyl iodide gives rise to a mixture of isomerization products **192** and adducts **193** [218].

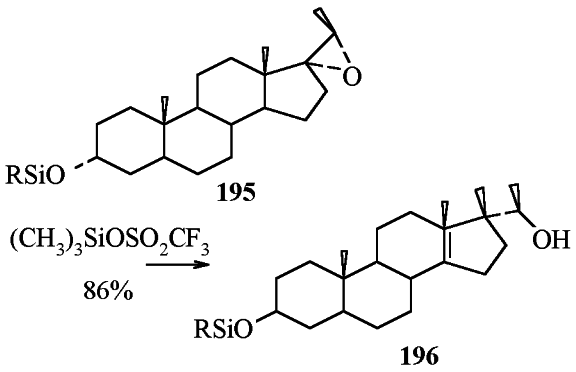
$$PhSeSi(Me)_2Bu\text{-}t + 1/2\ I_2 \rightarrow ISi(CH_3)_2Bu\text{-}t + 1/2\ PhSePh$$



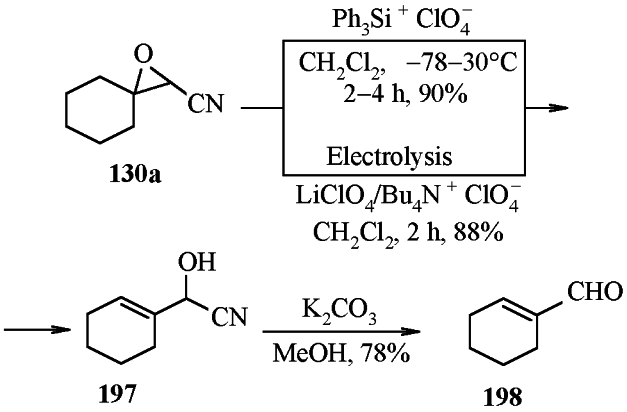
In reactions of oxiranes with trimethylsilyl trifluoromethenesulfonate (TMSOTf) (**194**) [220] was presumed preliminary formation of a strained oxonium ion favoring the reaction course to substituted allyl alcohols.



Murata *et al.* [220] pointed out the participation of a carbon-carbon σ-bond in reaction of steroid 17a,20-epoxide (**195**) that afforded unsaturated (but not allyl) alcohol (196). Here the expected reagent attack was prevented by the shielding effect of the neighboring methyl group. Instead the angular methyl group underwent 1,2-migration, and as a result formed a single rearrangement product **193**.

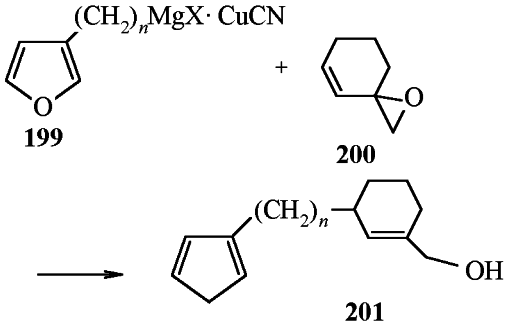


A selective isomerization of spirooxirane having a cyano group in the α-position (**130a**) occurred in high yield in the presence of triphenylsilyl perchlorate [221]. The resulting α-hydroxy-βγ-unsaturated nitrile (**197**) under alkaline hydrolysis readily affords aldehyde (**198**). The isomerization into nitrile (**197**) proceeded with as high yield under electrolysis conditions [221].

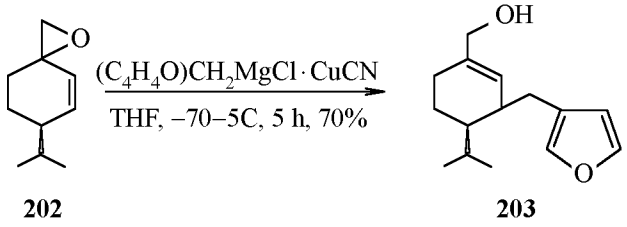


A special interest in the studies of spiro compounds reactivity attract reactions of vinyloxiranes with compounds containing magnesium, copper, and tin [117, 22–224]. In the latter case the overall yield of isomerization products attains only 25% [222], but the other investigations provide a possibility to value this method as very promising and important for understanding of stereochemical laws of organic reactions in general and of reactions with participation of unsaturated spirooxiranes in particular. These reactions are related to the reactions of organoelemental compounds with alkyl halides and the other electrophilic reagents. In such reactions with allyl electrophile the reaction can take either of two routes, namely direct S_N2 substitution or the so-called S_N2'-attack on the double bond resulting in the allyl alcohol. The addition of various Grignard reagents (**199**, n = 1–3, X = Cl, Br) as complexes with copper cyanide to the simplest spirovinylepoxide

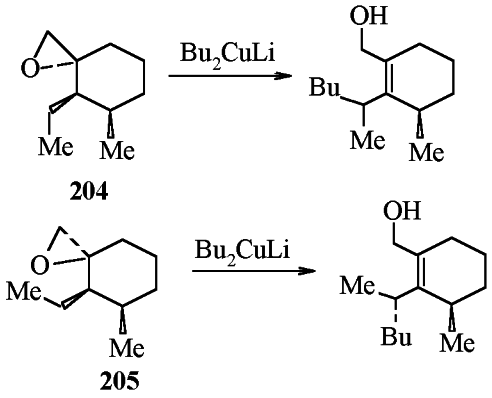
(**200**) led to its regioselective rearrangement into allyl alcohols (**201**) in a plausible yield [224].



Later this procedure was used with epoxide (**202**) [117] in attempt to synthesize an unsaturated carbinol of complicated structure (**203**).

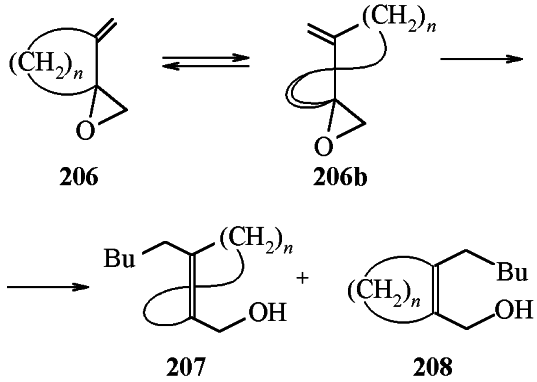


Important stereochemical laws on isomerization of spirovinylepoxides with exocyclic double bonds were derived by Ziegler and Cady [225], and also in the studies of Marshall *et al*. on the synthesis of [*a*,*b*]-



betweenanenes [226–229]. In [223] was performed comprehensive and detailed analysis of factors governing the stereochemical features of organocuprates addition to various vinyloxiranes, also to spiroepoxide systems (**204, 205**, R = Me, Bu) and (**206**, $n = 8–14$). The stereochemistry of dialkylcuprates (Me_2CuLi, Bu_2CuLi) addition to alkylidenepoxides (**204, 205**) is governed by sterical hindrances arising at formation of prevailing products of syn or anti-S_N2'-addition [225].

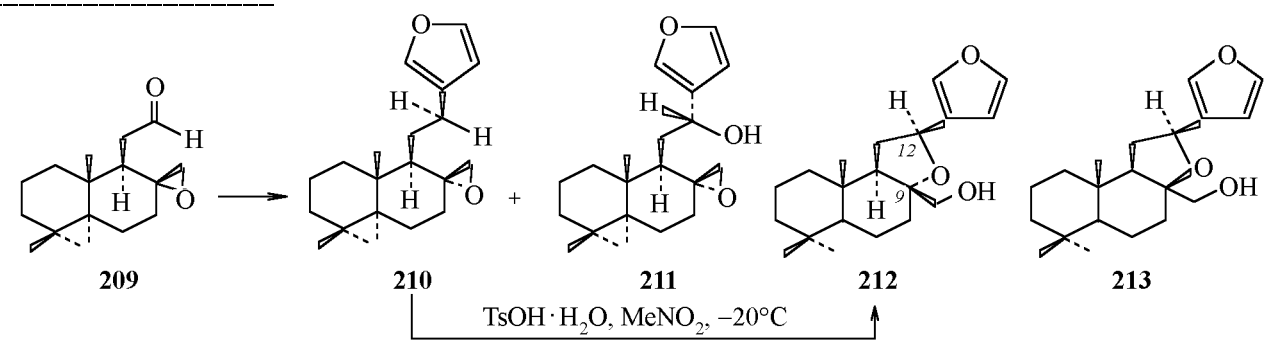
The addition of cuprates [BuMgBr–CuI–Me_2S, Bu_2CuLi, BuCu(CN)Li] to vinyloxiranes (**206a, b**) also proceeds stereoselectively due to the high content of *s-trans*-conformers of epoxides (206b) in the transition state of the reaction. The fraction of *trans*-isomers of allyl alcohols in the (**207** + **208**) mixture amounted to 85–95% [223].



VIII. FORMATION OF NEW CYCLIC SYSTEMS PROCEEDING FROM SPIROOXIRANES

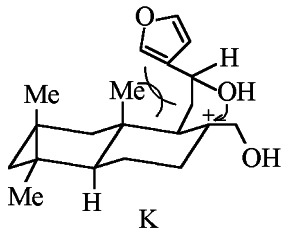
Within the last two decades were published interesting syntheses of new cyclic systems generated from epoxy compounds, in particular, from spirooxiranes. These are mostly oxygen-containing heterocycles including one or several oxygen atoms [92, 230–235], and also other atoms [236, 237].

In some cases the prepared polycyclic systems are intimately linked with the natural substances, e.g.,

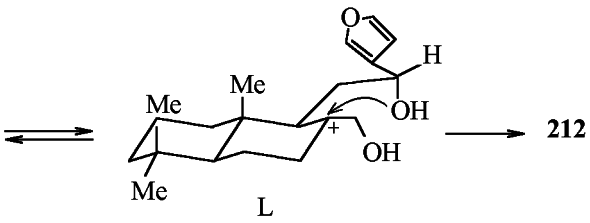


acuminolide and derivatives of this diterpenoid that possess cytotoxic activity and are highly active against melanoma and prostatitis [238]. At treating epoxyaldehyde (**209**) with 3-furyllithium occurred chemoselective transformation only of the aldehyde group to afford (12*S*)- and (12*R*)-isomeric alcohols (**210, 211**) in 45 and 32% yield respectively. The dissimilar spatial arrangement of the compounds was decisive for the acid-catalyzed cyclization. One of epoxides (**210**) was in high yield transformed into cyclization product (**212**) (90%), and presumed isomer (**213**) was not obtained.

This fact was rationalized by conformational analysis of carbocation intermediates (K, L). One among the latter is close in structure to the intermediate state of heterocyclization. The sterical (conformational) factor in the transformation of epoxide (**211**) was also very important [238].

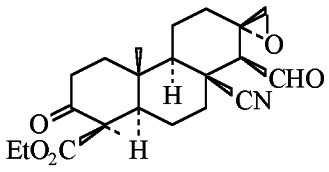


K



L

Recently complicated syntheses were carried out in the field of biologically active tetracyclic diterpenes related to spongiatriol, epispongiatriol, and diosphenol [239]. As in the preceding synthesis the key stage was heterocyclization of spirooxiranes, but



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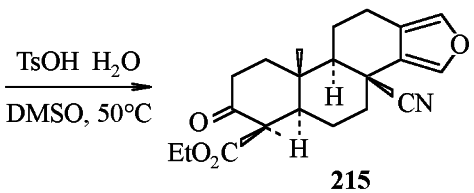
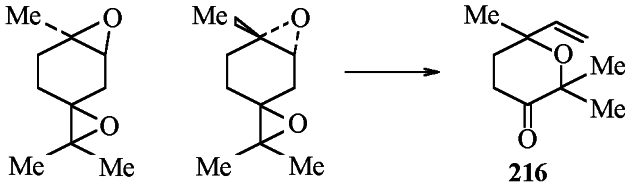


215

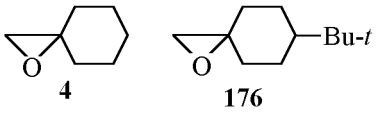
here basing on oxirane (**214**) was built up an aromatic furan fragment of compound **215**.

An uncommon behavior was observed at boiling one of terpinolene diepoxides (**51b**) in toluene in the presence of alumina under nitrogen atmosphere [92]. At subsequent chromatography pyranone (**216**) was isolated. Under similar conditions diepoxide (**51a**) remains intact, also when the boiling is performed with the mixture of diepoxides under the same conditions.

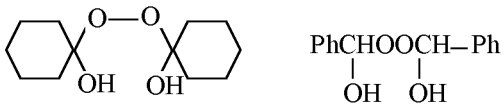


51a **51b** **216**

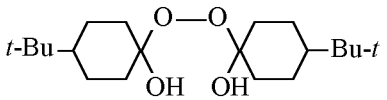
The reaction of spiroepoxides (**4, 176**) with peroxides (**217, 219**) in the presence of vanadium trioxide and catalytic amounts of chlorosulfonic acid afforded 1,2,4-trioxanes in 17–42% yield, in particular compounds **220, 221** [230].



4 **176**



218 **217**



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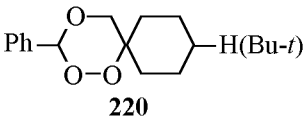

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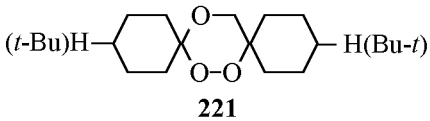
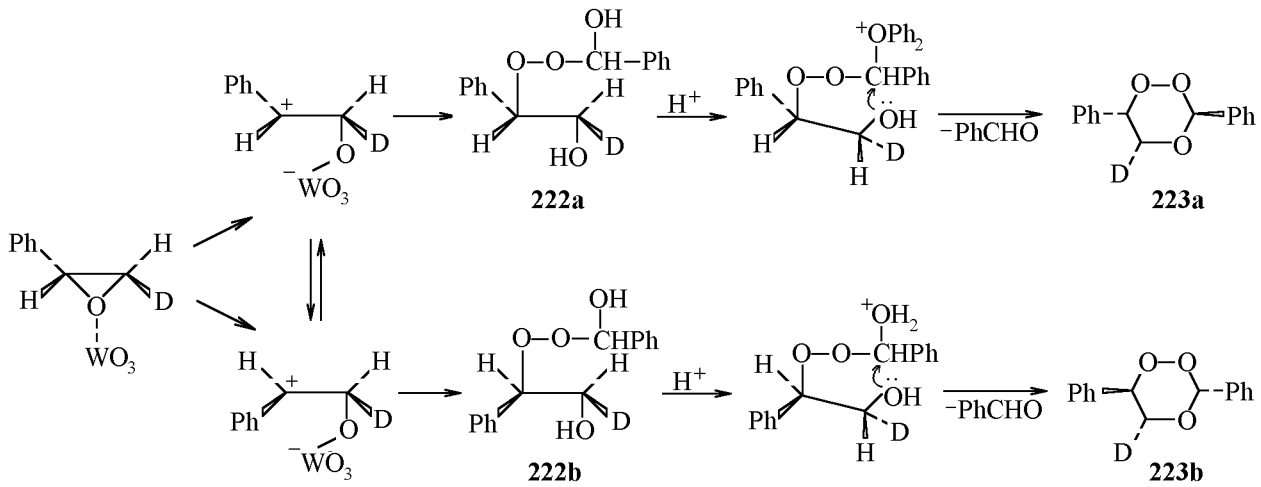


221

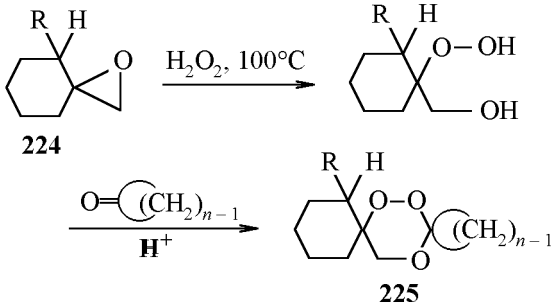
The course of reaction was studied in detail by an example of styrene oxide and peroxide **217**. Hydroperoxide **222a, b** was isolated as intermediate, and its subsequent cyclization under treatment with the



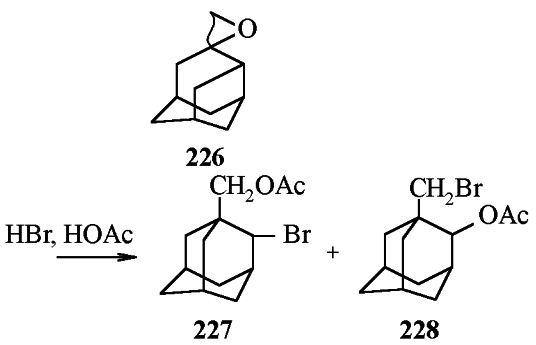
catalyst furnished 1,2,4-trioxane (**223a, b**) in quantitative yield.

Reactions of 1,2,4-trioxanes with various nucleophilic reagents (triethylamine, sodium ethoxide, lithium diisopropylamide, lithium aluminum hydride, Grignard reagents, triphenylphosphine, etc.) was studied in [230].

Similar polyciclic systems (**225**) possessing antimalarial activity were prepared later by reaction of spiroepoxides (**224**) with hydrogen peroxide followed by treating with carbonyl compounds [231].

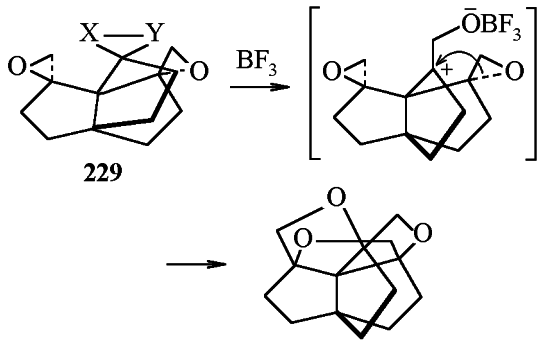


"Abnormal" opening of the epoxy ring in spiroepoxide (**226**) activated by aluminum bromide addition results in formation of adamantylcarbinol due to 1,2-alkyl shift [240]. Later in acetic acid medium from a mixture of stereoisomeric epoxides **226** (*exo*:*endo* 3:2) was obtained a mixture of bromoacetates (4:1) with prevailing 1-acetoxymethyl-2-bromoadamantane (**227**) [157].



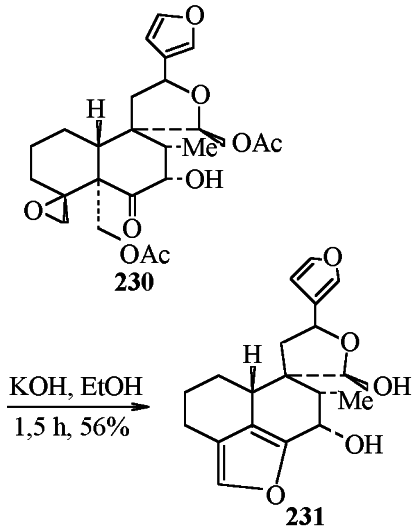
A very interesting triple transannular cyclization of spirooxirane (**229**) into a heterocyclic C_{17} hexaquinane was carried out by two research groups, Paquette and Vazeux [235], and Simmons and Maggio [241]. According to [235] triepoxide (**229**) prepared by treating 2,8,9-trimethylene[3.3.3]propellane with *m*-$ClC_6H_4CO_3H$ (0°C, 24 h) exists as two isomers (nonsymmetrical and symmetrical, 50:50; X = CH_2, Y = O; X = O, Y = CH_2). In [241] their separation was performed by GLC.

The heterocyclization of compound **229** was effected ether with boron trifluoride [235] or by protonation and heating of the triepoxide [241].



The transformation of spirooxiranes into derivatives of furan, pyran etc. was described also in other publications. In particular, conversion of eriocephalin (**230**), a natural diterpenoid from clerodane series, under the treatment of alcoholic potassium hydroxide

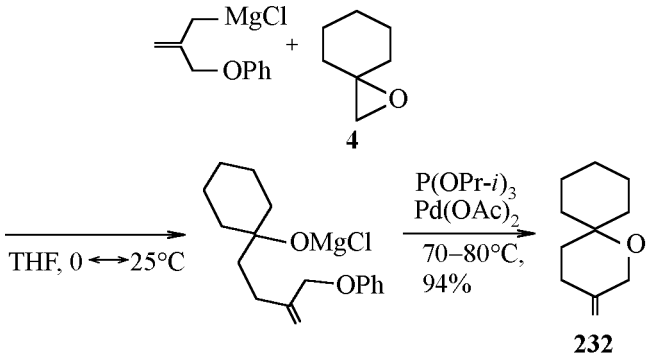
solution furnished compound **231** with two furan and one tetrahydrofuran fragments [242].



230 **231**

Similar transformations of alicyclic epoxides under action of bases were described in [233].

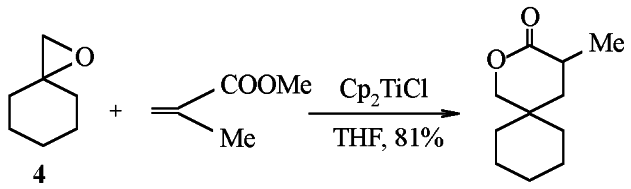
Methylenetetrahydropyran (**232**) was obtained by a single catalytic process from epoxy derivative of methylenecyclohexane and 2-(phenoxymethyl)-2-propenylmagnesium chloride [243].



4 **232**

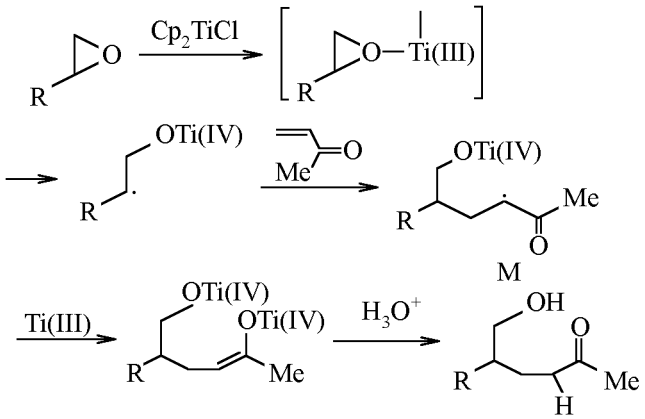
The first (and main) stage of the process consists in alkylation of the epoxide with organomagnesium compound; the epoxy ring opens in conformity to Krasusky rule. A catalytic quantity of palladium and additional heating facilitates cyclization of the intermediate.

New carbon-carbon bonds and oxygen-containing heterocycles form at addition of spiroepoxide (**4**) to activated olefin (methyl methacrylate) in the presence of titanium catalysts [232].

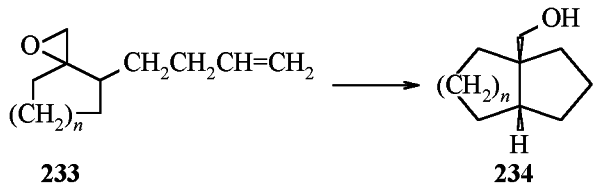


4

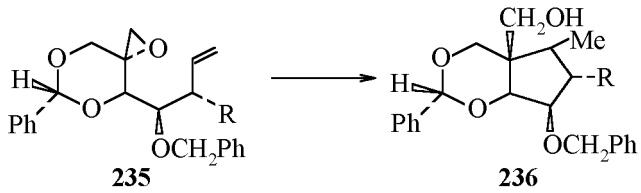
Reaction started as homolysis of C–O bond of the epoxy ring; therewith the carbon radical reacted with methyl methacrylate, and H-radical preferred to react with the second equiv of titanium catalyst than with the second olefin molecule.



The reaction turned out to be a convenient procedure for functionalization of various epoxides [232]. In the later study performing by the same Subbaraju group was shown that at the presence of an alkenyl fragment in the radical occurred a fast (10^{-5} s) cyclization originating from intramolecular addition to a double bond and affording cycloalkyl fragments and further cycloalkylmethanols. Thus 1-oxaspiroalkanes (**233**, $n = 1$, 2) cyclize into derivatives of bicycloalkanes (**234**), and spirotrioxanes (**235**) yield compounds **236**.



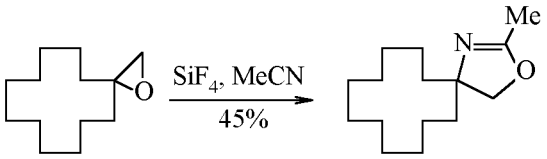
233 **234**



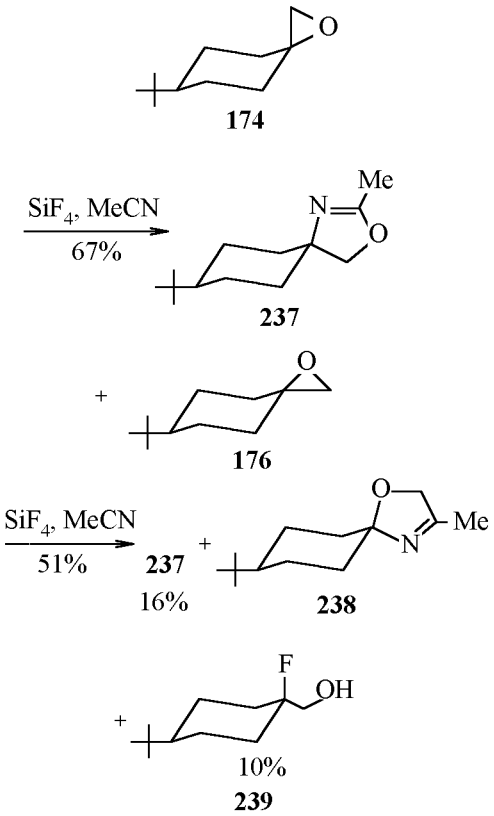
235 **236**

The formation of nitrogen-containing heterocycles from spiroepoxides is poorly studied. As an example can be cited 2-oxazolines formation in reaction of oxiranes with acetonitrile promoted by silicon tetrafluoride [237]. It was stated that the fluoride efficient-

ly played the role of Lewis acid and that it was able to activate epoxides of different types. The reaction mechanism was not investigated but presumably the catalyst facilitated the regiospecific cleavage of the epoxy ring to produce a carbocation that further attacked the nitrogen as the nucleophilic center of nitrile molecule.

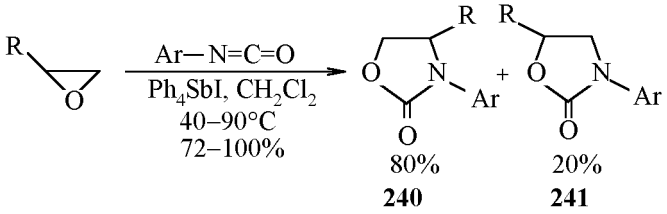


The reaction stereochemistry was studied by the example of 4-*tert*-butylcyclohexane derivatives (**174, 176**) [237].

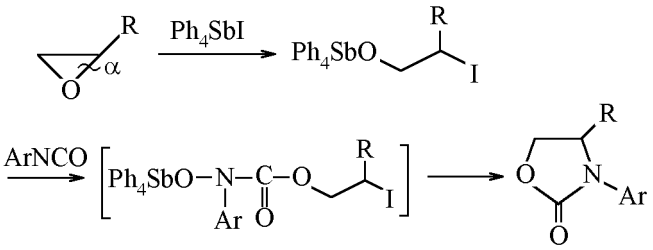


The composition of conversion products **237–239** evidence that the S_N1-process is hampered in **176** stereoisomer apparently due to increased torsional strain at an equatorial attack [237].

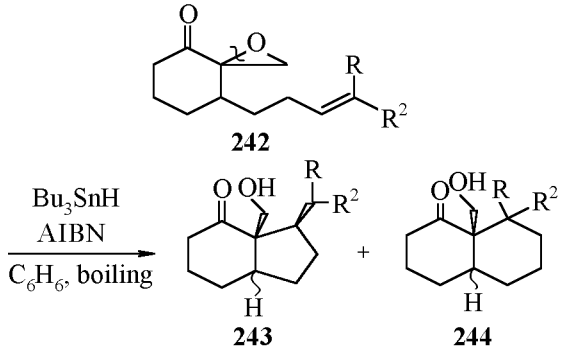
Oxazolidines **240, 241** are conveniently prepared by cycloaddition of oxiranes to heterocumulenes (aryl isocyanates) catalyzed by tetraphenylstibonium iodide [236].



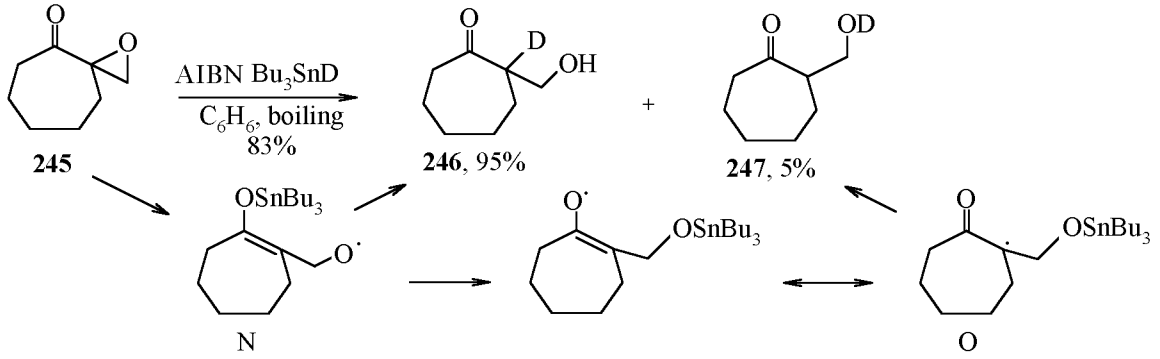
It was established that in the first stage of the process opened the α-bond of the oxirane. The isomer ratio in the products is apparently governed by the ratio of the arising intermediates. The assumed reaction mechanism [236] includes three stages: epoxy ring opening, heterocumulene insertion, and intramolecular cyclization of the forming tetraphenylstibonium carbamates.



In nineteen nineties Kim *et al*. investigated transformations of spirooxiranes containing in α-position carbonyl [245] and methylene [246] groups. Under conditions of radical process [initiated by 3,3-azabis-(2-methylpropionitrile)] (AIBN) in the presence of tributyltin hydride epoxide (**242**) underwent an intramolecular cyclization affording two bicyclic ketones (**243, 244**) in a ratio depending on the substrate structure [245]. Both products are formed with the rupture of the α carbon-oxygen bond in the oxirane (**242**). At R = H the yield of ketones **243** and **244** was respectively 31 and 9%, at R = Me 26 and 15%.

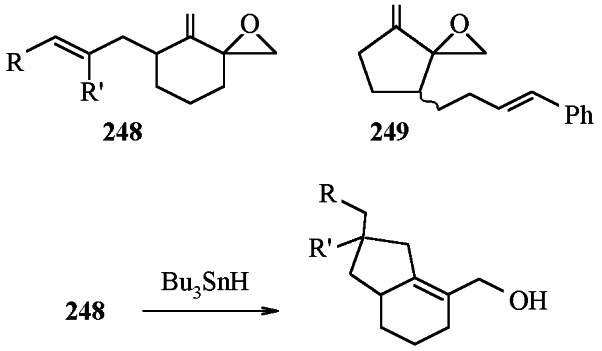


Oxaspiro]2.6]nonanone (**245**) under similar conditions also afforded in 95% yield alcohol (**246**) through cleavage of the C–O bond in the epoxy ring neighboring to carbonyl group.

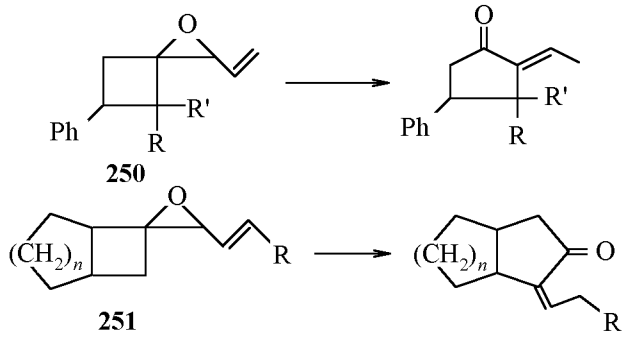


Kim *et al.* [245] think that the above radical cyclization of epoxides is initiated by addition of Bu_3Sn^- radical followed by fragmentation of epoxide to (N) radical. The latter is converted into radical (O) by 1,5-shift of a hydrogen or of the organometallic fragment, and the latter radical affords the isomeric alcohol (**247**).

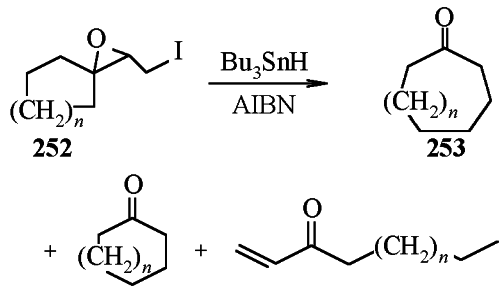
Analogously react vinylepoxides (**248, 240**) that in reaction with tributyltin hydride undergo a regioselective intramolecular cyclization preceded with 1,5-shift of the organometallic moiety [246].



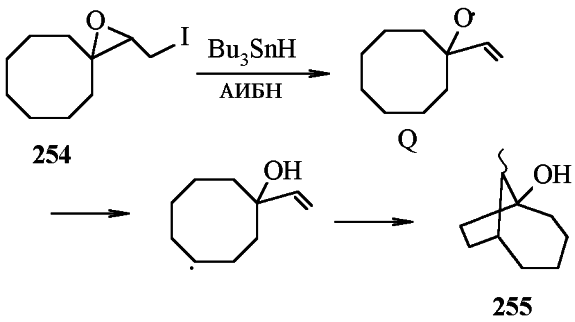
Kim *et al.* also carried out cycle expansion in vinylspirooxiranes (**250**, R,R' = H, Me; **251**, R = H, Me, n = 1, 2) in the presence of 4-nitrophenol and $Pd(PPh_3)_4$ as catalyst [247].



The transformations of iodine-containing spirooxiranes (**252**, n = 1–3, 8) in a radical reaction with tributyltin hydride are very numerous [248].



In the most cases the main product was ketone **253**, and only in reaction of 8-membered spiroepoxide **254** the 1,5-hydride shift in the intermediate (P) led to bicyclic reaction product **255**.



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