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Cationic molecular rearrangements of natural terpene compounds in superacidic media: reality and predictions

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Abstract. The main factors affecting the pathways of multistep cationic molecular rearrangements of natural terpenes and their analogues are considered. Methods for predicting the most probable pathways of cationic rearrangements are proposed. The bibliography includes 85 references.

I. Introduction

Carbocationic reactions play a prominent role in molecular rearrangements of organic compounds. The regularities of these reactions are most efficiently studied by modelling methods based on 'direct visualisation' of ion conversions in hypernon-nucleophilic superacidic media at superlow temperatures. Specially synthesised simple organic compounds are normally used as subjects for the investigation. The use of this approach in a particular field of organic chemistry in which cationic molecular rearrangements play a central role (*e.g.*, terpene chemistry) seems to be highly efficient. The study of regularities of carbocationic reactions of terpenoids and their analogues pursues three main goals:

1. Elucidation of regularities of molecular rearrangements of complex polycyclic cations.

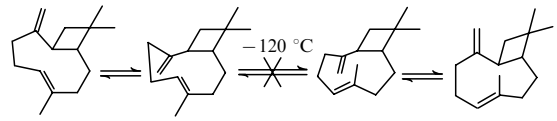
2. Broadening of the range of available natural compounds suitable for the preparation of novel substances.

3. Chemical proof of validity of biogenetic schemes.

II. Conformational control of reactions

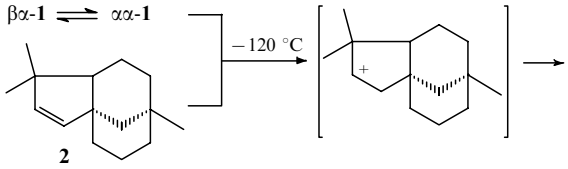
Polyfunctionality and conformational mobility are the most characteristic features of terpenes. Studies of conformational mobility and its effect on the reactivity of terpenes at low temperatures have generated an entirely new field of research, *viz.,* the chemistry of conformationally controlled carbocationic reactions. In synthetic organic chemistry, conformational control is usually restricted to deamination of aliphatic amines and related compounds, but it plays a prominent role in biogenetic reactions of carbocationic cyclisation. The discovery of conformationally controlled reactions of stable ions derived from terpenes at low temperatures has made it possible to fill the gap between the biogenetic and chemical processes and provided a way for experimental realisation of biogenetic reactions.

Conformational control can be manifested both in initial steps of reactions and in subsequent transformations of the intermediate carbocations. The former can be exemplified in rearrangements of a sesquiterpene diene, *viz*., caryophyllene (**1**). According to ^{13}C NMR spectral data, which are consistent with the molecular mechanics (MM2) calculations, compound **1** may exist in four stable conformations, *viz*., βα, αα, αβ and ββ.[1,2]



	βα-**1**	αα-**1**	αβ-**1**	ββ-**1**
ΔH_f° (MM2), /kcal mol^{-1}	12.6	14.2	17.3	12.4
Content (MM2) (%)	39	3	0	58

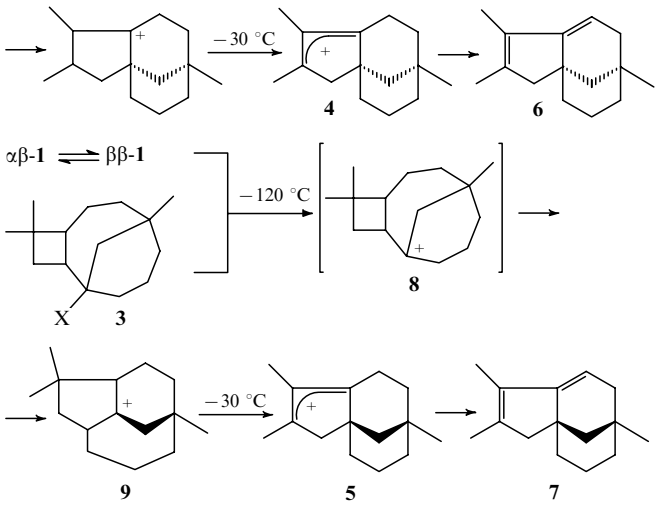
The experimental barrier to the transition between the pairs βα ⇄ αα and αβ ⇄ ββ (16.25 kcal mol^{-1}) cannot be virtually overcome at temperatures employed for the ion generation (HSO_3F-SO_2FCl, from −120 to −100 °C). Indeed, the ratio of reaction pathways of two conformers, *viz*., αα and ββ, the transannular cyclisation of which gives radically different intermediate carbocations and different reaction products, correlates with the ratio of the above conformers.



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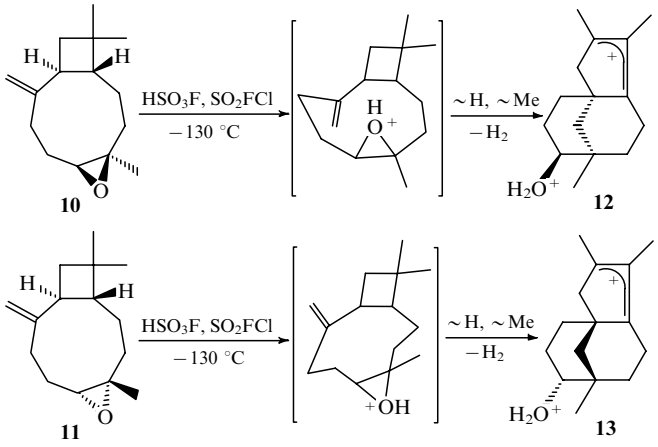
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Heating of the diene **1** in HSO_3F-SO_2FCl to −30 °C and its subsequent neutralisation yield a mixture of enantiomeric dienes **6** and **7** in which the diene **6** with a clovane backbone [judging from optical rotation dispersion (ORD) curves)] is predominant. The reaction proceeds *via* the intermediate allylic ions **4** and **5**. The ratio of dienes **6** and **7** corresponds to the ratio of the conformers βα-**1** and ββ-**1** in SO_2FCl at −120 °C.

The stable ions derived from conformers αα and ββ can be generated separately from clovene **2** and 1-substituted caryolanes **3** *via* ions **8** and **9**.

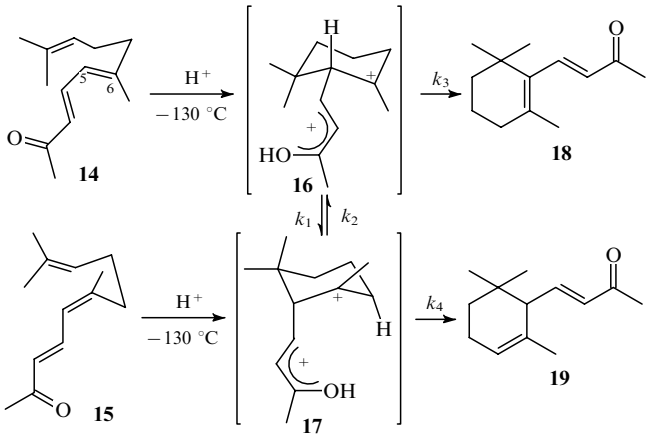
The conformational control can be effected after the carbocation has been formed and be manifested in different ways. The conformationally controlled molecular rearrangements of 4β,5β- (**10**) and 4α,5α-epoxides (**11**) of isocaryophyllene in superacids occur enantioselectively and result in the formation of the enantiomeric carbocations **12** and **13** from an epimeric pair of epoxides.[3]



Presumably, such enantioselective rearrangements take place when the opening of the epimeric monoepoxides generated from an optically active and conformationally flexible cyclic polyene occurs in acidic media with the participation of σ- and π-bonds. The direction of skeletal shifts is determined by the spatial structure of the epoxide. The optically active diene ultimately gives two enantiomeric products without recourse to any optically active reagents, *i.e.,* 'partial asymmetric synthesis' takes place.

The reaction which is controlled by the conformation of the intermediate carbocation may proceed in a structurally selective manner, as is the case with the low-temperature cyclisation of *trans*-5,6- (**14**) and *cis*-5,6-φ-ionones (**15**) in a superacidic medium. It was reported previously[4,5] that the structural direction of cyclisation of isoprenoids containing a conjugated 5,6-double bond does not depend on its configuration. This was explained by decreased nucleophilicity of the double bond as a result of conjugation and, ultimately, a decrease in the cyclisation rate.

More recent studies have shown[6] that protonation of the ketones **14** and **15** in HSO_3F-SO_2FCl at −130 °C yields con-formers **16** and **17** of the same dication. Quenching of an acidic solution of the conformer **16** leads to elimination of the axial proton from the tertiary carbon atom linked with the side chain to give β-ionone (**18**). The conformer **17** eliminates the axial proton from the secondary carbon atom of the ring (in conformity with the ionic elimination rules) and is converted into α-ionone (**19**).



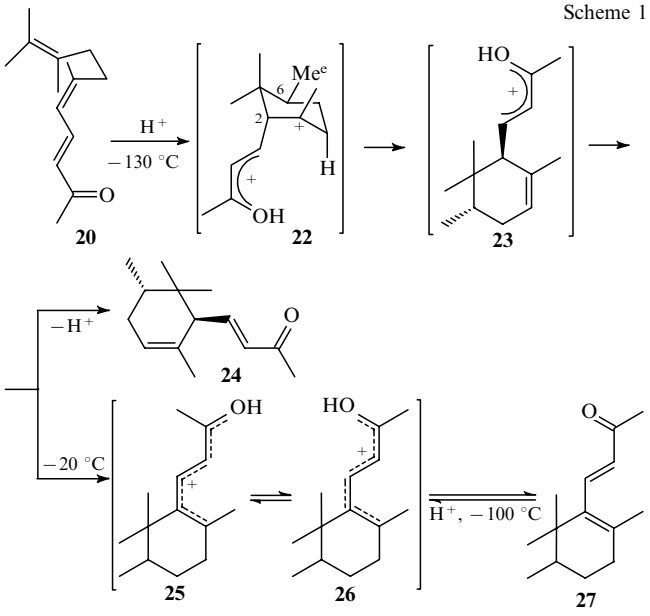
$k_3, k_4 > k_1, k_2$

Thus, in this case the conformational stability of intermediate monocyclic carbocations at low temperatures ensures conformational control and, as a result, the structural selectivity of the rearrangement.

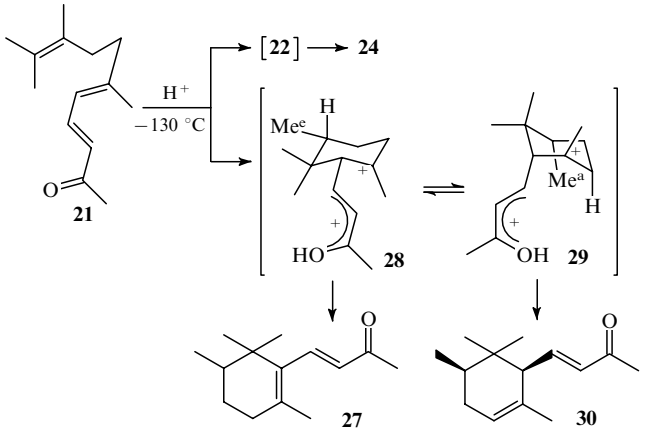
A more complex situation is observed in the protonation of *cis*- (**20**) and *trans*-φ-irones (**21**).[7]

Protonation of the ketone **20** in HSO_3F-SO_2FCl (−130 °C) gives the dication **22** in which the methyl group at C(6) is in the *trans*-position relative to the side chain at C(2). The elimination of the axial proton from the secondary carbon atom in the dication **22** is accompanied by its conversion into the 'apparent' ion **22**; 'quenching' of the latter gives *trans*-α-irone (**24**). Heating of an acidic solution of the ion **23** to −20 °C results in pentadienyl ions **25** and **26**; their 'quenching' yields β-irone (**27**). Protonation of the latter at −100 °C gives a mixture of ions **25** and **26**. It is noteworthy that the ion **23** is not generated in the temperature range from −100 to −10 °C. Structurally selective and stereoselective transformation of the ketone **20** in HSO_3F-SO_2FCl is probably due to the lack of conformational transitions at −130 °C (Scheme 1).

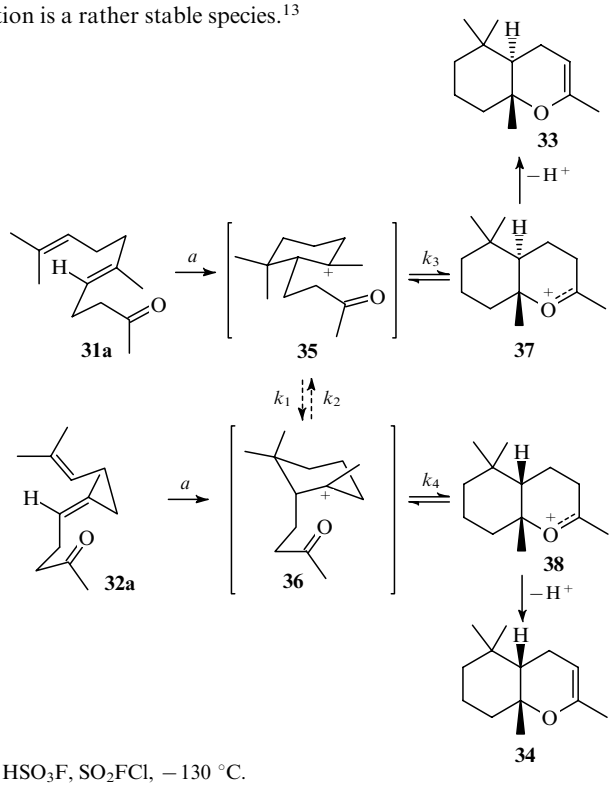
Scheme 1



The transformation of the *trans*-isomer **21** in HSO_3F-SO_2FCl occurs differently. At −130 °C, it gives a mixture of dications **22** and **28**. The latter exists as a mixture with the dication **29** due to conformational transitions of the *chair* ⇄ *chair* type. 'Quenching' of the reaction mixture gives ketones **24** and **27** and *cis*-α-irone (**30**).

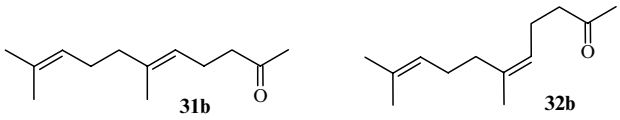


Generation of an ion, which exists in two different conformations that are more rapidly stabilised by intramolecular interactions than by interconversions, from different conformational isomers is yet another typical example of conformational control. However, in contrast with the above examples, this process ensures not only structural selectivity but also stereospecificity of cyclisation reactions. Thus the cyclisation of *trans*- (**31**) and *cis*-geranylacetone (**32**) in 100% sulfuric or fluorosulfonic acids is stereospecific and yields *trans*- (**33**) and *cis*-chromenes (**34**), respectively.[8,9] It has been suggested [10–12] that the stereospecificity of cyclisation of dienones **31** and **32** is due to the formation of stable conformers **35** and **36**. However, it has been found [6] that monocyclic ions **35** and **36** were not detected in the NMR spectra after dissolution of dienones **31** and **32** in HSO_3F-SO_2FCl even at −120 °C because of their rapid cyclisation into carboxonium ions **37** and **38**. It should be noted that the methylcyclohexyl cation is a rather stable species.[13]



(*a*) HSO_3F, SO_2FCl, −130 °C.

^1H and ^{13}C NMR spectral data point to the formation of carboxonium ions **37** and **38**, which have not been considered previously at all as intermediates in the cyclisation of dienones **31** and **32** into chromenes **33** and **34**.[10–12] Presumably, the stereospecificity of these reactions is determined not by the conformational stability of monocyclic ions **35** and **36** as such, but rather by the ratio of rate constants of their conformational transitions as well as by the ratio of rate constants for the formation of bicyclic ions (k_3, $k_4 \gg k_1$, k_2).[6] In this case, we are dealing with conformational control, since the ratio of the reaction products is approximately the same as the conformer ratio.[14] The formation of conformationally isomeric monocyclic ions **35** and **36** from dienones **31** and **32** seems to be due to the fact that they react in the most stable conformations **31a** and **32a**.[10] This conclusion is confirmed by the strain energies (E) of the conformations of dienones **31** and **32** calculated by the molecular mechanics method using parametrisation described in Ref. 15. It was found [6] that the majority of geranylacetone atoms in conformations **31a** and **32a** fall into the attraction field of non-valent (van-der-Waals) interactions. Therefore, the energies of these conformations are by 6–8 kcal mol^{-1} lower than those of non-valent interactions in other conformations, *e.g.,* **31b** and **32b**.

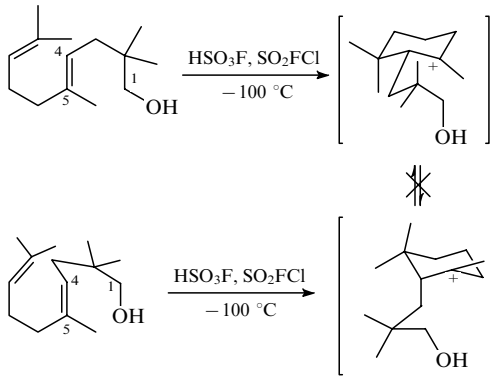


Conformation	**31a**	**32a**	**31b**	**32b**
E /kcal mol^{-1}	218.6	219.5	226.7	225.5

The calculations of the barriers $\Delta H^{\#}$ to the conformational ion transitions **35** ⇄ **36** (MMX) and the opening of heterocycles **37** and **38** (PM3)[16] corroborate the conclusion [6] that k_3, $k_4 \gg k_1$, k_2.

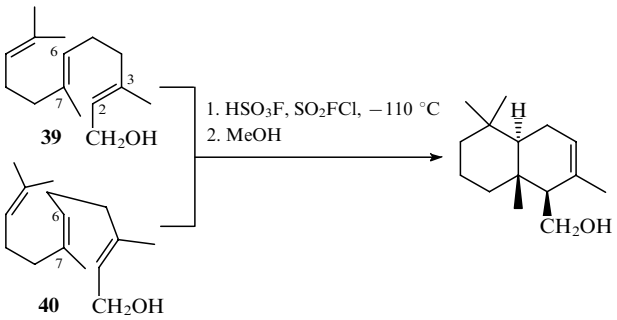
The stepwise mechanism of generation of ions **37** and **38** proposed by Gavrilyuk *et al.*[6] agrees well with the transition state energies of cyclisation of *cis*- and *trans*-undeca-6,10-dien-2-yl cations into decalin derivatives calculated by the MINDO/3 method. These calculations showed that the activation energies of synchronous processes are by 23–24 kcal mol^{-1} higher than those of stepwise processes.[17] In addition, experimental data suggest that biogenetic cyclisation of isoprenoids occurs in a stepwise manner.[18]

The formation of conformational isomers of cyclic ions as the manifestation of conformational control in the cyclisation of 2,6-dienes stereoisomeric with respect to the 4,5-double bond having a carbonyl or a hydroxy oxygen atom at C(1) is of general character [19] and is observed in the cyclisation of stereoisomeric 2,6,9,9-tetramethyl-2,6-decadien-10-ols.



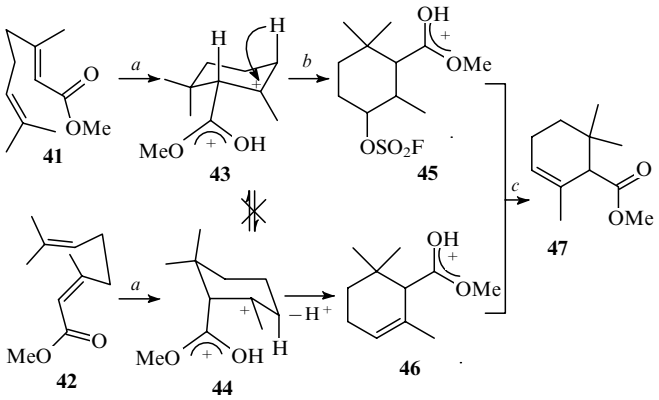
In the above examples, the interaction of the cationic centre in the conformers of monocyclic carbocations containing sufficiently nucleophilic carbonyl or hydroxy groups occurs faster than conformational transitions. In the cyclisation of *trans, trans*-(**39**) and *cis,trans*-farnesols (**40**), which are isomeric at the 6,7-double bond, the configuration of this double bond does not influence the steric direction of the reaction. Both isomers yield a

product with *trans*-fused rings. Apparently, this is due to decreased nucleophilicity of the 2,3-double bond caused by the −I-effect of the hydroxy group.[20]



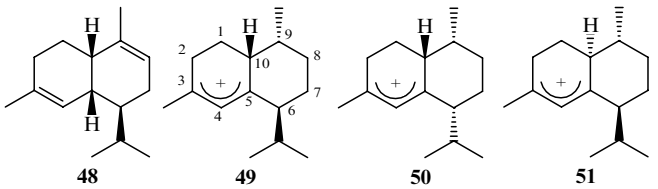
Conformational control is also effected in the stage of formation of intermediate carbocations where the same ion exists in different conformations which give rise to different (but not isomeric) ions.[21] Thus protonation of methyl 2,3-*trans*- (**41**) and *cis*-geranate (**42**) in HSO_3F-SO_2FCl at −120 °C gives dications **43** and **44**, which are conformers but are not practically interconverted at temperatures below −70 °C. In the dication **43**, the 1,2-hydride shift prevails, so that the cationic centres become more remote. Subsequent addition of the fluorosulfonyloxy group results in the ion **45**. In the dication **44**, the axial proton is eliminated exclusively from the secondary carbon atom to give the ion **46**. It is interesting that 'quenching' of acidic solutions of ions **45** and **46** yields the same compound, *viz*., methyl α-cyclogeranate (**47**). Thus, the studies of intermediate carbocations generated at low temperatures under 'long-life' conditions allowed Gavrilyuk *et al.*[21] to conclude that it is the configuration of the 2,3-double bond that determines the structure of primary cyclisation products (*viz*., intermediate carbocations) in the cyclisation of acyclic isoprenoids containing an ester group conjugated with the double bond.

It has been shown [22] that conformational control can influence the ratio of intra- and intermolecular reaction products in the stage of generation of an intermediate carbocation. Thus stable



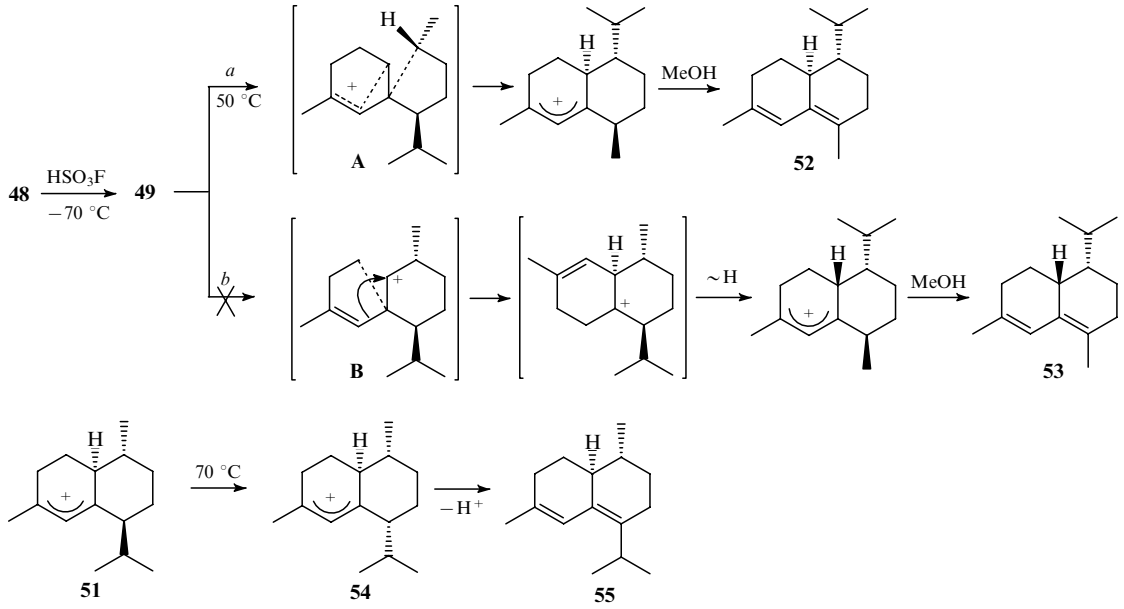
(*a*) HSO_3F, SO_2FCl, −120 °C; (*b*) OSO_2F^-, ~H; (*c*) MeOH.

diastereomeric allylic ions **49**–**51** generated from (−)-α-murolene (**48**) differ only in the configuration of the asymmetric centre at C(6) or C(10).[23]

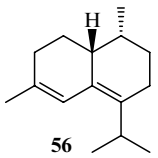


This, in turn, affects the conformation of the corresponding ion and, ultimately, the dihedral angle between the vacant *p*-orbital of the cationic centre and the C(10)–C(9) σ-bond. This angle determines the probability of intramolecular rearrangements in these ions with a 'turnover' of a six-membered ring relative to another. Thus one of the epimers (ion **49**) undergoes intramolecular ring 'turnover' at 50 °C to give the diene **52** (Scheme 2), while the other epimer (cation **50**) is converted into the ion **49** at −70 °C. In the case of the ion **51**, only intermolecular rearrangement into the ion **54** is realised even upon heating to 70 °C; its 'quenching' gives compound **55** (see Scheme 2).

Scheme 2



Intramolecular rearrangement of the ion **49** may occurs in two pathways, *a* or *b*. Which of them is realised in each concrete case can be established by comparing the ORD curves of dienes **55** and **56** mimicking compounds **52** and **53**, respectively.

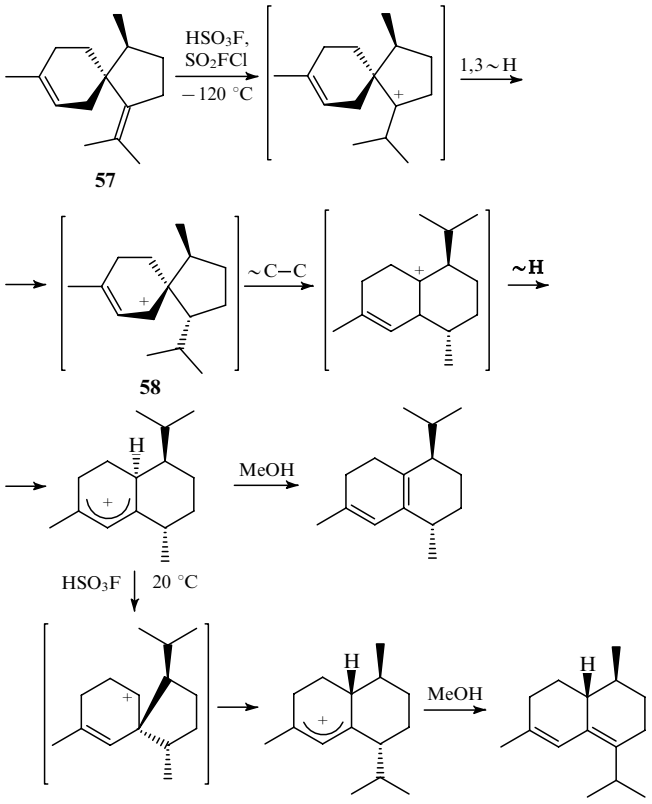


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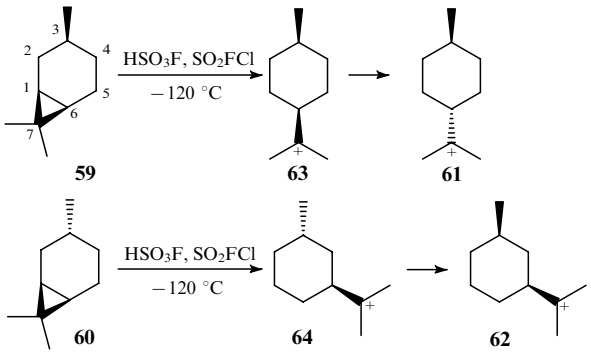
The experimental results[21] suggest that the rearrangement follows pathway *a*. This is probably due to the fact that of the two secondary spirocations **A** and **B** only the former can be stabilised by homoallylic conjugation. In the case of pathway *b*, such an efficient interaction is impossible due to the perpendicular position of the *p*-orbitals of the cationic centre and the double bond.

It should be noted that superacidic media favour profound molecular rearrangements that cannot be achieved in 'ordinary' media even under most drastic conditions. Since solutions of stable ion salts can be heated up to 100 °C and above, direct observation of 'cation–cation' rearrangements with an activation barrier of ~ 30 kcal mol^{-1} and higher can be observed. Molecular cationic rearrangements which occur in superacidic media with an activation barrier of ~ 20 kcal mol^{-1} cannot be reproduced under conditions of an ordinary acid catalysis (*cf.* Ref. 24).

The possibility of intermediate formation of the spirocyclic carbocation **58** in the previously discovered[22] rearrangement of allylic cations of the type **49** with the cadalene skeleton has been demonstrated with a sesquiterpenoid hydrocarbon β-alaskene (**57**) having a spiro[4.5]decane backbone as an example.[25]



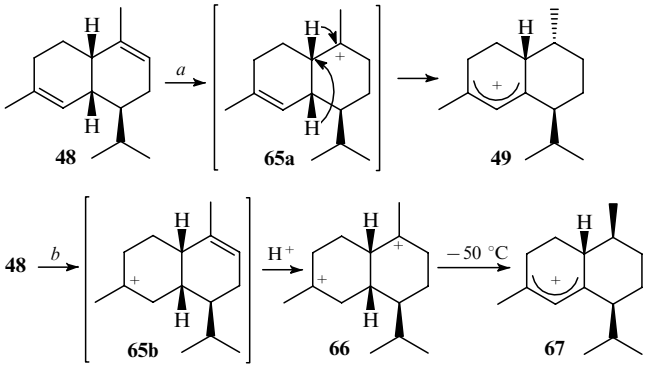
Steric factors have a profound influence on the ratios of intra- and inter-molecular transformations of stable carbocations. They can also affect the regio- and stereoselectivity of these rearrangements as can be exemplified in the isomerisation of *cis*- (**59**) and *trans*-caranes (**60**) in HSO_3F-SO_2FCl (−120 °C) resulting in the formation of apparent ions **61** and **62**, respectively.[26]



The opening of the cyclopropane rings in epimers **59** and **60** is accompanied by seeming inversion of configuration. This is due to the fact that in the case of long-living cations the conversions of initially formed ions **63** and **64** into thermodynamically more stable cations **61** and **62** occur through hydride shifts as can be judged from the molecular mechanics calculations.[27] The calculations of the geometry of the ground states of compounds **59** and **60** made with the use of the parameters described in Ref. 28 suggest certain elongation of the C(1)–C(7) bond relative to the C(6)–C(7) bond in the *cis*-isomer **59** and of the C(6)–C(7) bond relative to the C(1)–C(7) bond in the *trans*-isomer **60**. These data are in good agreement with the results of conversions of compounds **59** and **60** in superacids.

III. The effect of polyfunctionality of the original substrates

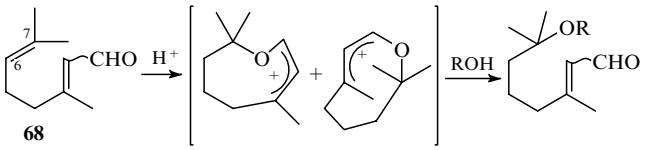
Yet another essential feature of terpenes as starting compounds in the generation of stable ions is their polyfunctionality. Thus terpenes may serve first as potential precursors of both mono- and dications with identical skeletons. The pathways of molecular rearrangements of mono- and dications often differ, which largely increases the diversity of terpene transformations. Thus it has been shown[23] that molecular rearrangements of mono- (**65**) and dications (**66**) generated from the same natural diene **48** give rise to diastereomeric allylic ions **49** and **67**.



(*a*) HSO_3F, SO_2FCl, −70 °C; (*b*) HSO_3F, SO_2FCl, −120 °C.

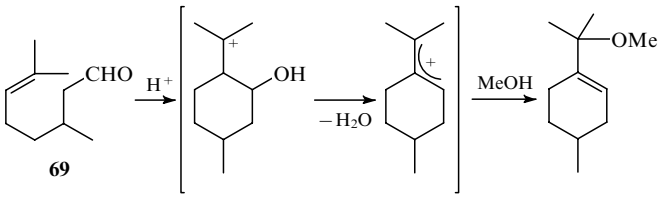
Second, a polyfunctional terpenoid molecule contains groups that can be both converted into an electrophile and simultaneously act as an internal nucleophile. The direction of a reaction often depends on the structural peculiarities of the original terpenoid. Minor structural changes in such strongly internally interrelated multicentre systems can result in dramatic changes in relative reactivities of different groups, in relative stabilities of intermediate carbocations and, ultimately, in the cyclisation pathway. The results of cyclisation of analogous acyclic terpenoids, *viz.*, citral (**68**), citronellal (**69**) and methyl geranate **41**, were compared under identical conditions (HSO_3F-SO_2FCl, −110 °C).[29]

In the citral molecule (**68**), the proton is added to the most nucleophilic 6,7-double bond. The oxygen atom of the carbonyl group, which attacks the cationic centre to give rise to cyclic allylic ions, acts as a nucleophile; quenching of allylic ions with alcohols gives 7-alkoxy-substituted 6,7-dihydrocitrals in good yields.



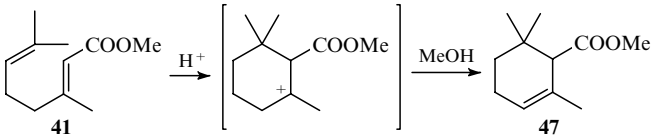
68

In contrast, in the aldehyde **69** the proton is added to the oxygen atom of the carbonyl group. The carbon atom in the latter attacks the 6,7-double bond to generate an allylic ion. Its 'quenching' gives 7-methoxymenthene.



69

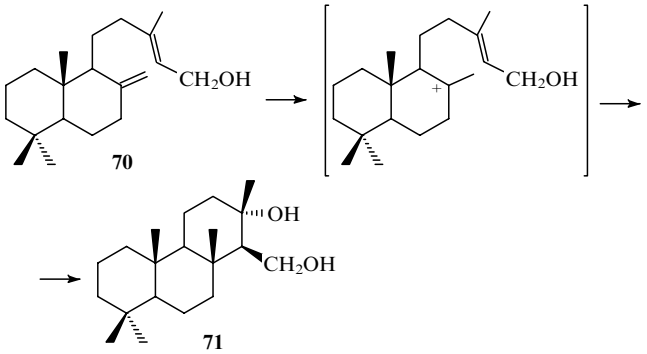
Finally, similarly to the aldehyde **68**, protonation of the ester **41** results in the addition of a proton to the 6,7-double bond. However, in this case the role of a nucleophile is played not by the oxygen atom of the carbonyl group but by the 2,3-double bond, eventually resulting in the ester **47** after 'quenching'.



41 **47**

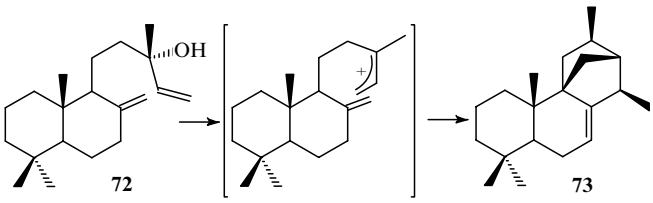
It has been shown [30] that isomeric bicyclic labdane diterpenoids **70** and **72**, which differ in the position of the allylic hydroxy group in the side chain undergo radically different conversions under identical conditions (HSO_3F-SO_2FCl, -100 °C).

Thus the protonation of the terpene **70** involves the exocyclic double bond to yield a cyclic carbocation; the role of the internal nucleophile is played by the double bond in the side chain. This structurally selective and stereoselective rearrangement gives rise to the bifunctionalised isoagatane **71**.



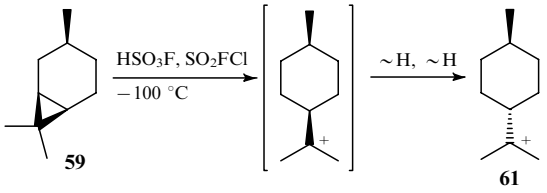
70 **71**

The generation of the cationic centre in the tertiary alcohol **72** is of by the solvolytic type and is accompanied by elimination of the allylic hydroxy group from the side chain. In this case, the exocyclic double bond plays the role of the internal nucleophile, eventually resulting in the tetracyclic hydrocarbon **73**.



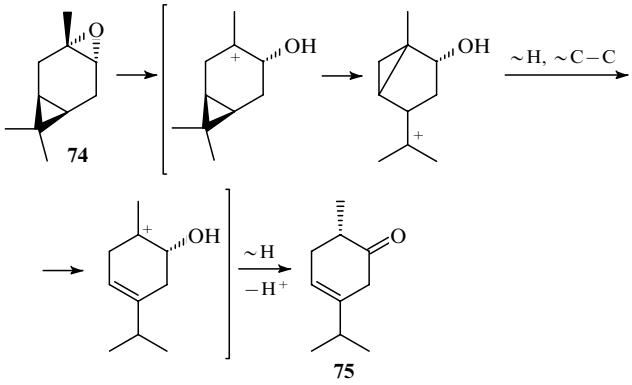
72 **73**

If a cationic centre is formed in a terpenoid molecule, it significantly affects the appearance of the second cationic centre in the same molecule (if this does take place) and its further behaviour. Thus the opening of a three-membered ring in carane (**59**) occurs through proton attack at C(1) of the cyclopropane ring.[26]



59 **61**

In α-*trans*-3,4-epoxycarane (**74**), the initial opening of the epoxide ring (HSO_3F-SO_2FCl, -100 °C) is followed by β-cyclopropylmethyl rearrangement and results ultimately in the formation of the ketone **75**.[31]



74 **75**

IV. Factors affecting the pathway of cationic rearrangements

The behaviour of stable π-conjugated carbocations is largely determined by charge delocalisation and the relative capacity to migration of substituents in 1,2-shifts.[32] If ions are generated from terpenes or their analogues, the crucial role will be played by other factors, *e.g.*, the nature of the acidic medium, the mode of generation of the cationic centre (solvolysis or electrophilic addition to the double bond) and the temperatures at which cations are generated and the acidic solutions are defrosted. The 1,2-shifts toward the cationic site are controlled by the competitive (rather than relative) migration capacity of the adjacent groups.

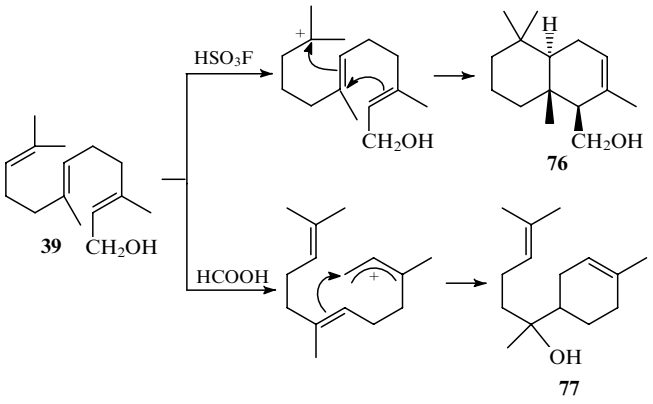
1. The nature of the acidic medium

Elucidation of the relationship between the chemical behaviour of stable carbocations generated in superacidic media and transformations of these original substrates under conditions of acidic catalysis is an important problem. Its solution will allow the use of regularities established in the studies of stable carbocations in prediction of the most probable pathways of multistep carbocationic rearrangements under conditions of conventional acidic catalysis. The solution of this problem is also important for designing organic syntheses in general and syntheses of terpene compounds in particular. However, the publications devoted to this problem are scarce and the conclusions made therein are

rather controversial. Thus Olah, who was a pioneer in the studies of the behaviour of cations generated in superacidic media, considers the chemistry of stable ions as an entirely independent field and conducts even applied investigations under extremely 'hypernon-nucleophilic' conditions.[33] In 1975, Sorensen *et al.*[34] generalised the data on carbocationic rearrangements of several monoterpenes in media of different acidities. According to these authors, the increase in the $\Delta G^{\neq}$ barrier to 'ion-to-ion' rearrangements is of the same order both in superacids and under conditions of acidic catalysis, while the stability of alkenes parallels that of the corresponding cations. It was thus concluded that the pathways of carbocationic rearrangements in acidic catalysis can be predicted from the results of direct observation of their rearrangements in superacids. No exceptions were reported.[34] In our opinion, this can be due to the limited choice of experimental objects investigated in this study [34] (as a rule, compounds with a norbornane skeleton were used). We have found several substantial limitations of Sorensen's statements. Thus in a more recent study, Brown [35] has shown that the chemical behaviour of stable ions and the pathway of solvolysis are in rather poor agreement with each other. In 1983, Arnett and Hofelich [36] established a correlation between the rate constants of solvolysis of certain chlorides in ethanol and enthalpies of ionisation of these chlorides in superacids and thus confirmed the formation of intermediate short-living carbocations in solvolysis that are analogous to stable ions generated in superacids. However, further multistep conversions of the initially formed ions have not been investigated.[36]

We believe that the data obtained in the studies of molecular rearrangements in superacids can be used for predicting the most probable pathways of their transformations in ordinary acids with allowance made for possible changes in the nature of the medium, *e.g.,* the site of generation of the cationic centre, the nature of the internal nucleophile, the 'qualitative' changes in the ratio of rates of intra- or inter-molecular rearrangements, the non-correspondence of changes in the relative stabilities of alkenes and the cations derived from them, *etc*. This must be taken into consideration altogether in designing isoprenoid syntheses.

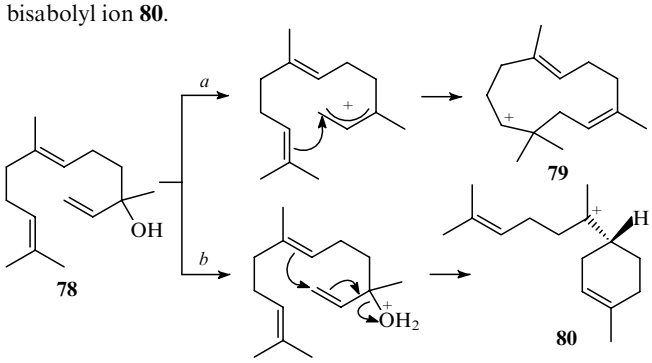
We have studied the effect of the nature of medium on the pathway of terpenoid rearrangements. Thus in the case of *trans, trans*-farnesol (**39**), the site of formation of the cationic centre has been shown to depend on the nature of the medium.[37]



Protonation of the double bond takes place in superacids endowed with high protonating capacity and results in drimenol (**76**). Formic acid, characterised by high ionising capacity, favours solvolysis with the formation of an allylic ion. Its subsequent cyclisation gives bisabolol (**77**).

The medium acidity affects the behaviour of labdanoids **70** and **72** (see above) in different ways. Cyclisation of compound **72** containing a tertiary allylic group in the side chain in both superacids and ordinary acids gives the tetracyclic product **73**. Compound **70** containing a primary allylic group generates the tricyclic diol **71** in superacids and the tetracycle **73** in ordinary acids.[30]

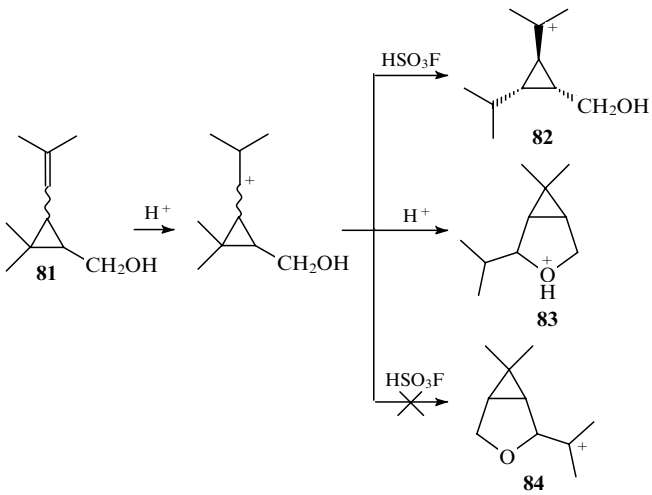
A study of transformations of nerolidol (**78**) in various acidic media has shown[37] that carbocylisation reactions involving different π-bonds can take place even in the presence of a good leaving group (*e.g.*, a tertiary allylic hydroxy group) and in the case where a cationic centre at the same carbon atom is formed in different media. For example, conformational control favours the approaching of the chain termini in superacids at low temperatures to give the secondary ion **79**. In weak acids and at room temperature, this reaction proceeds with the formation of a more stable tertiary bisabolyl ion **80**.



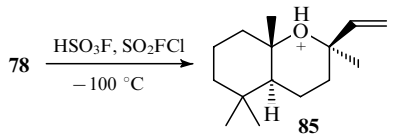
(*a*) HSO_3F, SO_2FCl, -100 °C; (*b*) $[H^+]$, 20 °C.

It has been shown [38] that cyclisation of chrysanthemyl alcohol (**81**) occurs differently in different media, since the medium determines the mode of reaction of a particular internal nucleophile with the cationic centre. This, in turn, significantly affects the ratio between carbo- and heterocyclisation reactions. Heterocyclisation in ordinary acids and carbocyclisation in superacids give cations **82** and **83**, which have identical stability (ΔH_f° = 114.9 and 114.6 kcal mol^{-1}, respectively, calculated by the MINDO/3 method). In other words, the reaction pathway is not determined by thermodynamic factors but is rather due to a lesser contribution of heterocyclisation because of the protonation of the heteroatom in superacids. In the study by Baig *et al.*,[39] the effect of the medium was neglected and the structure **84** was ascribed to the ion generated from the alcohol **81** in a superacid. As a matter of fact, this ion has the structure **82**[38] (Scheme 3, see Ref. 40).

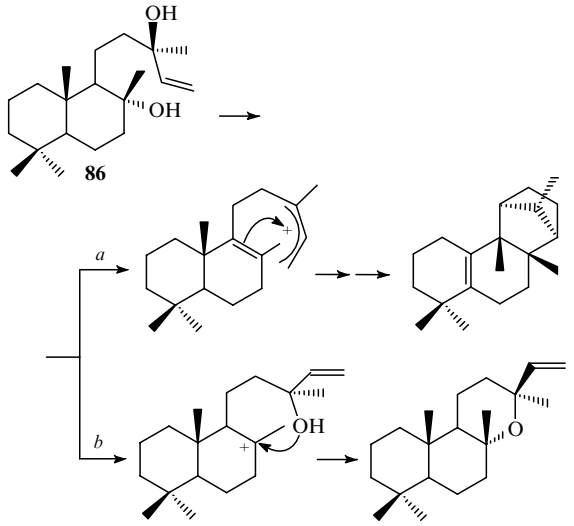
Scheme 3



The direction of a reaction can be affected not only by the nature of the medium but also by changes in the superacid:substrate ratio. Thus cyclisation of the alcohol **78** in the presence of a large (20 : 1) excess of a superacid results predominantly in carbocyclisation with the formation of the ion **79**, whereas heterocyclisation resulting in the cation **85** occurs at the HSO_3F : **78** ratio = 5 : 1.[37]

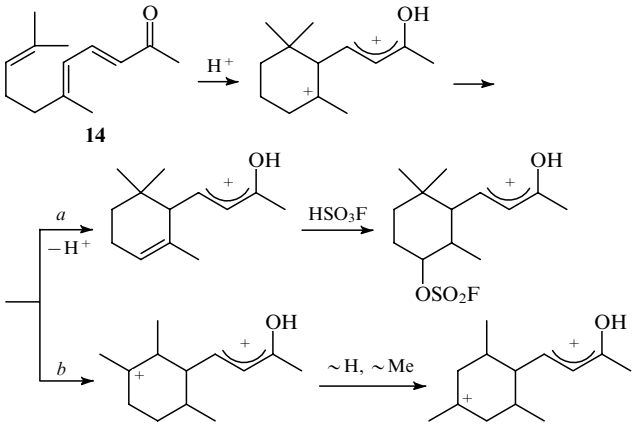


A similar effect of the excess of an acid on the carbo- to heterocyclisation ratio was observed with the diol **86**.[41]



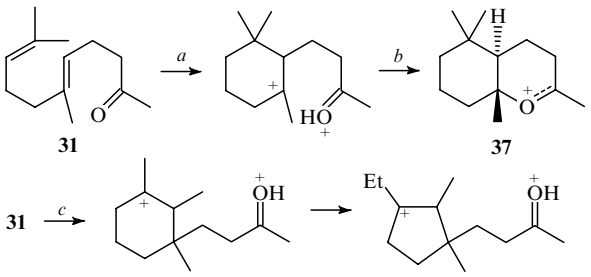
(*a*) HSO_3F : **86** = 2.5 : 1; (*b*) HSO_3F : **86** = 5 : 1.

In the above examples, the ratio of carbo- and heterocyclisation reactions changed with variations in the excess of an acid as the result of translocation of the cationic centre and the internal nucleophile. The effect of the medium can also be manifested in a different way. By varying medium acidity and excess of acid with respect to the substrate, one can generate structurally different mono- or dications from the same substrate. Thus by conducting the cyclisation of the ketone **14** in acids of various strengths, one can generate allylic ions (pathway *a*) or dications (pathway *b*) at the same temperature.[6]



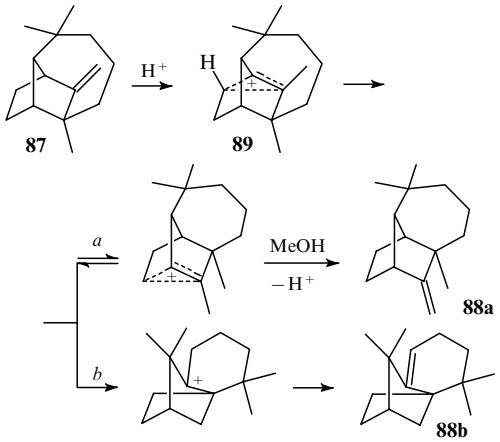
(*a*) HSO_3F, SO_2FCl; (*b*) HSO_3F : SbF_5 = 1 : 1, SO_2FCl, ~H, ~Me.

A significant effect can be produced by varying only the excess of an acid relative to the substrate without changing medium acidity and reaction temperature. Thus by varying the excess of an acid in the cyclisation of the ketone **31**, one can generate either the bicyclic carboxonium ion **37** or monocyclic dications with six- or five-membered rings.[6]



(*a*) HSO_3F : SbF_5 = 1 : 1, SO_2FCl; (*b*) HSO_3F : **31** = 3 : 1; (*c*) HSO_3F : **31** = 8 : 1.

Probably, the first example of a change in the ratio of the rates for intramolecular rearrangements upon transition from a superacid to ordinary acidic catalysis, which may alter both the stereoisomeric composition and the structure of reaction products, was described in 1981.[42] Thus the difference in the optical activities of isolongifolene (**88**) specimens ($[\alpha]_D^{20} = 0°$ and $-83°$) obtained by isomerisation of longifolene (**87**) in HSO_3F and AcOH can be attributed to the change in the ratio of the rates for intramolecular rearrangements upon transition from a superacid to a degenerate (pathway *a*, racemisation) or non-degenerate acetic acid (pathway *b*, retention of optical activity). On going to a more nucleophilic solvent (AcOH), the degree of solvation of ion **89** increases, while the 'requirement' of the cationic centre formed at C(1) for the σ-bond decreases. As a result, the orientation of the vacant *p*-orbital of the cationic site relative to the σ-orbitals of the migrating groups and atoms changes, which affects the rate of their migration (sp^2-alignment factor).



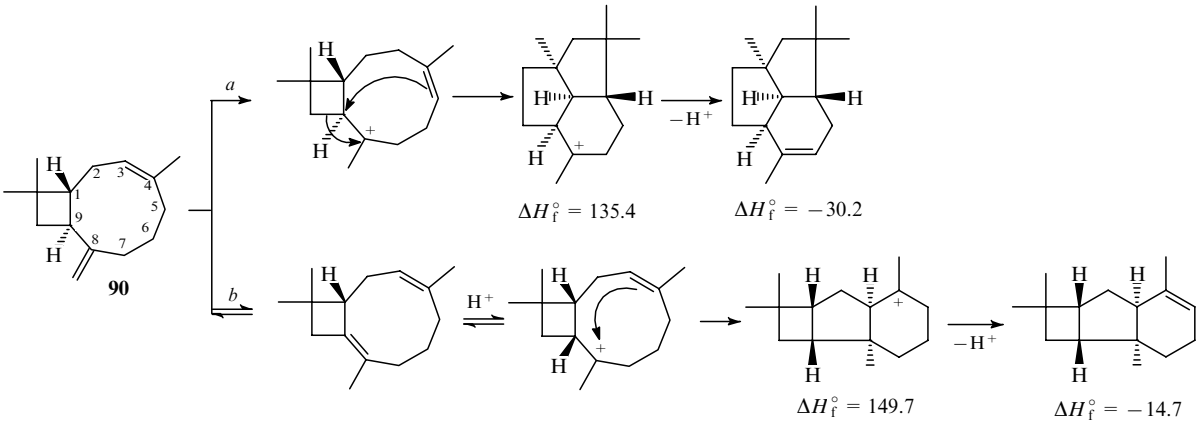
(*a*) HSO_3F; (*b*) AcOH.

In the studies by Sorensen *et al.*,[34] it was shown that the rearrangements in mono- and polymethylnorbornyl cations formed as intermediate species independently of the medium gave 2-norbornyl ions; their further transformations occurred only by intramolecular pathways. In other cases, the contribution of intermolecular reactions can influence the comparability of rearrangement processes that occur in different media.

The change in the ratio of rates of intermolecular rearrangements of an isocaryofyllene isomer, *viz.*, the diene (**90**) (Scheme 4), has been established.[43] In superacids (pathway *a*), the double bond from position 3,4 migrates to position 4,5 faster than from position 8,12 to position 8,9. An opposite ratio is observed in ordinary acids (pathway *b*). This finding cannot be explained by thermodynamic factors as can be seen from the calculation of enthalpies of formation of the final ions and alkenes (hereinafter ΔH_f° and $\Delta\Delta H_f^\circ$ values are expressed in kcal mol^{-1}).

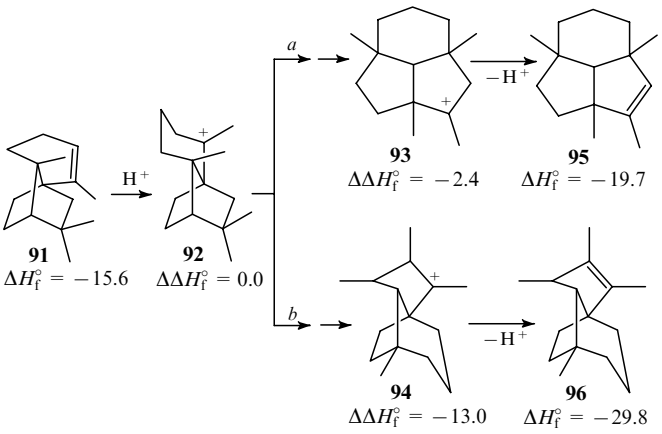
The pathways of neoclovene (**91**) conversions in superacids and ordinary acids differ drastically despite the similar character

Scheme 4



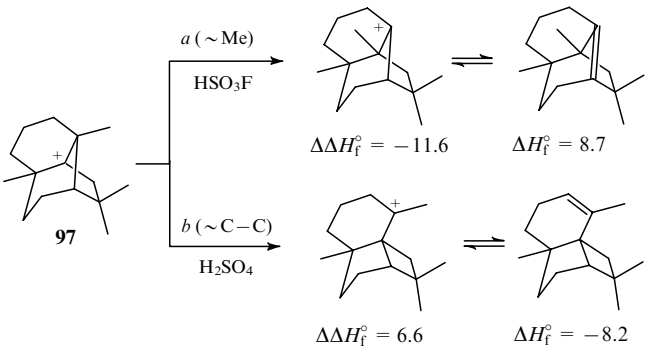
(*a*) HSO_3F; (*b*) $[H^+]$.

of stabilities of the final ions and alkenes.[44] Calculations of the enthalpies of formation of ions and alkenes were carried out using the parameters described in Refs 45 and 46. According to NMR spectral data, pathway *b* is predominant in superacids and yields the ion **94**, which is more stable than the ion **93** formed from the ion **92** by pathway *a*. It is still unclear, however, why in sulfuric acid this reaction gives the alkene **95**, which is less stable than the alkene **96** generated by pathway *b*.



(*a*) H_2SO_4; (*b*) HSO_3F.

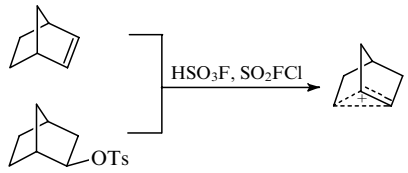
In conversions of the intermediate ion **97** in various acidic media, the changes in relative stabilities of carbocations are opposite to those of the corresponding alkenes (NMR data and calculations). In ordinary acids, the direction of these rearrangements is determined by relative stabilities of intermediate alkenes.



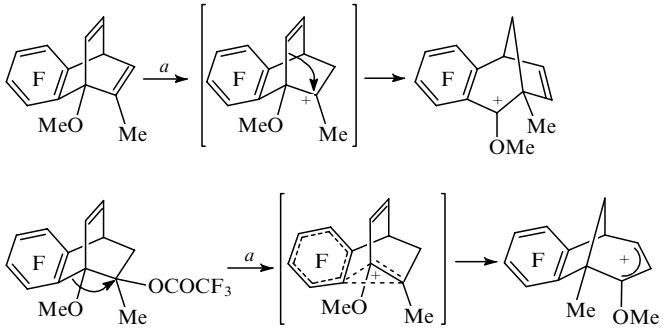
As can be seen from ΔH_f° and $\Delta\Delta H_f^\circ$ values, the Sorensen principle of parallelism of relative stabilities of carbocations and the corresponding alkenes[34] is violated in this case. It may be assumed that if several alternative pathways of rearrangements resulting in generation of ions with different skeletons (bridged, open, monocyclic or fused structures) do exist, the trends of changes in relative stabilities of ions and the corresponding alkenes form opposite series. Thus bridged structures can give rise to stable non-classical ions and the corresponding unstable 'anti-Bredt' alkenes. Stable 'Bredt' alkenes corresponding to unstable classical ions are generated from open, monocyclic and fused compounds.

2. The mode of generation of the cationic centre

A difference in the stereochemical results of solvolysis of an acyloxy derivative and of protonation of the corresponding alkene in identical weakly acidic media has been established.[47,48] According to Brown,[47] this effect is due to the fact that more 'loose' carbocations formed upon protonation are trapped by the nucleophile prior to complete establishment of an equilibrium between the ions. An alternative hypothesis[48] rests on the formation of isomeric non-classical (solvolysis) and classical ions (protonation). However, according to literature data, stable carbocations generated upon protonation of alkenes or upon solvolysis of esters (halides) normally yield identical species irrespective of the reaction type (*e.g.*, see Ref. 49).



In a more recent study,[50] models were selected for the first time in such a way that isomeric stable ions could be generated upon alkene protonation and ester solvolysis. Their formation was confirmed by NMR spectroscopy.

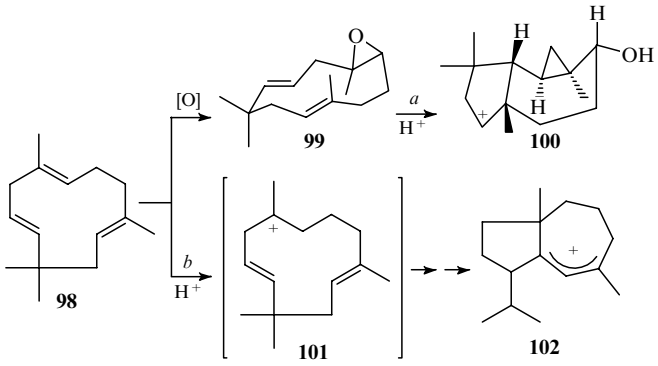


(*a*) HSO_3F, SO_2FCl, −100 °C.

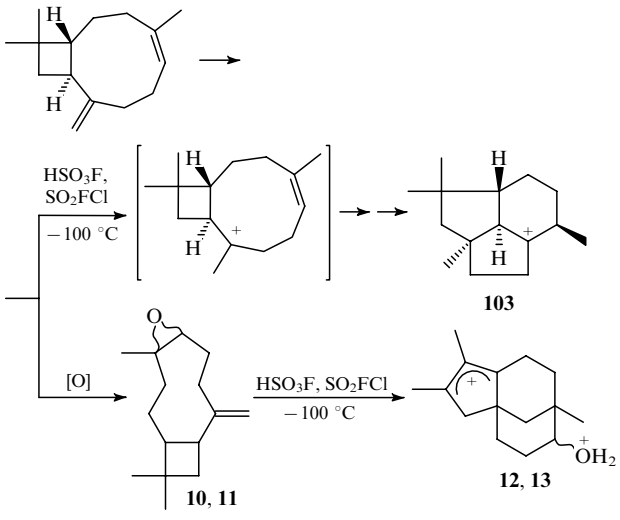
On transition from these model compounds to terpenes, the problem of elucidating the dependence of the main pathway of

cationic rearrangements on the mode of generation of the cationic centre becomes more complicated. First of all, this is due to polyfunctionality and conformational mobility of terpenes. In the following, we will compare the behaviours of an alkene in the protonation and its monoepoxide in the solvolysis. This is of interest for both physical organic chemistry (studies of solvolysis) and terpene chemistry. The opening of epoxides can initiate biomimetic processes.

Two cases should be taken into consideration in comparing the behaviours of an alkene and the corresponding monoepoxide, *viz*., the coincidence or non-coincidence of the charge localisation sites. However, further rearrangements of the carbocation may occur according to different pathways even in the former case. For example, the conversions of α-humulene (**98**) and its 6,7-epoxide **99** [51] with the identical localisation of the initially formed cationic centre occur by different routes, *viz*., by concerted, conformationally controlled pathway *a* (epoxide) or by barrier-free conversion of the alkene into the cation **101** (pathway *b*) and then into the ion **102**. The configuration of all the chiral centres in the ion **100** formed by pathway *a* was confirmed by X-ray analysis of the 'quenching' product. The original epoxide **99** seems to have the most stable CT-conformation. Analysis of the ^{13}C NMR spectra of compound **99** at −120 to −70 °C revealed the absence of conformational transitions at these low temperatures.

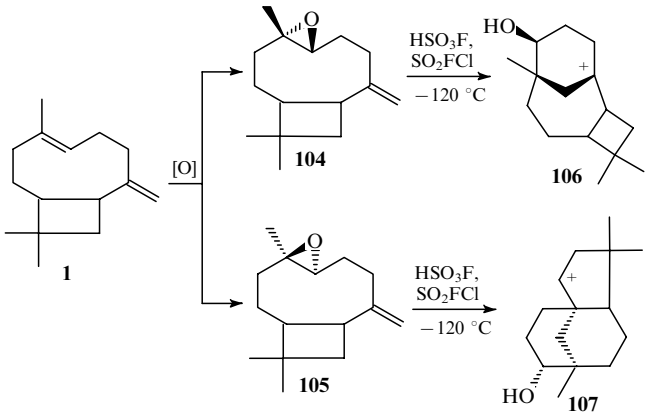


Isocaryophyllene [43] and epimeric epoxides **10** and **11** [3] derived from it generate different stable ions in superacidic media at all temperatures.

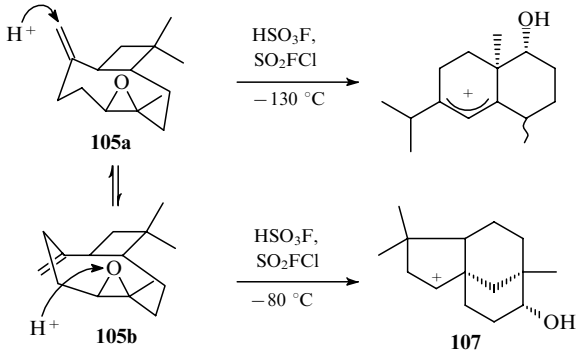


In isocaryophyllene, the energy barriers between individual conformers analogous to those of caryophyllene **1** are rather low, as a result of which it generates only one ion, **103**. The transition to epimeric monoepoxides **10** and **11** is accompanied by stabilisation of individual conformations which further generate enantiomeric ions **12** and **13** (see Section II).

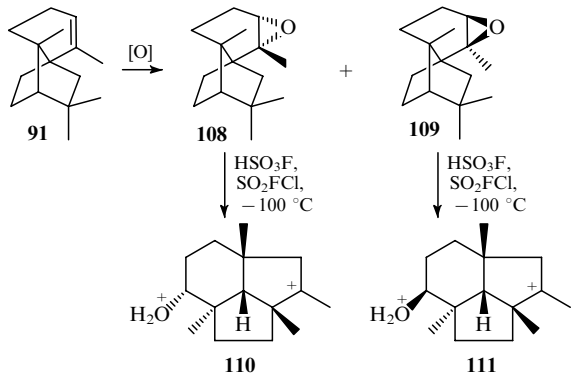
Caryophyllene (**1**) [2] gives rise to a mixture of carbocations corresponding to the original mixture of conformers (HSO_3F–SO_2FCl, −120 °C). Since diene **1** conformers cannot be isolated in the individual state, the structure of the ion generated from one or another conformation cannot be established experimentally. Epimeric 4,5-monoepoxides **104** and **105**, which may be regarded as 'fixed' conformers, were used to generate one ion each (**106** and **107**) corresponding to those derived from the diene **1**.[3]



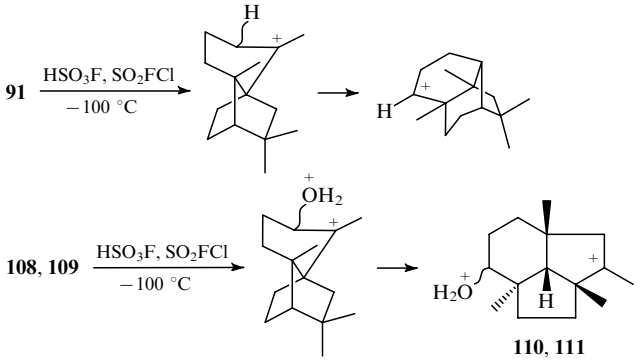
Naturally, the mode of formation of the carbocationic centre is affected by other parameters of cationic rearrangements. Studies with the epoxide **105** have shown [3] that a change in temperature alters the position of the cationic centre. This, in turn, changes the composition of the reaction products formed from the monoepoxide **105** at different temperatures and, correspondingly, the pathways of rearrangements in the original diene **1** and its monoepoxide **105** occurring under identical conditions. Obviously, it is the ratio of epoxide **105** conformers that is changed with a change in temperature. As the barriers to the conformational transitions **105a** ⇄ **105b** and to the reactions of the primary ions are comparable, a change in temperature results in the change in the rearrangement pathways.



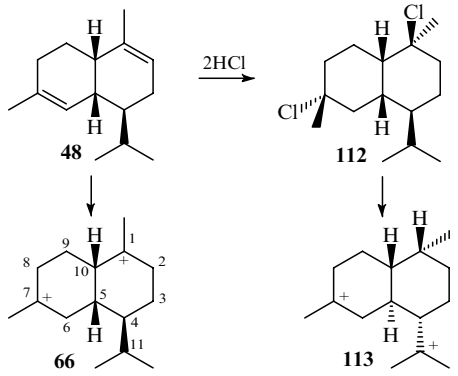
The epoxide transformations described above are concerted processes. However, they can be realised only for such relative arrangement of the epoxide ring that is opened and the part of the molecule where hydride and alkyl shifts toward the cationic site formed occur without difficulty. In other cases, non-concerted epoxide conversions may take place. The latter case has been described [52] where stable ions **110** and **111**, differing in configuration of the carbon atom containing a hydroxy group, were generated in superacids from neoclovene epoxides **108** and **109**. The stereochemical result of this reaction suggests that conversions of epoxides **108** and **109** into the corresponding alcohols **110** and **111** occur in a non-concerted way.



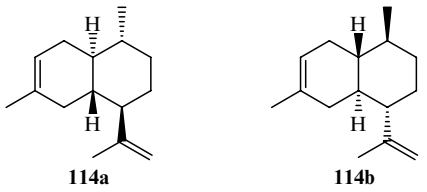
The non-coincidence of pathways of rearrangements of an alkene and the derived epoxide may reflect the differences in the behaviour of mono- and dications with identical skeletons. For example, different stable ions were obtained from neoclovene (**91**) and epimeric epoxides **108** and **109** with identical backbones and identical sites of formation of the cationic centres under the action of a superacid. The epoxide opening generates a dication with charges on the carbon atom and the oxygen atom of the hydroxy group. Spatial separation of the charges is the driving force for the rearrangement of such a dication. It thus follows that a rearrangement of a cyclic alkene and the derived epoxide will yield the same ion only in the case where the rearrangement of an ion generated from the alkene is accompanied by translocation of the positive charge away from the site of proton addition.



The mode of generation of the cationic centre is also reflected in the structure of carbodications generated from dienes and the corresponding hydrogen chloride addition products. Stable isomeric carbodications **66** and **113** were generated from α-murolene **48** and the dichloride **112** with identical backbones and identical position of the cationic centres formed under identical conditions ($SbF_5-HSO_3F-SO_2FCl$, −120 °C).[53]



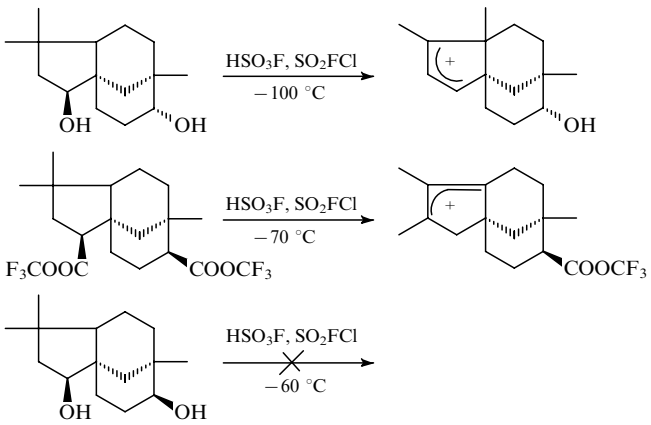
As has been noted earlier, isomeric stable ions were obtained upon changes in the mode of their generation.[50] The difference in the reaction routes was ascribed [50] to the formation of non-classical ions upon ester solvolysis and of classical ions upon alkene protonation. However, non-classical ions are formed mainly in reactions of bridged polycyclic systems.[54] If the conversion of the dichloride **112** into the dication **113** occurs through a scheme involving a 1,5-hydride shift from C(11) to C(1), the quenching product should possess the structure **114a**. If this process involves only 1,2-hydride shifts, the diene formed should have the structure **114b**. It has been established [53] that ionisation of the dichloride **112** gives the diene **114b** and, correspondingly, translocation of the positive charge from C(1) to C(11) occurs as consecutive 1,2-hydride shifts.



In the dichloride **112**, elimination of the chlorine anion from C(7) is followed by translocation of the positive charge to C(11) through 1,2-hydride shifts and only after this process has been completed, the second chlorine anion is split off from C(1) giving rise to the dication **113**. Protonation of the diene **48** results in immediate generation of the dication **66** in which translocation of the positive charge through 1,2-hydride shifts from C(1) to C(11) does not occur, since the barriers to transition from a classical tertiary carbocation to a classical secondary isomeric carbocation usually exceed 14 kcal mol^{-1} at −120 °C (see Ref. 55). Further translocation of the positive charge from C(1) to C(10) is hampered due to the presence of a cationic centre at C(7).

Thus, depending on the mode of cation generation, the difference in reaction routes can be caused by: (*i*) intermediate formation of classical and non-classical isomeric ions; (*ii*) concerted epoxide rearrangement and non-concerted rearrangement upon alkene protonation; (*iii*) change in the site of formation of the cationic centre; (*iv*) non-coincidence of pathways of rearrangement of mono- and dications having identical backbones and (*v*) peculiarities of the spatial structure of the original compounds including the ratios between the conformation barriers and barriers to reactions of the primary ions.

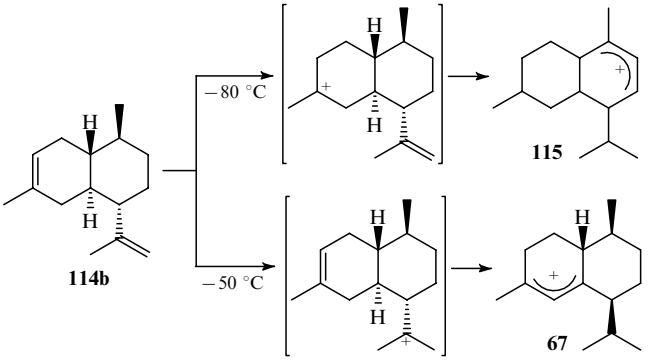
The effect of spatial structure of original compounds, *i.e.*, configuration and the nature of the leaving group, on the direction of a cationic rearrangement can be well illustrated by the following reactions:[56]



3. Cation generation temperature

The temperature at which carbocations are generated is a crucial factor which determines the pathways of multistep cationic rearrangements. It is assumed that ions generated at low temperatures are not converted upon heating into cations that are formed at higher temperatures. In some cases, a change in cation generation temperature influences the position of the cationic

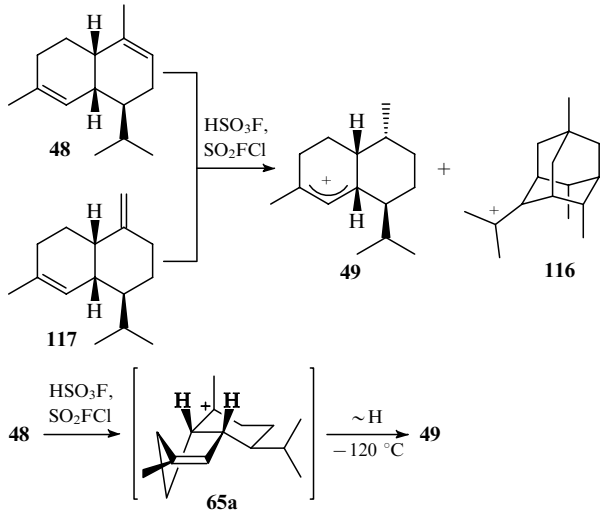
centre. Thus the diene **114b** predominantly generates the ion **115** at −80 °C and the ion **67** at −50 °C in HSO_3F-SO_2FCl:[53]



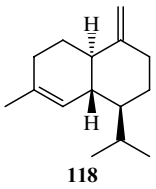
A change in the conformational composition of the original diene **114b** does not account for the temperature-dependent generation of allylic ions, since the ^{13}C NMR spectra of this diene in CD_2Cl_2 are not changed in the temperature range from −85 to +10 °C. Rather, a change in temperature may affect the direction (the exo- or the endocyclic double bond) of primary protonation.

A temperature-dependent change in the ratio of protonation rates of two endocyclic double bonds has been described.[23] Thus ions **66** and **49** are generated upon protonation of the diene **48** at −120 °C in HSO_3F-SO_2FCl, whereas heating to −50 °C yields ions **67** and **49** in a ~ 2.5 : 1 ratio. If the ions are generated at −70 °C, the ion **49** is predominantly formed (see Section II). Thus, the ratio of diastereomeric ions can be altered by varying the temperature at which these ions are generated.

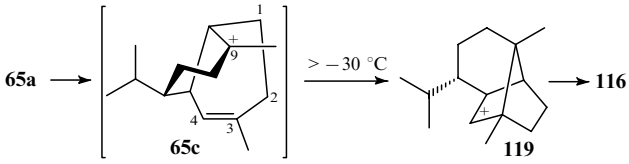
The effect of temperature on the ratio of bi- and tricyclic ions formed has been observed.[57] Thus a mixture of bicyclic (**49**) and tricyclic (**116**) ions is formed from the diene **48** (HSO_3F-SO_2FCl, −30 °C) in a ~ 2 : 1 ratio (data from ^1H NMR spectroscopy).



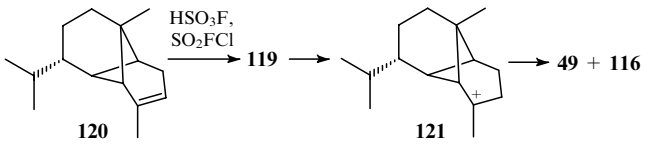
Since the temperature at which ions are generated does not influence the conformational composition of the original diene **48** (the ^{13}C NMR spectra are not changed at temperatures from −90 °C to +10 °C), it may be supposed that its protonation at −120 to −70 °C will yield the cation **65a** in the most stable *half-chair–chair* conformation (according to calculations carried out by the MM2 method). 1,2-Hydride shifts in the ion **65a** result in the allylic ion **49**. In the conformation **65c**, the reaction centres are at the shortest distance favourable for transannular cyclisation. The conformation of the ion **65a** is more favourable for transannular cyclisation than that of the ion **65b** as can be judged from the formation of the ion **116** (in addition to the ion **49**) from γ-murolene (**117**) (HSO_3F-SO_2FCl, −30 °C). At −120 °C, the protonation of the diene **117** in HSO_3F-SO_2FCl gives the ion **49**;[23] at lower temperatures, it is the monocation **65a** that is exclusively formed due to the greater ease of protonation of the exocyclic double bond. γ-Cadinene (**118**), the isomer with a *trans*-fusion of the rings, does not generate either the ion **116** or any other tricyclic cations in HSO_3F-SO_2FCl at −30 °C.



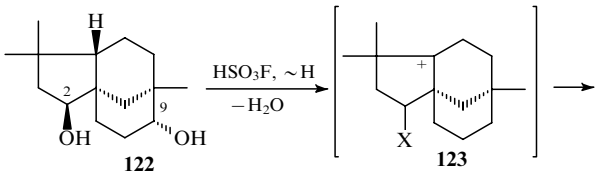
Obviously, the $\Delta H^{\neq}$ value calculated by the MM2 method for the conformational transition **65a** → **65c** (10.9 kcal mol^{-1}) significantly exceeds the barriers to 1,2-hydride shifts in the ion **65a** in the conversion of one tertiary ion into another (< 4 kcal · mol^{-1}).[58] This explains the effect of the conformational composition of the ion **65** on the ratio of ions **49** and **116** at −120 to −70 °C. The rise in ion generation temperature (but not in defrosting temperature) favours the conformational transitions **65a** → **65c** and increases the contribution of transannular interaction of the carbocationic centre with the double bond, resulting in the initial generation of ions **119** and **120**. Taking into account the difference in ΔH_f^o values for these ions (22.9 kcal mol^{-1}) and the short C(3)–C(9) and C(4)–C(9) distances in the conformation **65c**, it may be supposed that the cyclisation of the ion **65c** gives a more stable ion **119**. The latter is further rearranged into the ion **116** according to the schemes[57] suggested on the basis of estimation of free energies of activation.[59]

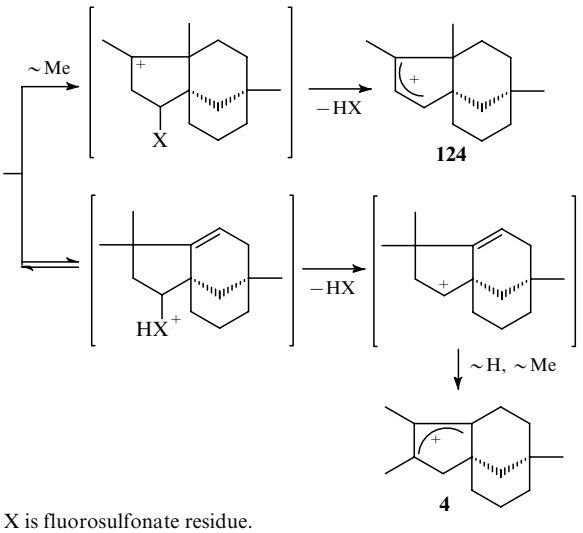


According to ^1H NMR spectral data, dissolution of α-copaene (**120**) in HSO_3F-SO_2FCl at −115 °C and subsequent heating to −30 °C yield a mixture of ions **49** and **116** (~ 3 : 1). Hydrocarbon **120** is a direct precursor of the ion **119**; which rearranges further into the ion **121**. The observed rearrangement corroborates the pathway proposed for generation of the ion **116**.



An interesting example of the effect of ion generation temperature on the pathway of a cationic rearrangement has been described.[56]





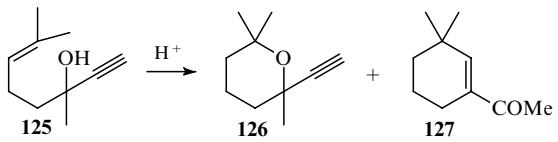
X is fluorosulfonate residue.

The hydroxy group at the C(9) atom in the diol **122** is the first to be eliminated under the action of HSO_3F. Subsequent 1,2- and 1,3-hydride shifts in the cation formed give the ion **123**. The latter is subject either to a 1,2-shift of the methyl group with subsequent elimination of an HX species (its nature is unknown) to give the ion **124** or to elimination of a proton and the HX species[4] to give ultimately the ion **4**. The ratio of the pathways of ion **123** conversions is determined by the temperature of its generation from the diol **122**. Thus, the ion **124** is predominantly formed at −100 °C, while the ion **4** is generated at 20 °C.

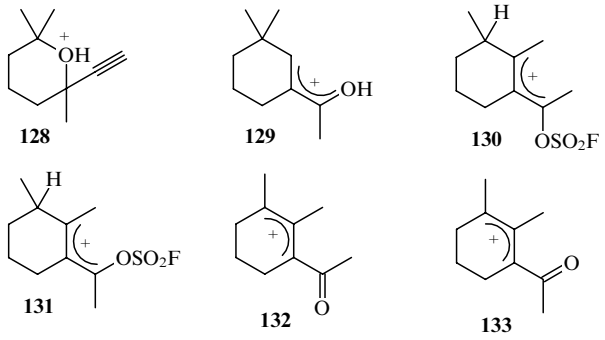
4. Defrosting temperature

Yet another factor which controls cationic rearrangements is the temperature at which an acidic solution is defrosted .

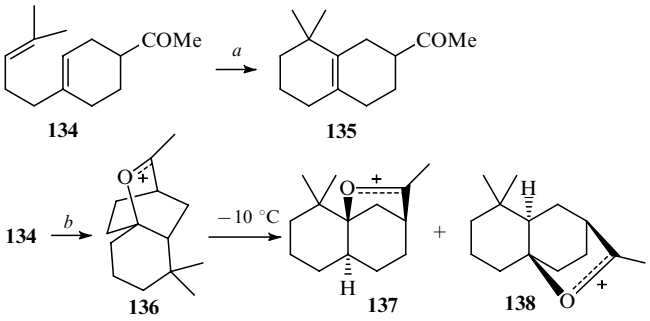
First, the reaction mixture obtained following treatment with superacids (HSO_3F, $HSO_3F-SbF_5-SO_2FCl$ in a solvent or without it) can be heated from −130 °C to +100 °C. This temperature range allows one to overcome the barriers to ion-to-ion transitions of up to 30 kcal mol^{-1}. Second, these 'hypernon-nucleophilic' media favour profound molecular rearrangements which have no analogues in acid-catalysed reactions. Thus cyclisation of dehydrolinalool (**125**) in 'ordinary' acidic media gives a mixture of compounds **126** and **127**.[60]



In superacids, the rearrangements resulting in the formation of stable ions **128**–**133** are much more diverse.[61]

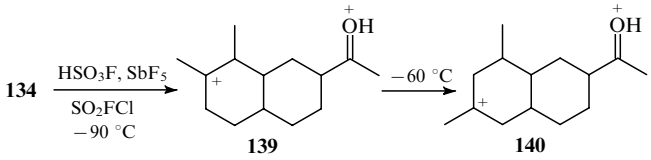


According to literature data,[62] acid-catalysed cyclisation of isolone (**134**) gives exclusively florione (**135**). Ketone **134** generates the ion **136** in HSO_3F-SO_2FCl at −110 °C. Heating of the resulting acidic solution to −10 °C yields a mixture of carboxonium ions **137** and **138**.[63]

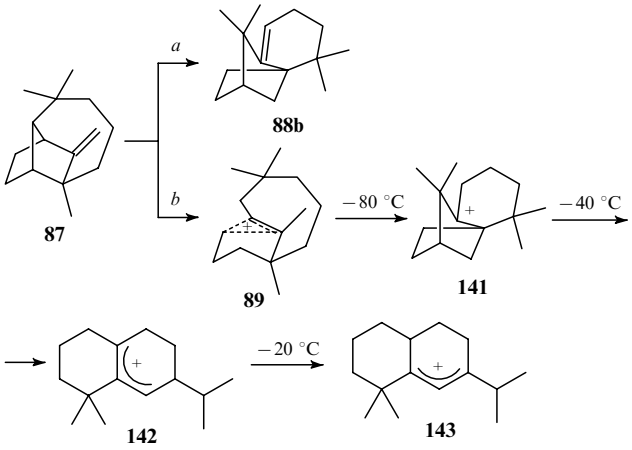


(*a*) [H+]; (*b*) HSO_3F, SO_2FCl, −110 °C.

The ketone **134** generates the dication **139** ($HSO_3F-SbF_5-SO_2FCl$, −90 °C); heating to −60 °C results in the dication **140**.

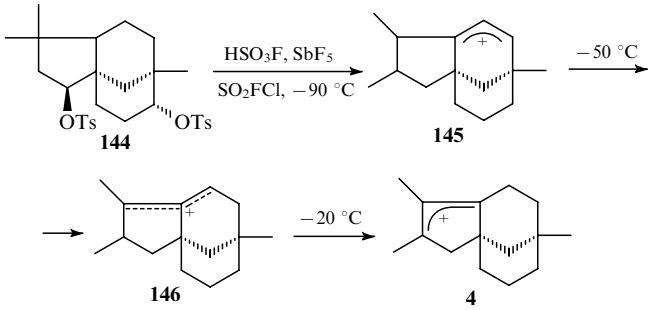


Longifolene **87** is predominantly converted into isolongifolene **88b** in acidic media.[64] Four carbocations (**89** and **141**–**143**) were generated in HSO_3F-SO_2FCl by varying the defrosting temperature;[42] these carbocations were successively interconverted with the rise in temperature.



(*a*) [H+]; (*b*) HSO_3F, SO_2FCl, −120 °C.

The effect of defrosting temperature on the structure of carbocations formed has been observed.[56] It has been shown that ditosylate **144** generates the ion **145** in $HSO_3F-SbF_5-SO_2FCl$ at −90 °C. Heating of the mixture to −50 °C leads to its rearrangement into the ion **146**, which is further isomerised into the ion **4** with the rise in temperature to −20 °C.



V. Selection rules

Irrespective of the complex structure of the original substrates, high selectivity of rearrangements of stable ions generated from terpenes is a very important factor which determines their behaviour in superacidic media. This selectivity is provided by a combination of regio- and stereocontrol.

Thus studies of diene **48** conversions in $HSO_3F-SbF_5-SO_2FCl$ have shown[23] that at temperatures from −120 to −50 °C all ionic isomerisations occur exclusively as 1,2-hydride shifts and deprotonation-protonation, but not as C−C shifts. Although the theoretically possible protonation–deprotonation reactions and 1,2-hydride shifts in the diene **48** can lead to an extremely complex mixture, this gives rise to a limited number of stable ions that are generated by several relatively short pathways. The selection rules realised in this case can be formulated as follows:

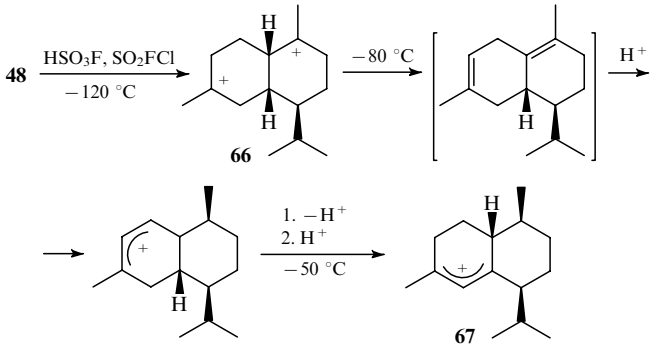
1. Protonation of double bonds and further rearrangements occur predominantly through the formation of both intermediate and final tertiary carbocations; secondary ions are not normally formed.

2. In superacidic media, 1,2-hydride shifts occur more easily than deprotonation reactions, if tertiary and allylic ions are formed.

3. Allylic ions in which all three carbon atoms are incorporated in a single ring and which do not involve two carbon atoms of the bond common to both rings are the most stable.

4. Protonation and deprotonation occur regio- and stereoselectively. This may be due to both inherent steric hindrances for approaching a protonating reagent or a base (the conformational transitions are strongly hampered at −120 to −50 °C) and stereoelectronic factors in the deprotonation. These peculiarities distinguish the compounds under study from more simple, monocyclic or aliphatic models, *e.g.*, those in which protonation is nonselective as a rule.

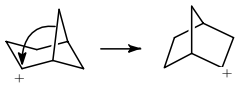
The conversions of the dication **66** into the allylic ion **67** described above may occur through stereoselective addition of protons to the double bonds of intermediate dienes. An alternative scheme implies that under kinetically controlled conditions the protonation occurs non-selectively, whereas under thermodynamically controlled conditions the equilibrium between diastereomeric ions is practically completely shifted toward the ion **67**. This suggestion seems unlikely, since diastereomeric ions **49**–**51** generated separately are stable and are not interconverted under these conditions.[23]



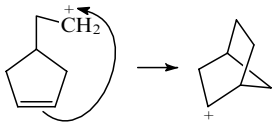
VI. Computational methods for predicting the most probable pathways of multistep cationic rearrangements

The 'selection rules' are valid in small groups of related compounds[23] and allow one to predict qualitatively the most probable pathways of multistep carbocationic rearrangements. Several approaches to quantitative estimations have been proposed.[16] An original computer programme 'ICARUS' was used to investigate plausible mechanisms of multistep carbocationic rearrangements.[65] This programme entails generation of the whole variety of multistep rearrangements of a definite chemical structure and control over realisation of the generated routes. All the cationic rearrangements can be divided into six main groups:

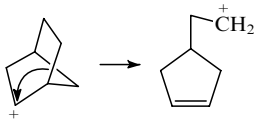
(1) 1,2-shift of the σ-bond



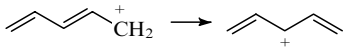
(2) addition at the multiple bond



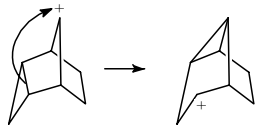
(3) β-fragmentation



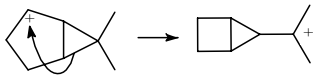
(4) allylic rearrangement



(5) β-cyclopropyl–carbinyl rearrangement



(6) α-cyclopropyl–carbinyl rearrangement



Validation of the pathways proposed by the programme is carried out using an empiric data base on the peculiarities of carbocationic rearrangements. In particular, the ICARUS data base involves the following selection rules:

1. Only the rearrangements occurring as 1,2-shifts of the C−C and C−H bonds fall under investigation; more distant 1,3-, 1-4-shifts, *etc.*, are not analysed.

2. Only intramolecular rearrangements (*i.e.*, those not resulting in degradation of the original structure into two independent species, *e.g.*, proton elimination followed by generation of an alkene) are subject to analysis.

3. Reactions resulting in generation of unstable intermediates (primary cations, structures containing strained small rings, *etc.*) are excluded from consideration. Also excluded are β-fragmentation reactions, since they produce high-energy intermediates: the formation of a double bond significantly increases the enthalpy of the reaction.

4. 1,2-Shifts of the σ-bonds in allylic ions are excluded from consideration.

However, estimation of the probability of such rearrangements on the basis of qualitative speculations alone does not always permit one to rule out improbable mechanisms. Quantitative estimations require calculation of thermodynamic characteristics of the intermediates by molecular mechanical or quantum mechanical methods. The enthalpy of a reaction can be calculated using a set of special force field parameters of the MM2 programme and bond increments for carbocations.[66] Estimation of the energy barriers demands simultaneous account of thermo-

dynamic and orbital factors, since their separate consideration often gives contradictory predictions. The enthalpies of formation of primary and final ions can be used as a thermodynamic factor. The orbital factor is associated with the value of the dihedral angle between the vacant *p*-orbital and the neighbouring migrating bond. It was assumed [59] that in the first approximation the internal barrier to the 1,2-shift (Λ) of a degenerate rearrangement is connected with the interorbital angle (φ) by equation (1):

$$\Lambda = \Lambda_0/\cos\varphi, \tag{1}$$

where Λ_0 is the internal barrier at $\varphi = 0\,^\circ$.

For a non-degenerate process, the thermodynamic factor was calculated by the Marcus equation (2) (in isoentropic approximation):

$$\Delta G^{\neq} = \left(1 + \frac{\Delta\Delta H}{4}\right)^2 \tag{2}$$

or in its linear Polanyi–Semenov approximation (3):

$$\Delta G^{\neq} = \Lambda + b\Delta\Delta H, \tag{3}$$

where $\Delta\Delta H$ is the difference between the ΔH_f^o values of the generated and rearranged ions; $b = 0.25$ (for $-4\Lambda < \Delta\Delta H < 0$), 0.75 (for $0 < \Delta\Delta H < 4\Lambda$), $\Delta G^{\neq} = 0$ (for $\Delta\Delta H < -4\Lambda$), $\Delta\Delta H$ (for $\Delta\Delta H > 4\Lambda$).

The internal barriers, Λ_0, for the orbitally optimum situation of a 1,2-shift were estimated according to Sorensen [24] from the values of barriers to 1,2-shifts of the C–C bond and the hydrogen atom in polymethylnorbornyl ions.

Degenerate 1,2-shifts can be estimated from equation (4):

$$\Lambda_0 = \Delta G_S^{\neq}\cos\varphi_S, \tag{4}$$

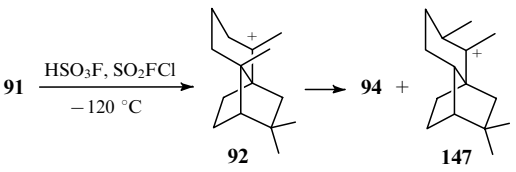
where $\Delta G_S^{\neq}$ is the barrier to the shift according to Sorensen and φ_S is the orbital factor in a norbornyl cation.

Since according to Sorensen's data the difference in the enthalpies of formation of secondary and tertiary isomeric norbornyl cations (in $\Delta\Delta H$) is equal to 5.5 kcal mol^{-1}, non-degenerate processes can be estimated from equation (5):

$$\Lambda_0 = (\Delta G_S^{\neq} + 5.5\,b)\cos\varphi_S. \tag{5}$$

The above equations allow one to predict the most probable pathways for the rearrangements of 1-chlorocaryolane,[59] clovene (**2**),[2] α-copaene (**120**) [57] and neoclovene (**91**) [44] in superacidic media.

Thus calculations have shown [44] that the ion **92** generated initially from neoclovene (**91**) is further converted into a mixture of two carbocations **94** and **147** with an energy gain, $\Delta\Delta H_f^o$, −13.0 and −10.7 kcal mol^{-1}, respectively. This result was confirmed in experiments on protonation of the alkene **91** in HSO_3F-SO_2FCl at −120 °C.[44]



Thus, the relatively simple technique for estimating the barriers to 1,2-shifts for the migrating ion [59] can efficiently be used for predicting rearrangements in alicyclic carbocations. However, this approach has some drawbacks. For example, the angle φ is not an unambiguous characteristic of the transition state strain. The internal barriers, Λ_0, were estimated [59] on the basis of kinetic data for rearrangements of σ-delocalised 2-norbornyl ions. The choice of such specific models has led to overestimated barriers for open and monocyclic ions.

The correlation ratios (6) and (7) for estimating $\Delta G^{\neq}$ for 1,2-shifts of the hydrogen atom and the methyl group in aliphatic and alicyclic carbocations which actually determine the barrier to a degenerate rearrangement have been proposed.[67]

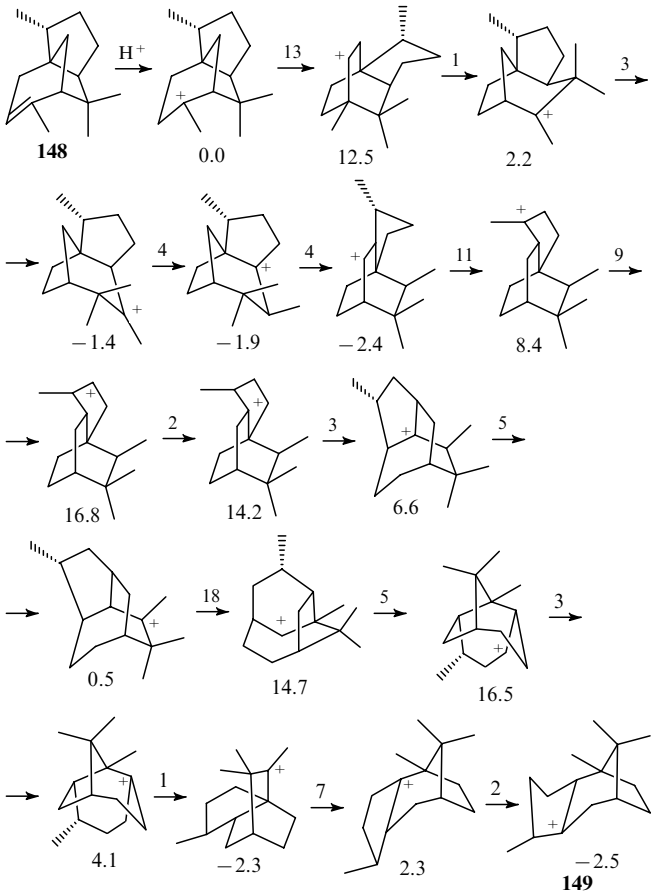
$$\Delta G_H^{\neq} = 15.33 - 10.79q_{\pi_x} + 0.232\log K_i,$$
$$r = 0.986,\ s = 0.9,\ n = 8, \tag{6}$$

$$\Delta G_{CH_3}^{\neq} = 25.74 - 21.48q_{\pi_x} + 0.303\log K_i,$$
$$r = 0.995,\ s = 0.8,\ n = 7, \tag{7}$$

where q_{π_x} is the value of the Hückel charge on the atom toward which the migrating group is displaced and K_i is the basicity constant of the *i*th position formed upon migrant detachment.

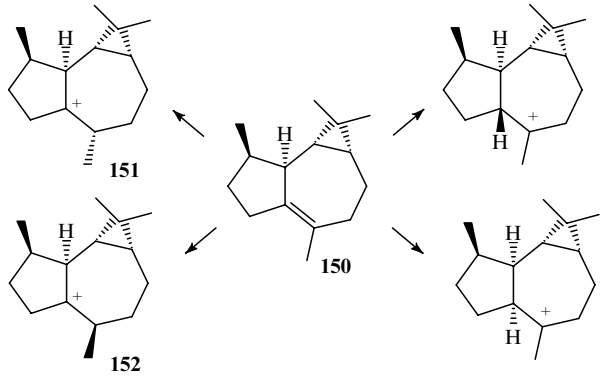
In this approach, the alkene formed upon elimination of the migrating group from the original cation serves as a model of the transition state of a 1,2-shift. The non-degeneracy of this process can be estimated by the Marcus equation (2). An advantage of this approach is the possibility of indirect estimation of the orbital factor and 'olefin strain',[68] since both these factors are included in the proton affinity value. However, the correlation ratios (6) and (7) are inapplicable to the Wagner–Meerwein rearrangement; in this case, $\Delta G^{\neq}$ can be determined only as described in Ref. 59.

The use of the above approaches [59,67] for estimating ΔH_f^o and $\Delta G^{\neq}$ has made it possible to propose the most probable pathway for α-cedrene (**148**) rearrangement in superacids resulting in the ion **149**.[69] The latter could be obtained experimentally (the figures under the structures refer to the $\Delta\Delta H_f^o$ values; the figures above the arrows indicate the values of the barrier to 1,2-shift in kcal mol^{-1}).

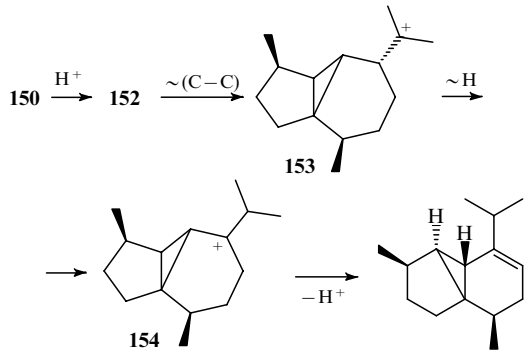


The primary site at which the cationic centre is formed in the alkene **148** having a trisubstituted double bond leaves no doubt. The primary proton attack in ledene (**150**) may involve both the double bond and the cyclopropane ring. Estimation of the proton affinity of the double bond and the three-carbon ring by the molecular mechanics method (MMX programme) revealed that the protonation of the double bond is much more preferable (by 3.5 kcal mol^{-1}).[69] As for the regio- and stereoselectivity of proton addition to the double bond, it has been found [69] that the protonation of the double bond at the carbon atom containing a

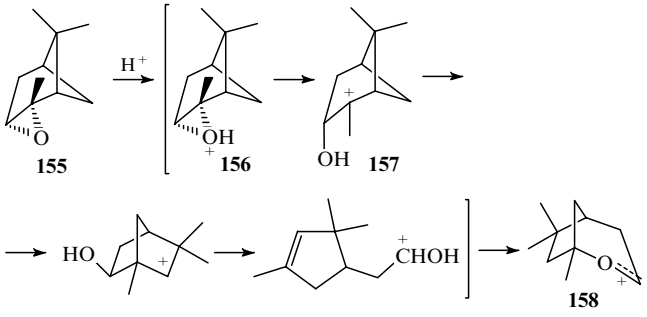
methyl group is more preferable for both α- and β-attack (by 9.2 and 8.3 kcal mol^{-1}, respectively) (MMX).



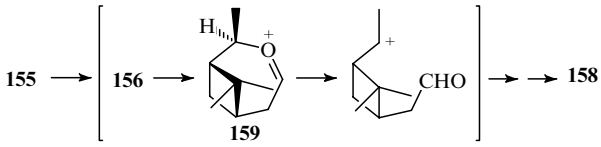
The isomeric ions **151** and **152** formed (ΔH_f^o = 157.4 kcal mol^{-1}) have identical stability. Therefore, the stereodirection of their protonation was established with the use of additional data, *viz.,* analysis of the Dreiding models of the alkene **150**, estimation of stability of epimeric epoxides prepared therefrom and estimation of steric accessibility of the double bond of the alkene **152** by the method described in Ref. 70. These data altogether suggest that the proton attack will occur largely from the α-side to yield the ion **152**.[69] The use of these approaches permits one to predict the rearrangement into the ion **153** and then into the ion **154** as the most probable pathway for alkene **150** transformations in 'long-living' ions; this conclusion was confirmed by the results of the reaction carried out in HSO_3F-SO_2FCl at −110 °C. The calculations predicted a gain in energy for the conversion of the ion **152** into the ion **154** (10.7 kcal mol^{-1}) (MMX).



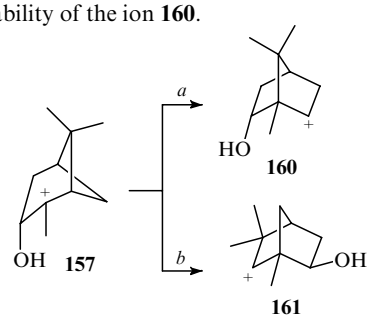
It should be noted that neglect of calculation methods in predicting the most probable pathways of multistep carbocation rearrangements may lead to serious misinterpretations of experimental data. Thus analysis of ^{13}C NMR data has led to a conclusion that dissolution of the epoxide **155** in HSO_3F-SO_2 at −70 °C yields the ion **158** according to the following scheme:[71]



The CH_2 group in the ion **157** undergoes a shift, although it is migration of the Me_2C group that should occur in this type of ions. To overcome this controversy, an alternative scheme has been proposed where the ion **156** is not converted into the ion **157** but undergoes an unusual for epoxides cleavage of the C−C bond in a three-membered ring.[71] This is followed by a hydride shift to the tertiary carbon atom with generation of the ion **159** and then into the ion **158**.

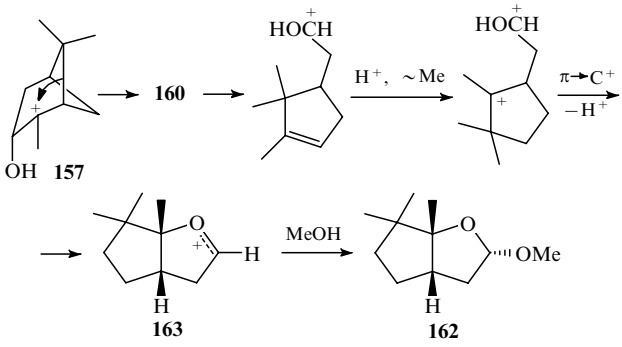


Later it was shown [72] that this scheme of epoxide ring cleavage contradicts both the experimental and calculated data. According to the calculations performed by the AM1 method, the ion **156** is converted into the ion **157** (but not into the ion **159**) without a barrier. Further rearrangements of the ion **157** occur predominantly by pathway *a* resulting in the ion **160** (ΔH_f^o = 145.1 kcal mol^{-1}) but not by pathway *b* (the ion **161**, ΔH_f^o = 150.3 kcal mol^{-1}), which is attributed to the greater stability of the ion **160**.

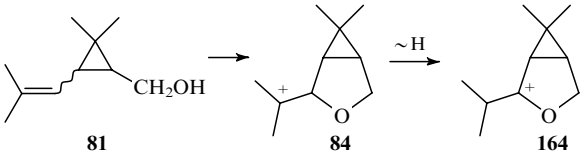


(*a*) $\Delta G^{\neq}$ = 5.9 kcal mol^{-1}; (*b*) $\Delta G^{\neq}$ = 6.5 kcal mol^{-1}.

In addition, it has been shown [72] that dissolution of the epoxide **155** in HSO_3F-SO_2FCl at −110 °C and subsequent 'quenching' with methanol yield acetal **162** as the main reaction product. The carboxonium ion **163** generated from the ion **158** by a standard route with a 1,2-shift of the Me_2C group is its immediate precursor.



We can cite another example of an error resulting from disregard of calculation methods. As has been noted above, the structure **84** was ascribed to the ion generated from the alcohol **81**.[39] However, quantum-chemical calculations by the MINDO/3 method (AMPAC programme) revealed that the cation **84** was converted into the ion **164** without a barrier. This suggests that the ion **84** could not be regarded as a stable species.



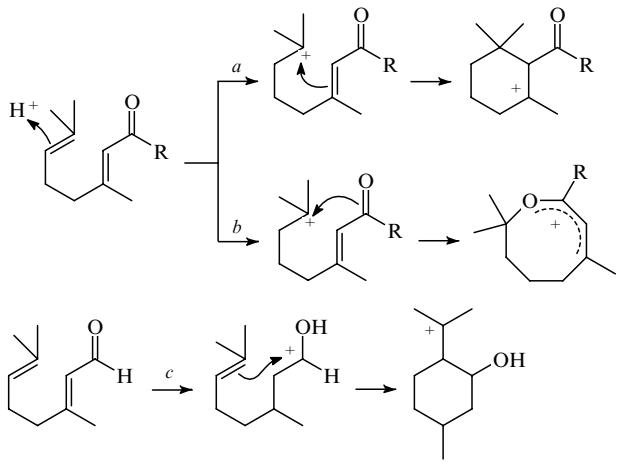
VII. A system of 'blocks' for aliphatic models

The synthesis of complex organic compounds from renewable plant material, particularly from widely accessible aliphatic monoterpenes by cationoid cyclisation acquires increasing importance (see Section VIII). Therefore, prediction of the most probable pathways of these processes becomes especially urgent. Unfortunately, pathways of structure-dependent cyclisation of acyclic compounds cannot be predicted either by quantum chemistry or molecular mechanics methods. By virtue of its 'non-rigid' geometry, the original compound can exist in different, relatively stable and energetically close conformations. Therefore, its cyclisation may occur by several different pathways; their choice is hampered by imperfection of the methods used.

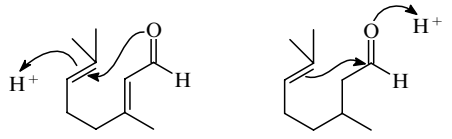
An alternative approach to the experimental proof of the cyclisation schemes consists in fixation of intermediate cations in the rearrangement of aliphatic monoterpenes and establishment of a correlation between their generation and the presence of definite structural 'blocks' in the molecule of the original compound.[73]

Systematic studies of the behaviour of terpenoids with identical carbon skeletons [*e.g.*, citral (**68**), ionone (**14**) and methyl geranate (**41**)] in superacidic media have made it possible to propose three main pathways of primary cyclisation,[73,74] *viz.*, proton attack at the terminal double bond resulting in generation of a tertiary carbocation and its subsequent addition to the carbon (pathway *a*) or oxygen atom (pathway *b*); addition of a proton to the oxygen atom and subsequent attack of the cationic centre at the terminal double bond (pathway *c*, Scheme 5).

Scheme 5

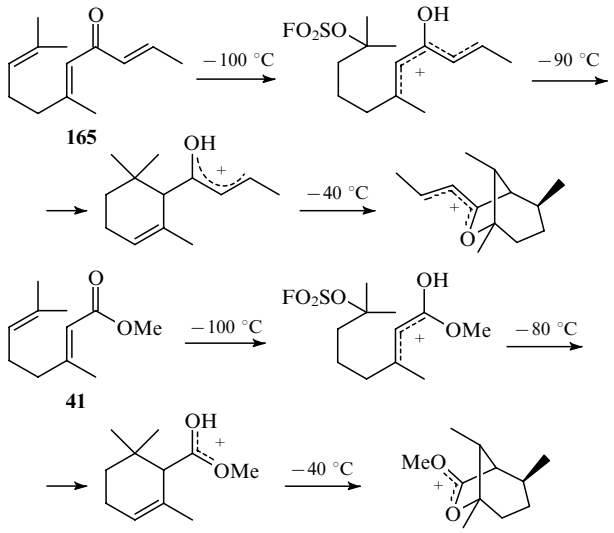


However, the cyclisation of citral (**68**) and citronellal (**69**), *i.e.*, two aldehydes with identical skeletons, occurs by totally different pathways.[29]

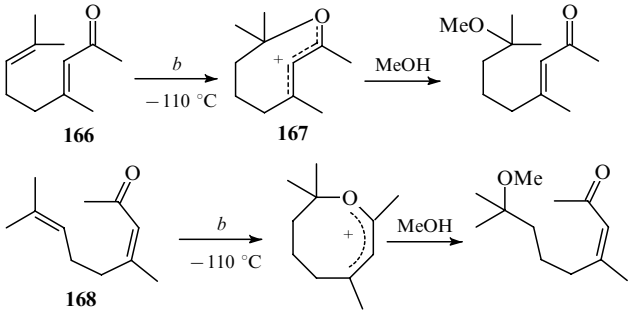


68 (pathway *b*) **69** (pathway *c*)

In some cases, compounds under study contain a common structural block which determines the pathway of cyclisation. This structural block is not necessarily identical with the carbon skeleton commonly used for classification of terpene compounds. For example, cyclisation in HSO_3F-SO_2FCl of φ-damascone (**165**) and methyl geranate **41** having different skeletons and belonging to different classes of organic compounds occurs by a similar route (pathway *a*, Scheme 5).[21]

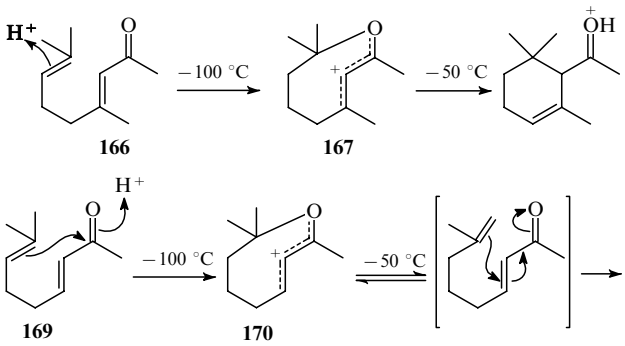


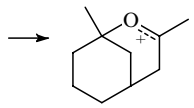
Studies with *trans*- (**166**) and *cis*-4,8-dimethylnona-3,7-dien-2-ones (**168**) have shown that reactions of isomeric acyclic isoprenoids with a conjugated 3,4-double bond can occur in HSO_3F-SO_2FCl in a stereospecific way (pathway *b*, Scheme 5) both in the stage of generation of intermediate ions and the formation of 'quenching' products from acid solutions. Hence, the structural direction and stereochemical result of cyclisation of α,β-unsaturated carbonyl compounds of the terpene series depend on the configuration of the 3,4-double bond.



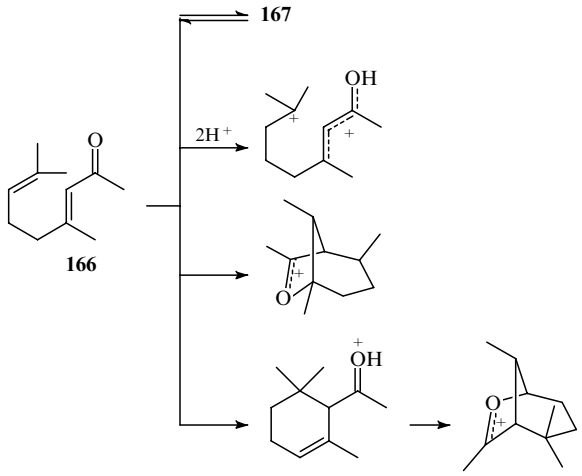
At first glance, ketones **166** and **168** share a common structural block with compounds **41** and **165** but the pathways of their primary cyclisation are totally different. Comparison of these models allows one to conclude that carbocyclisation requires that the structural fragment, $Me_2C=CH(CH_2)_2C(Me)=CHCO$, was linked with a substituent X able to stabilise the positive charge by a mesomeric effect (OMe, CH=CHMe); otherwise heterocyclisation will take place.

Substitution of the hydrogen atom for the methyl group at C(4) in the ketone **166** (→ **169**) changes substantially the pathways of cyclisation of compound **166** (Scheme 5, pathway *b*) and compound **169** (Scheme 5, pathway *c*) due to secondary conversions of the homologous carbocations **167** and **170**.

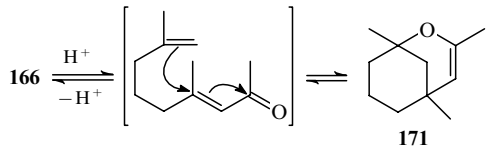




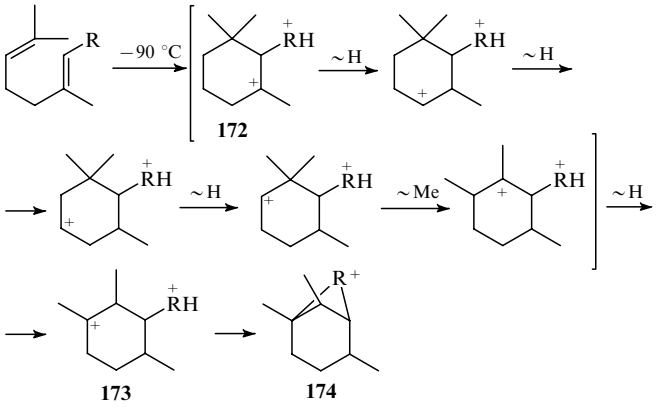
Varying the conditions of ion generation, particularly the acidity of the medium and temperature, makes it possible to carry out directed multistep rearrangements, *e.g.*, carbo- or heterocyclisation of ketones **166** and **168**.[73] In this case, heterocyclisation strongly depends on the configuration of the conjugated 3,4-double bond. Cyclisations of the 'ionone' type are independent of the spatial structure of the original substrate.



It is of note that compound **171** is the main product formed from the ketone **166** in dilute sulfuric acid.[73] In this case, the main pathways of cyclisation in superacids and 'ordinary' acids are different, since in the latter case intramolecular rearrangements prevail, which is not the case with superacids.

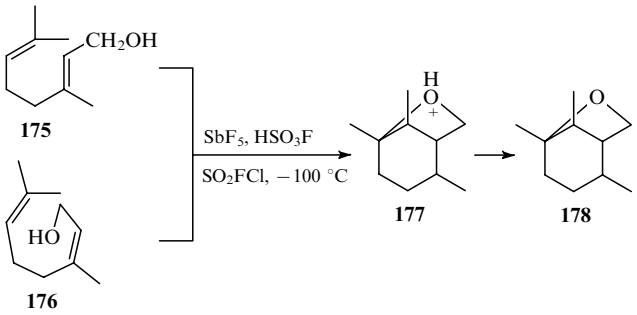


It was shown[21,73,74] that many acyclic terpenoids (compounds **14**, **15**, **41**, **165**, **166**, **168**) undergo similar conversions in $SbF_5-HSO_3F-SO_2FCl$ according to the following scheme:

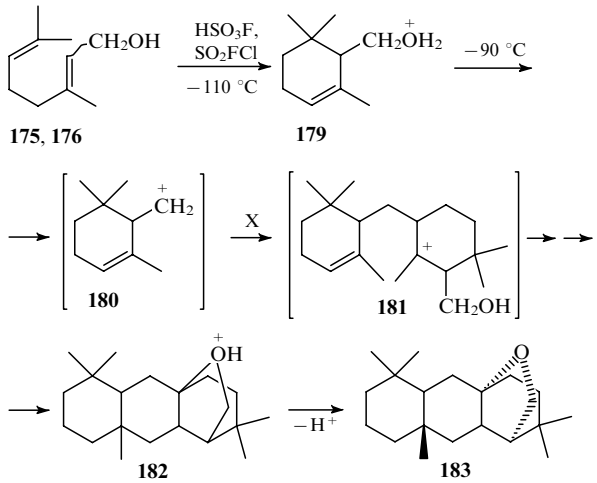


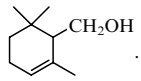
R = COCH=CHMe, COMe, CH=CHCOMe, COOMe.

Electrostatic repulsion of positive charges in the primary dication **172** is the reason for its rearrangement into the dication **173** (from ketones **14** and **15**) or a bridged ion of the type **174** (from the ester **41** and ketones **166** and **168**). Erroneous structures were ascribed to the conversion products of geraniol (**175**) and nerol (**176**) in superacids.[75,76] We assumed[77] that rearrangements of aliphatic alcohols **175** and **176** proceeded in accordance with the above scheme and gave the ion **177** and the ester **178**, since they have a common structural block with compounds **165**, **166** and **168**. This hypothesis was confirmed experimentally.

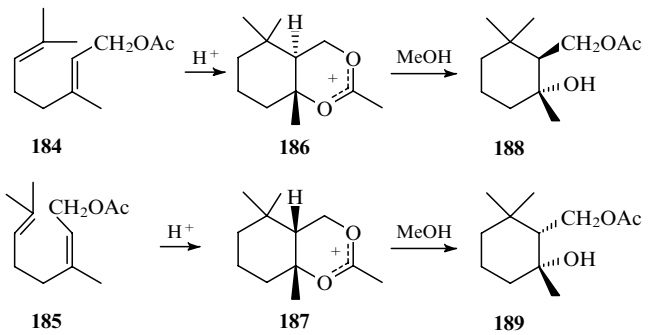


The type of rearrangements of alcohols **175** and **176** depends on reaction conditions. Thus the cyclic oxonium ion **179** was obtained in HSO_3F-SO_2FCl at -110 °C, while the tetracyclic ion **182** was formed from intermediates **180** and **181** upon heating of the reaction mixture to -90 °C. Deprotonation of the ion **182** gives the ether **183**. Such a conversion of a monoterpene into a diterpene has no analogues either among cyclisation reactions of acyclic isoprenoids occurring in superacids or among monoterpene reactions realised in ordinary acidic media.[78]



X = 

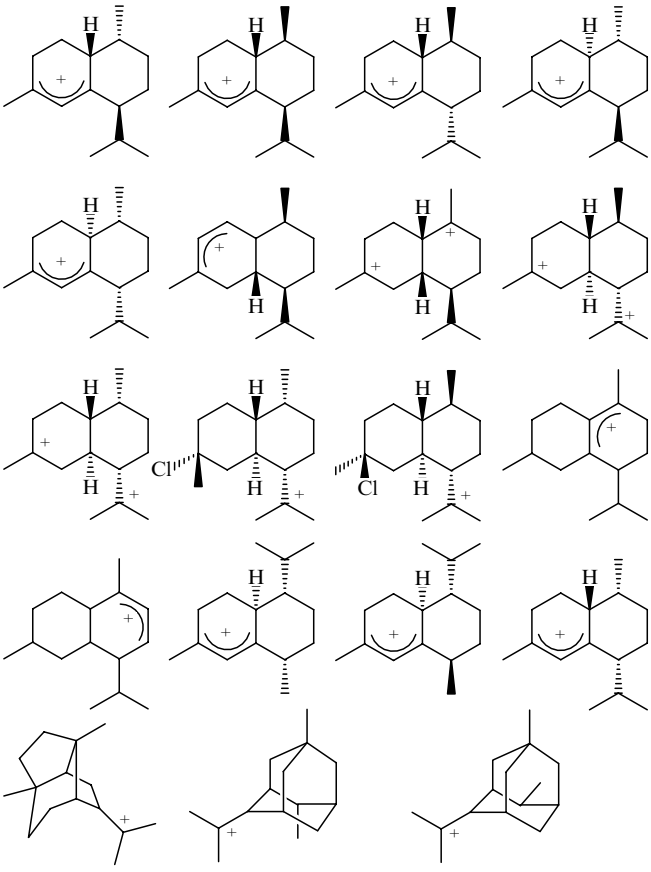
The outcome of rearrangements of stereoisomeric alcohols **175** and **176** is independent of the configuration of the 2,3-double bond,[77] while reactions of geranyl (**184**) and neryl acetates (**185**) gave different products. In HSO_3F-SO_2FCl (-120 °C), these compounds are predominantly converted into acyloxonium ions **186** and **187**, respectively. 'Quenching' of acidic solutions of ions **186** and **187** results in diastereomeric hydroxy acetates **188** and **189**.



VIII. Synthetic aspects of terpene reactions in superacidic media

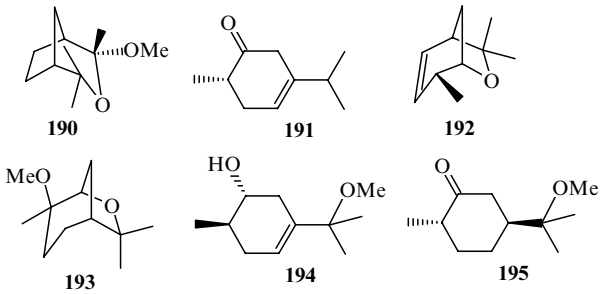
One of the goals of studies of behaviour of terpenoids in superacids is to extend the range of new synthetic substances that can be prepared from accessible natural compounds and their analogues. Structural features of these compounds and the use of superlow temperatures and hypernon-nucleophilic media in the reactions ensure great diversity of molecular rearrangements. In contrast with acid-catalysed processes, the use of superacids allows for: (*a*) multistep conversions due to hypernon-nucleophilicity of the medium; (*b*) the possibility to obtain dications, which has no analogues in acid-catalysed reactions; (*c*) rapid conversion of original substrates into carbocations, which prevents cationic polymerisation due to high acidity; (*d*) high structural and stereochemical selectivity owing to the use of superlow temperature.

The preparation of 19 stable carbocations (which represent optical isomers) from an optically active diene, *viz*., (−)-α-murolene (**48**), serves as an illustrative example of synthesis of different compounds from terpenes in superacids.[53] The direction of reaction was changed by varying the mode of ion generation (protonation of the diene or solvolysis of the corresponding dichloride), the acidity of the reaction system and the temperature at which ions were generated or 'defrosted'. Reactions of these ions with nucleophiles gave rise to different dienes, *viz*., natural terpenes or previously unknown isomers.



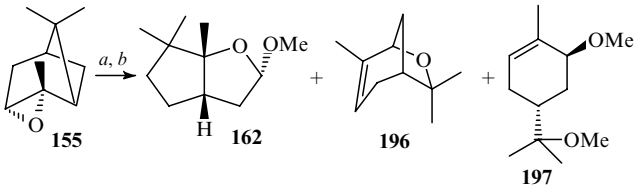
The conversions of compounds **14**, **15**, **31**, **32** and **125** considered in this review demonstrate the possibility of synthesis of various compounds through intermediate generation of di- and monocations having identical skeletons.

Conducting reactions in superacidic media provides greater possibilities for varying the structure of reaction products in comparison with ordinary acidic media.[72, 79] Thus treatment of the epoxide **74** with proton acids usually gives products with retention of a carane skeleton and few compounds with a bicyclo[3.1.0]hexane skeleton.[80] In HSO_3F-SO_2FCl at −110 °C, this epoxide generates a mixture of compounds **190**–**195**.



Compounds **190**–**195** have not been previously obtained upon acid-catalysed cleavage of the epoxide **74**. Their formation can be ascribed to the initial opening of the epoxide ring, subsequent rearrangements with cleavage of the cyclopropane ring and stabilisation of cations by virtue of reactions with internal or external nucleophiles or elimination of a proton.

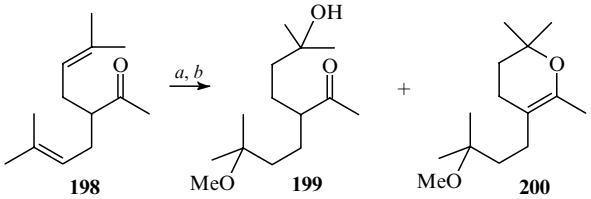
The behaviour of the epoxide **155** in HSO_3F-SO_2FCl (−110 °C) has been studied.[72] The three main reaction products were acetal **162** and esters **196** and **197**.



(*a*) HSO_3F, SO_2FCl, −100 °C; (*b*) MeOH.

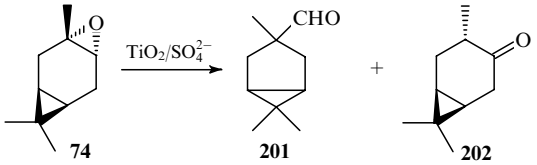
These compounds have also not been isolated earlier upon acid-catalysed cleavage of the epoxide **155**.

6-Methyl-3-(3-methylbut-2-enyl)hept-5-en-2-one **198** does not yield monomeric products under acid-catalysed conditions but is resinified. However, it gives a mixture of compounds **199** and **200** (yield 80%) upon treatment with HSO_3F-SO_2FCl (−110 °C) with subsequent 'quenching'.[29]

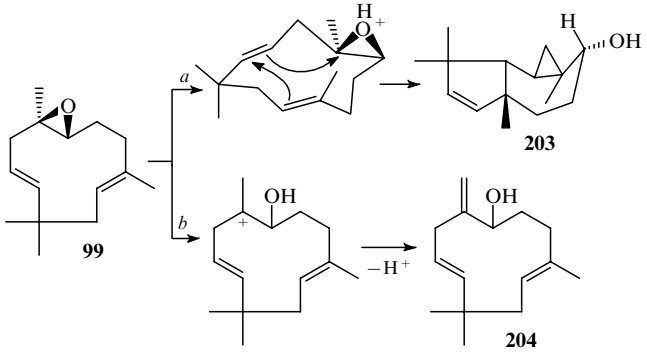


(*a*) HSO_3F, SO_2FCl, −110 °C; (*b*) MeOH.

As has been noted above, the use of liquid superacidic media allows one to obtain a more complete set of substrate transformation products. If the problem is to prepare a specific compound, it is necessary to choose an appropriate solid catalyst, *e.g.*, a solid superacid. The role of such catalysts may be played by sulfates of transition metal oxides, which, according to literature data, have not been used previously as acid catalysts in terpene reactions. It has been shown [79] that the use of TiO_2/SO_4^{2-} as an acid catalyst in isomerisation of the epoxide **74** allows one to obtain a mixture of reaction products in which the aldehyde **201** and the ketone **202** predominate, which is different from the results obtained with liquid superacids. Earlier, compounds **201** and **202** were considered to be intermediate products in the preparation of the acetal **190** and the ketone **195** in liquid superacids.



The pathways of conversions of conformationally flexible substrates in both liquid and solid superacids can be different. Thus the isomerisation of the epoxide **99** in a liquid superacid (HSO_3F-SO_2FCl) differs from that on a solid catalyst (Al_2O_3/SO_4^{2-}) and alcohols **203** and **204** are formed, respectively.[81]

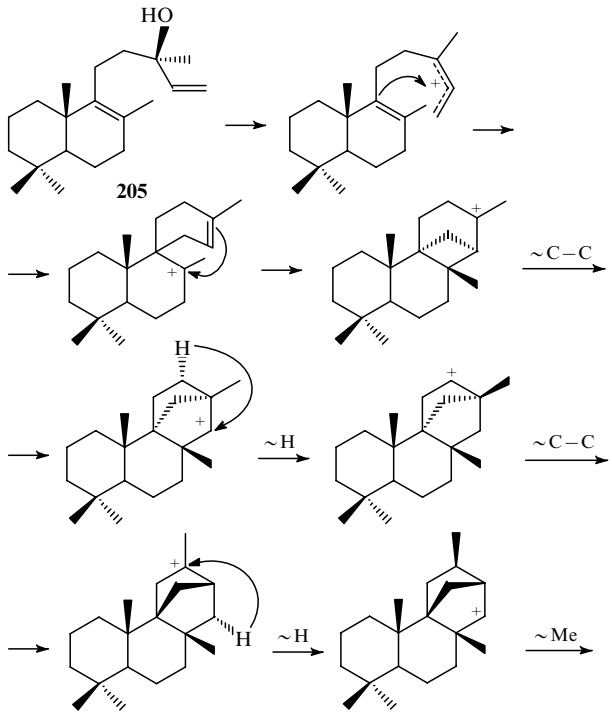


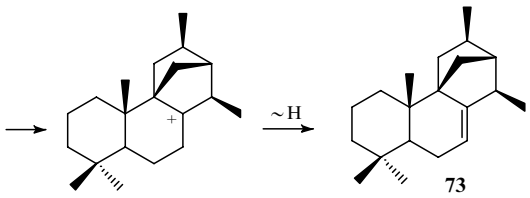
(*a*) HSO_3F, −80 °C; (*b*) Al_2O_3/SO_4^{2-}, 20 °C.

This phenomenon can be explained by the difference in conformational control due to low temperature and epoxide binding on the catalyst surface.

IX. Biogenetic aspects of terpene reactions in superacidic media

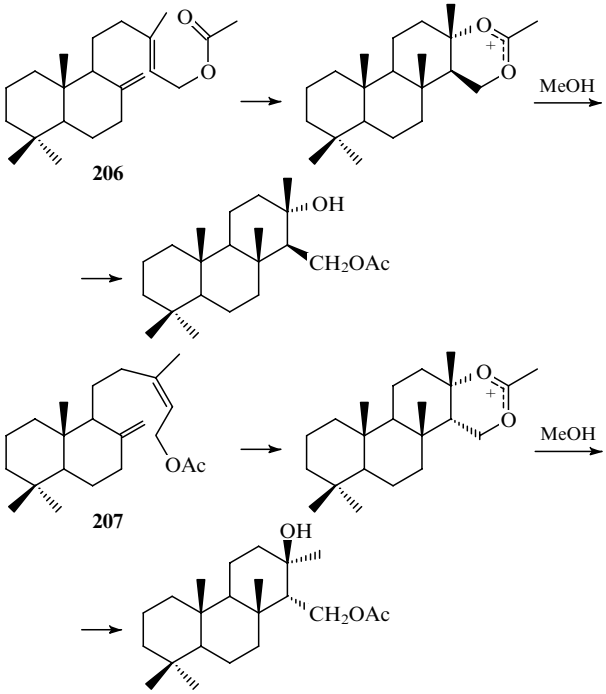
The biogenetic aspect is the last to be considered in this review. A question then arises about the relationship between the processes occurring under natural conditions and in superacidic media. According to Nishizawa *et al.*,[18] biomimetic cyclisation of terpene alkenes is a 'stepwise' process which involves intermediate formation of cationic species. Their properties are best studied by modelling the behaviour of carbocationic salts under 'long-life' conditions. Low temperatures favour regio- and chemoselectivity of the reactions and conformational control, whereas hypernon-nucleophilic media are beneficial for more profound conversions. An example of such a conversion is cyclisation of isomanool (**205**) in HSO_3F-SO_2FCl (−110 °C) into tetracyclic compound **73**, which occurs in nine steps.[30]



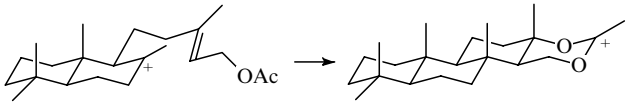


The conditions of acid catalysis are much more distant from those of biogenetic reactions because they occur in accordance with the Curtin–Hammett hypothesis, *i.e.*, in the absence of conformational control, and the reactions do not involve profound rearrangements and are often stopped due to interactions with nucleophiles. Thus, superacidic media favour biomimetic reactions 'mimicking' natural processes and provide chemical evidence for practicability of various biogenetic schemes.

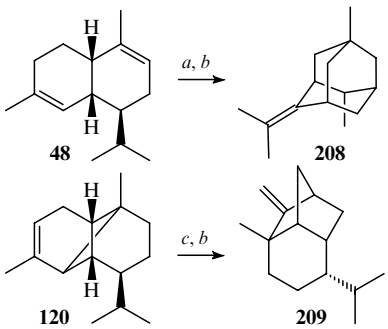
Thus it has been shown[30] that cyclisation in superacids (HSO_3F-SO_2FCl, −100 °C) of labdane diterpenes **206** and **207** with primary allylic oxygen-containing groups in the side chain can be used for stereoselective syntheses of bifunctional compounds of the isoagatane series of specific structures. The ease of their cyclisation at low temperatures suggests that bicyclic labdanes might be biogenetic precursors of isoagatane compounds. Cyclisation of these compounds in ordinary acids yields a very complex mixture of reaction products in which the content of isoagatanes does not exceed 10%.



A similar mechanism has earlier been proposed for biogenetic cyclisation by Nishizawa *et al.*[18]

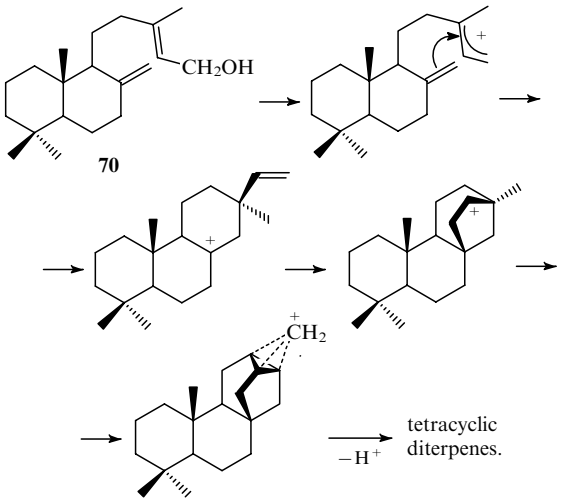


A key role in biogenetic schemes of sesquiterpenes has been ascribed to the diene **48**, which is considered as a precursor of tricyclic compounds with cubebane, copabornane and copaane skeletons. However, attempts to synthesise tricyclic products from the diene **48** and the alkene **120** by acid-catalysed reactions have failed. In contrast, tricyclic compounds **208** and **209** were obtained in HSO_3F-SO_2FCl.[57]

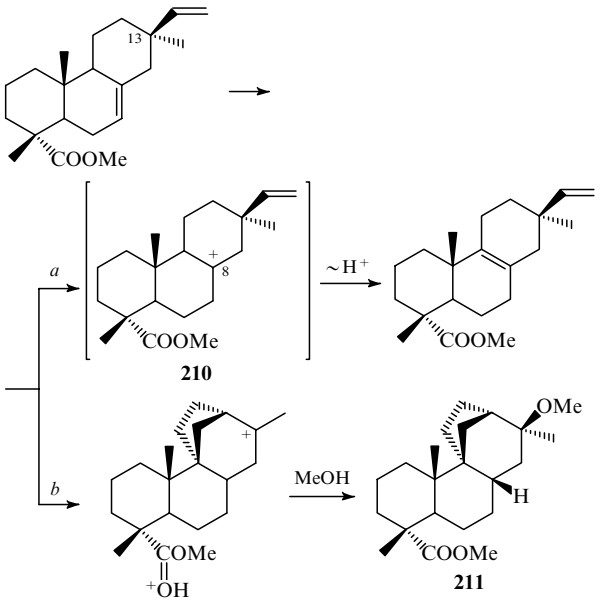


(*a*) HSO_3F, SO_2FCl, −30 °C; (*b*) MeOH; (*c*) HSO_3F, SO_2FCl, −110 °C.

Wenkert [82] has hypothesised that tetracyclic diterpenoids with different skeletons are formed from bicyclic diterpenoids according to the following scheme:

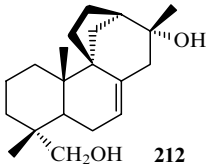


However, the attempts at *in vitro* synthesis of tetracyclic diterpenes from tricyclic ones have not met with success.[83] Thus treatment of pimaradienes with ordinary acids resulted merely in their isomerisation. It was therefore concluded that in contrast with the Wenkert scheme, pimaradienes are not biogenetic precursors of tetracyclic compounds. However, the use of superacidic media allowed, for the first time, cyclisation of pimaradienes into the tetracyclic compound **211**.[84] The failure to effect this cyclisation under conditions of acid catalysis was due to the higher rate of cation deprotonation at C(8) (compound **210**) resulting in the formation of a sterically hindered tetra-substituted double bond in comparison with the rate of cyclisation involving the vinyl group.



(*a*) $[H^+]$; (*b*) HSO_3F, SO_2FCl, −100 °C.

The skeleton of compound **211** is similar to that of stemarine **212** isolated recently from a natural source.[85]



It is assumed that the latter is biosynthesised from pimaradienes. The preparation of the same stemarane-type stereoisomers from compounds of the pimaric and isopimaric series that are diastereomeric at the C(13) atom [84] provides evidence for the practicability of the Wenkert scheme postulating intermediate generation of a non-classical ion.

X. Conclusion

Thus, the main factors that control multistep multiroute cationic molecular rearrangements in superacidic media at superlow temperatures are the following: the nature of the acidic medium, the mode of generation of the cationic centre (solvolysis or proton addition to the alkene double bond), the temperature at which the cationic centre is generated and the temperature at which the acidic solution is 'defrosted'. The most probable pathways of multistep cationic rearrangements can thus be predicted with due regard to the orbital and thermodynamic factors. In practical syntheses of products of multistep cationic rearrangements, preference should be given to solid acidic (particularly superacidic) catalysts rather than to liquid superacids.

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