Superacidic cyclization of terpenoids

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Abstract. A general highly efficient structure-selective and stereospecific method of superacidic cyclization of terpenoid alcohols and their acetates, acids, esters and also of homo- and bishomoterpenoid alcohols, acids and esters has been elaborated. The terminal terpenic epoxides do not cyclize, undergoing isomerization and opening of the oxirane cycle.

The peculiarity of natural terpenoids of composition C_{10}-C_{30} is the diversity of their primary carbocyclic structure differing by their carbon backbones although there are only five acyclic precursors - polyprenols. Despite this diversity, for the majority of cyclic isoprenoids, biogenetic schemes have been suggested, which correlate their structure and stereochemistry with aliphatic precursors. The theoretical basis for this was the biogenetic isoprene rule formulation by Ruzicka and coworkers in the early 1950s.

Further investigations carried out with the aim to prove this rule by chemical means resulted in the clarification of the chemical regularities of the electrophilic cyclization, its mechanism and the elaboration of the most general and effective ways for cyclic terpenoid synthesis. One of these ways is the electrophilic cyclization of aliphatic isoprenoids, including also those with a terminal epoxy group, under the influence of external electrophiles; another way is the solvolysis of sulfonate esters, acetals and allylic alcohol esters of close terpene analogs [ref 1-4]. However, the solvolytic way leads to cyclic compounds of irregular terpenic structure. Moreover a very complex problem is the synthesis of the starting compounds. A great variety of reagents have been used as external electrophiles for cyclizations, but for the preparation of cyclic terpenoids of regular structure, common protic acids turned out to be the most universal ones. The disadvantage of this method is the low structure-selectivity of the reaction due to deprotonation and isomerization of the intermediates.

However, it should be pointed out that in spite of some success in the investigation of electrophilic cyclization, one failed to obtain, in good yields, the regular terpenoids containing more than two carbocycles in their molecule.

Our research has shown that superacids are highly effective reagents for performing electrophilic cyclization without the above-mentioned drawbacks, when the reaction is carried out at low temperature. Thus, the superacidic cyclization of acyclic and partially cyclized terpenols takes place according to general
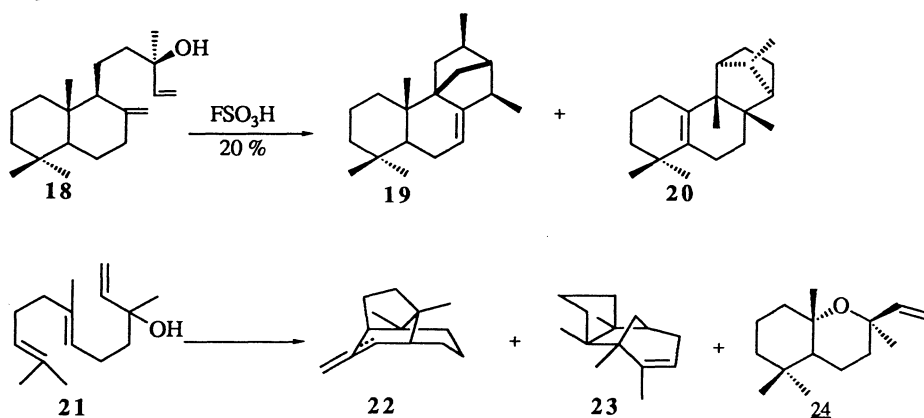
Scheme I
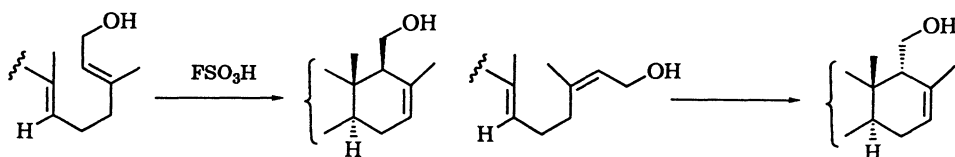
scheme I, giving completely cyclized homoallylic alcohols ; the configuration of the hydroxymethylene group of these products is governed by the configuration of the starting allylic alcohol. Concrete examples of the cyclization of polyprenols C_{10}-C_{25} are given in scheme II [ref. 5-10].
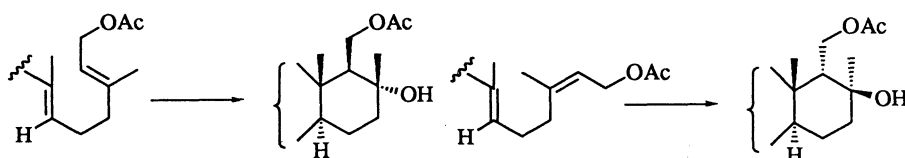
Scheme II
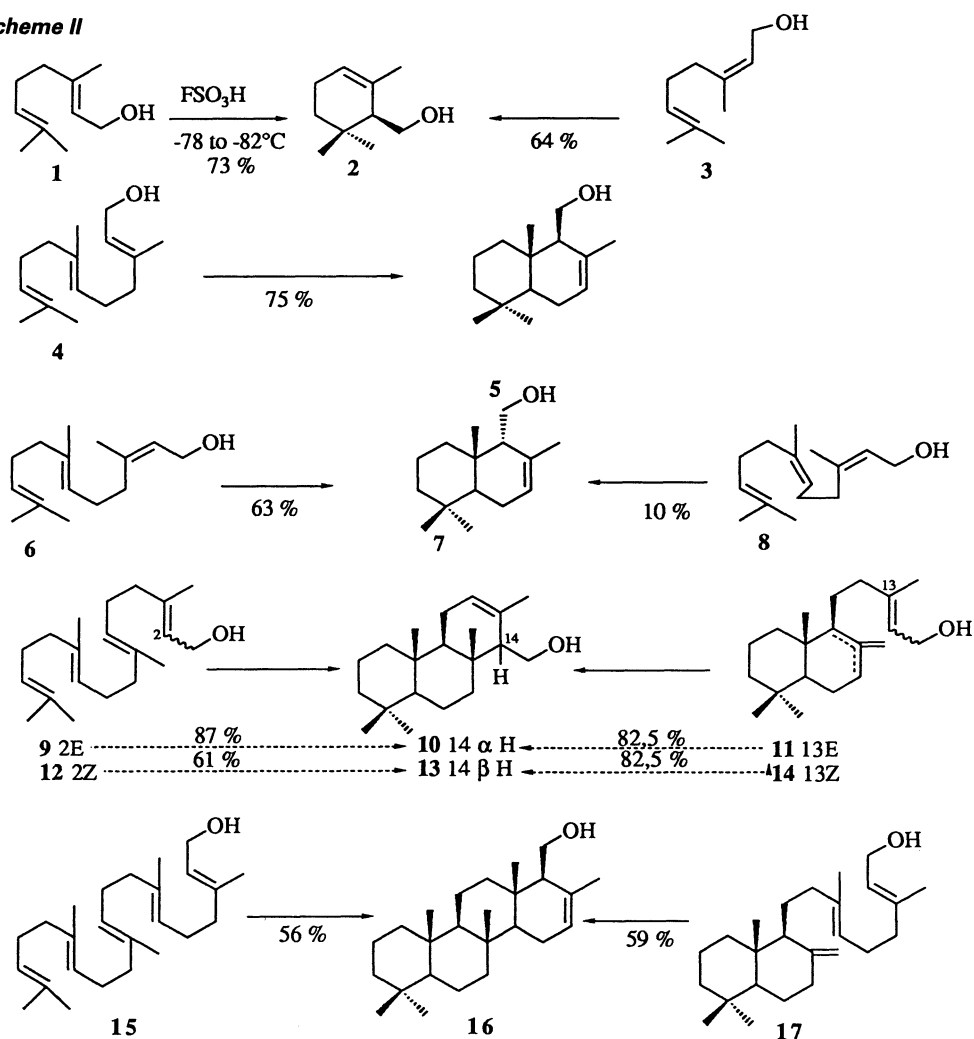
Hence, the superacidic cyclization of polyprenols is structure- and chemo-selective, stereospecific, and for the aliphatic alcohols is also biomimetic. The only by-products of the reaction are hydrocarbons (5-12 %) and polymeric compounds. The cyclization can be carried out directly without protection of the hydroxy group. Unlike the reaction of polyprenols with conventional acids, on their interaction with superacids the primary and tertiary allylic alcohols give different products. For example, compounds **11**, **18** (scheme II) [ref. 11] and **21** [ref. 10] (scheme III) yield different substances.

Scheme III

The cyclization of polyprenol acetates also occurs in a structure-, chemo-selective and stereospecific way but leads to bifunctional derivatives according to the general scheme IV. In this case as well, the by-products are small amounts of hydrocarbons (5-15 %) and polymeric compounds. Concrete examples of such reactions are given in scheme V [(ref. 5-10)].

Scheme IV

Scheme V
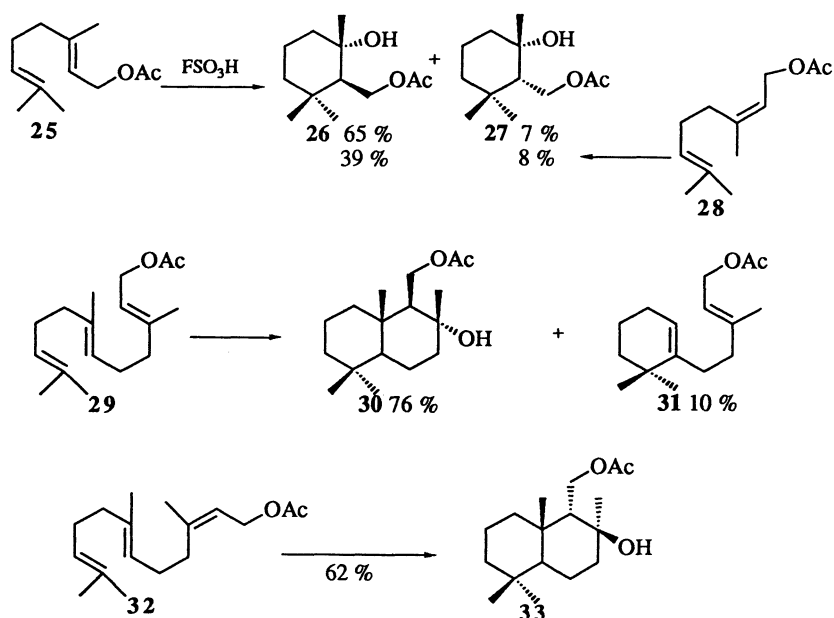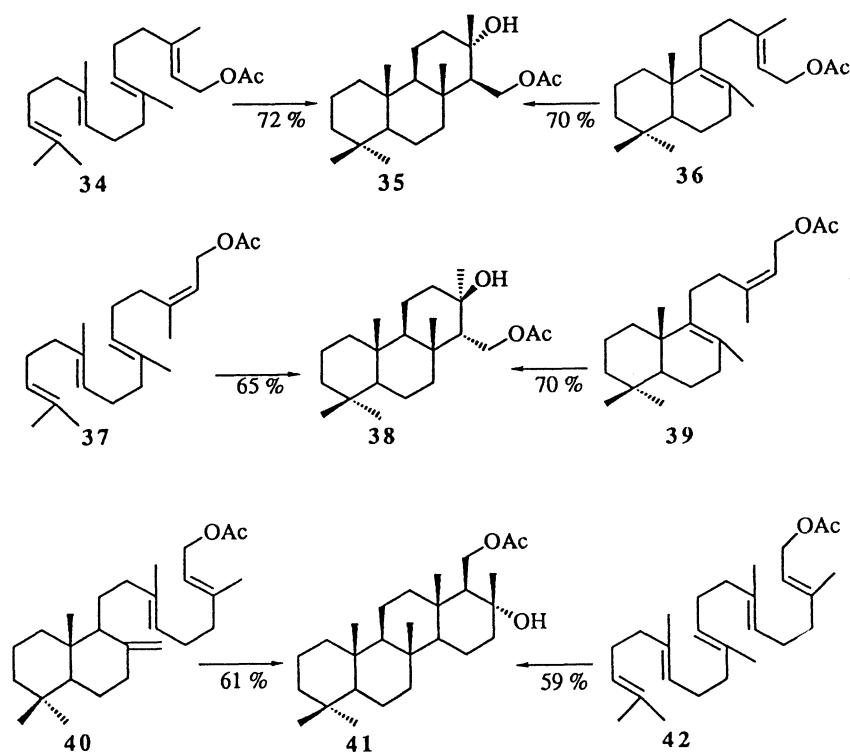
The formation of the mixture of compounds 26 and 27 on cyclization of geranyl-25- and neryl-28-acetates is due perhaps to the conformational mobility of the monocyclic system. The cyclization of E,E-farnesyl acetate 29 gives in low yield β-monocyclofarnesyl acetate 31, which becomes predominant (yield 70 %) if the reaction is interrupted after one minute. Both this fact and the formation of epidrimenol 7 on cyclization of Z,Z-farnesol 8 [ref. 10] indicate that the cyclization process is a stepwise and not a concerted one. It should be particularly mentioned that the superacidic cyclization of the aliphatic sesterterpenoids 15 and 42 affords stereospecifically in one step and high yield the tetracyclic scalarane sesterterpenes 16 and 41, containing respectively seven and even eight (!) chiral carbon atoms.

Taking into account the labile character of allylic alcohols and their esters, it was interesting to reveal the general regularities of superacidic cyclization of terpenoid acids and their esters, particularly in the di- and sesterterpenic series because attempts to cyclize such compounds by conventional acids had turned out to be unsatisfactory [ref. 12,13]. Some of the results obtained are given in scheme VI [ref. 14-16].

Rather impressive are the results of cyclization of acyclic sesterterpenic acids and esters, the yields of the reaction reaching about 70-80 % [ref. 16]. On cyclization of acids the yield was lower than that of the esters by 2-5 %. The only by-products of the reaction were polymeric compounds. On passing from terpenols to the corresponding acids and esters, the reaction needs more vigorous conditions (for example, the cyclization reagent : substrate ratio 25:1 and -40 °C).

Hence, the superacids represent choice reagents for the biomimetic cyclization of regularly-structured terpenoids. Being supernonnucleophilic media, they contribute to a greater development of positive charges on the carbocationic centers, and suppress the elimination and isomerization reactions of

Scheme VI
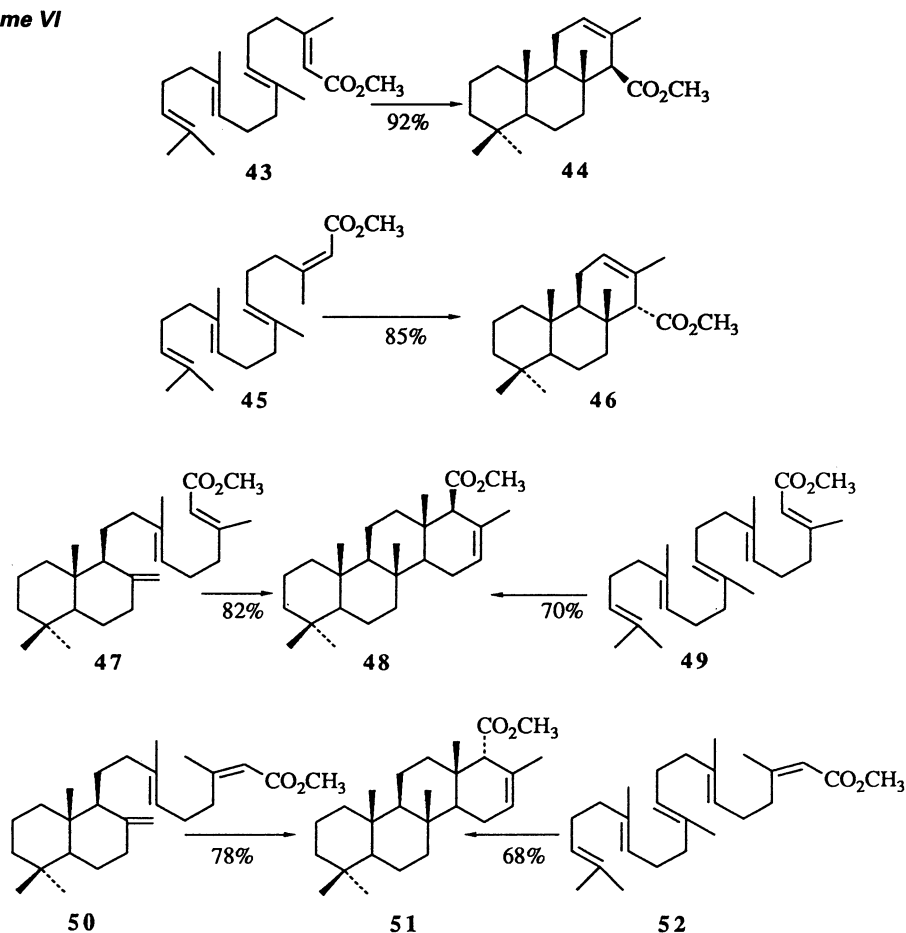
intermediates. Therefore it was possible to expect that they would favour the internal trapping of carbocations by appropriately placed nucleophilic functional groups (OH, COOH, CO_2R and others). That is why we have studied the cyclization of homo- and bishomoterpenoid alcohols, acids and esters, choosing substrates whose cyclization products are either important natural compounds or useful ones. In such a way Ambrox[R] 54 and homofixateur 57, both valuable compounds for the perfumery industry, were prepared respectively from E,E-homo- 53- and E,E bishomo- 56- farnesols [ref. 17] (scheme VII).

Scheme VII
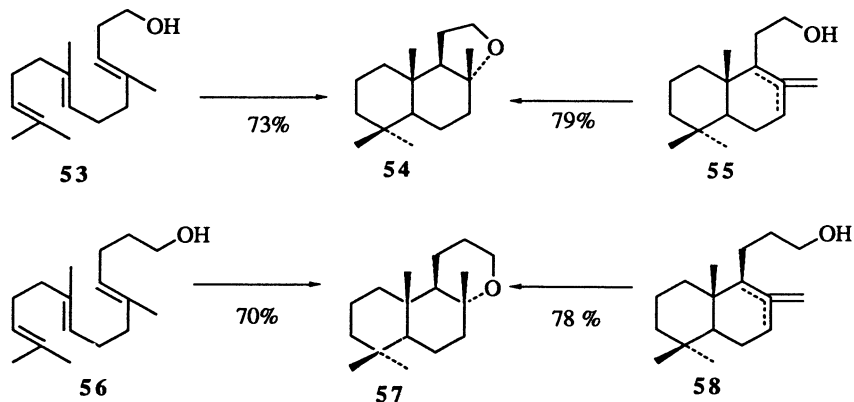
These are the shortest and the most efficient syntheses of their racemic forms. In the optically active form, they were obtained by superacidic cyclization of the unsaturated alcohol mixtures 55 and 58.

The superacidic cyclization and lactonization of homo- and bishomoterpenoid acids respectively into γ- and δ-lactones take place more easily and efficiently than by other means (scheme VIII) [ref. 18] : on treatment with conventional acids, these compounds yield substance mixtures, and in each particular case it is necessary to undertake an empirical search for cyclization reagents and conditions.

Scheme VIII
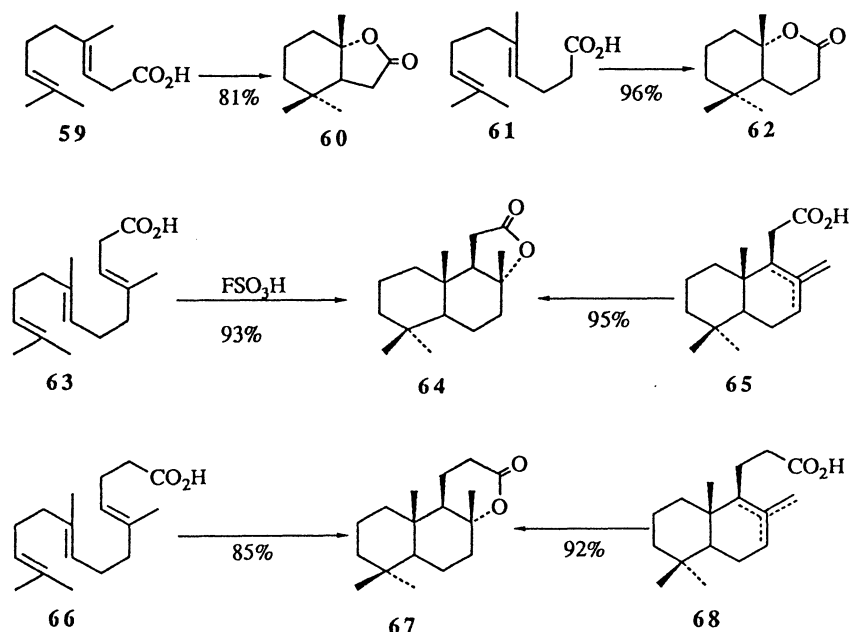
It is also important to note that unlike the conventional acids, the superacids do not isomerize the trans-fused γ-lactones 60 and 64 into the thermodynamically more favoured cis-fused lactones.

Taking methyl bishomofarnesate 69 as an example, the cyclization of such compounds was shown to occur with the formation of hydroxy esters (scheme IX).

Scheme IX
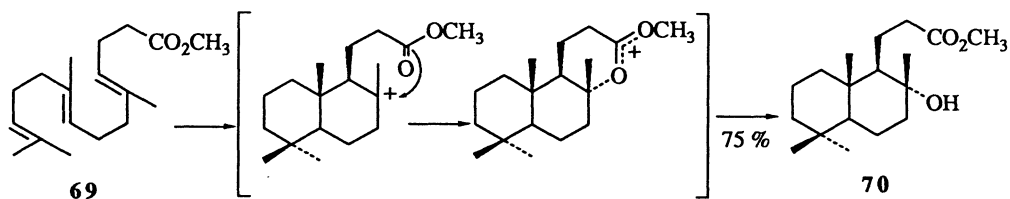
In connection with the synthesis of oxygenated terpenoids, the study of the reaction of terminal α- and β-epoxy terpenoids with superacids was of particular interest. Unfortunately, under the conditions used, the main course of the reaction was the isomerization of the epoxy group (scheme X).

Scheme X
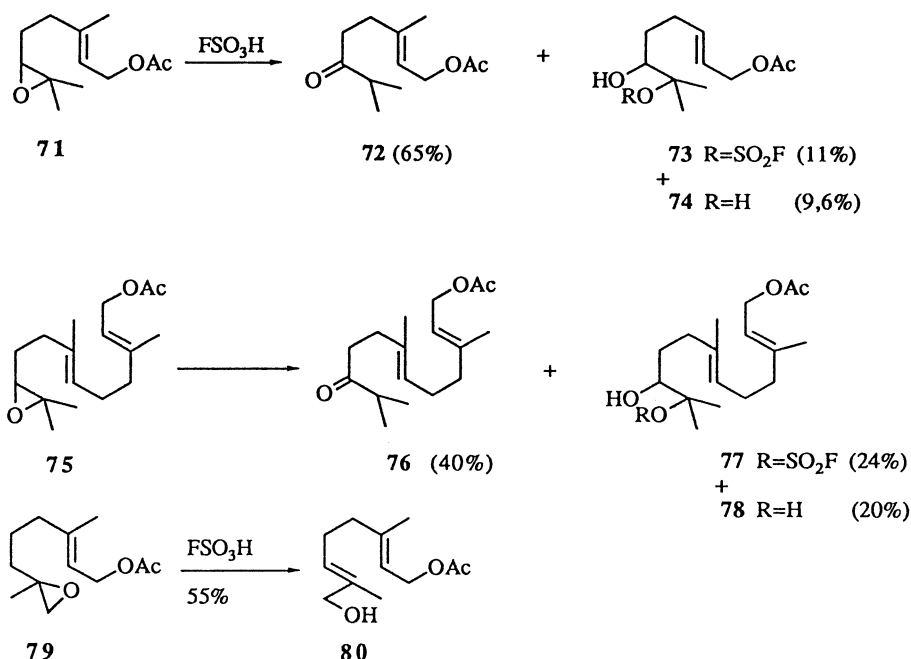
The aforementioned data convincingly demonstrate that the synthetic possibilities of the reaction of electrophilic cyclization of isoprenoids are considerably extended by passing from the usual acids to superacids. Varying such parameters as acid-substrate ratio, temperature, medium acidity, acid concentration and reaction duration, it is largely possible to govern the structural and stereochemical reaction course, which is illustrated by the transformations in scheme XI (ref. 10,19).

Scheme XI
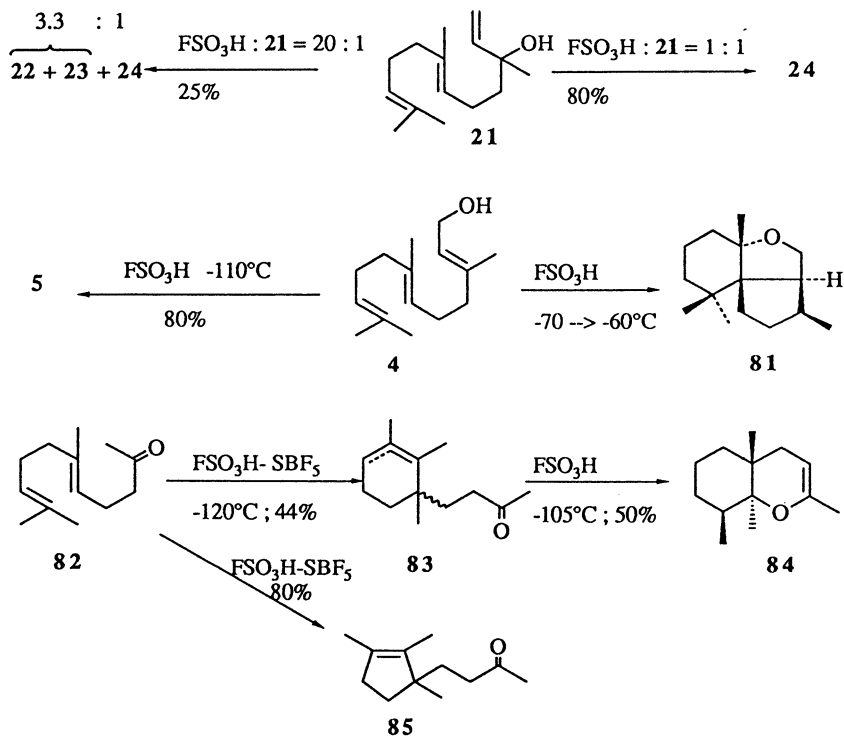
It is very important to note that in the superacidic medium it is possible to follow the behaviour of the carbocations by NMR and consequently to select conditions to carry out the reaction to the desired product. Finally, in a superacidic medium it is possible to obtain compounds which are not formed with usual acids. In scheme XI this is illustrated by the transformations of geranylacetone **82**.

In conclusion, it should be pointed out that certainly the superacidic cyclization of isoprenoids (and not only of them) has become a new, important synthetic tool for the preparation of a great diversity of cyclic terpenoid compounds otherwise hardly accessible. Undoubtedly its further study will substantially widen the synthetic applications of terpenoids.

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