Cyclization and Rearrangements of Farnesol and Nerolidol Stereoisomers in Superacids

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Acid-catalyzed cyclization of 2,3-*trans*- and 2,3-*cis*-farensol proceeds regioselectively and stereospecifically, yielding drimenol and *epi*-drimenol, respectively. The *trans* and *cis* isomers of nerolidol undergo carbo- and heterocyclization reactions. The *trans* isomer gives tricyclic caged hydrocarbons with new skeletal types, while the rearrangements of the *cis* isomer produce derivatives of 2-oxabicyclo-[4.4.0]decane. The ICAR computer program was used to derive reasonable mechanisms for the acid-catalyzed transformations of nerolidol, and the probability of the mechanisms was evaluated by the molecular mechanics method.

Introduction

Superacid-induced electrophilic cyclizations of acyclic isoprenoids have been studied in a series of papers.[1] The intermediate carbocations were directly observed by NMR spectroscopy to establish the dependence between the structure of the initial molecule and the preferred direction of the carbocationic transformations. In the present work, our attention was directed mainly toward farnesol (**1**), which is known to be an important representative of natural acyclic sesquiterpenoids.[2]

According to biogenetic schemes, pyrophosphates of *trans, trans* (**1a**) and *cis, trans* (**1b**) isomers of farnesol, as well as that of *trans*-nerolidol (**2a**) tend to undergo enzyme-catalyzed ionization of the pyrophosphate group, yielding allylic cations. The cyclization of these cations can explain the origins of most known sesquiterpenoids,[3] and the investigation of the reactions provides an excellent opportunity for revealing new ways of interconversion between natural terpenoids.[4]

Treatment of the isomeric alcohols farnesol (**1**) and nerolidol (**2**) with formic acid yielded a complex mixture of acyclic and monocyclic compounds containing predominantly α-bisabolol[5] and α- and β-bisabolenes.[6] The cyclization of **1a,b** in the presence of boron fluoride etherate produced a mixture of products containing α-, β-, and γ-bisabolenes, γ-selinene, α- and 2-*epi*-cedrene, α-curcumene, and five compounds with the cadalene skeleton.[7]

Results

Superacid-catalyzed rearrangements of isomers **1a–d** gave different sets of products. The dissolution of **1a** in HSO_3F–SO_2FCl at −110 °C, followed by quenching with a CH_3OH–$(C_2H_5)_2O$ mixture led to a reaction mixture containing predominantly drimenol (**3**) according to GC analysis. Improved yields of **3** (up to 70%) were achieved when the reaction was performed in a HSO_3F–1-nitropropane mixture at −80 to −85 °C. No derivatives of bisabolol, bisabolene, selinene, cedrene, curcumene, and cadalene were revealed in the reaction mixture by GC and NMR analyses (see references 5–7). The structure of **3** was confirmed by the ^1H and ^{13}C NMR data and also by the comparison of the spectral data with the published values.[8] The skeletal structure and the absolute configuration of the asymmetric centers in **3** were established in 1959,[9] and this compound is the first known bicyclic sesquiterpenoid with the absolute configuration that is characteristic to the rings A and B in many naturally occurring bi- and triterpenoids. This fact enables the

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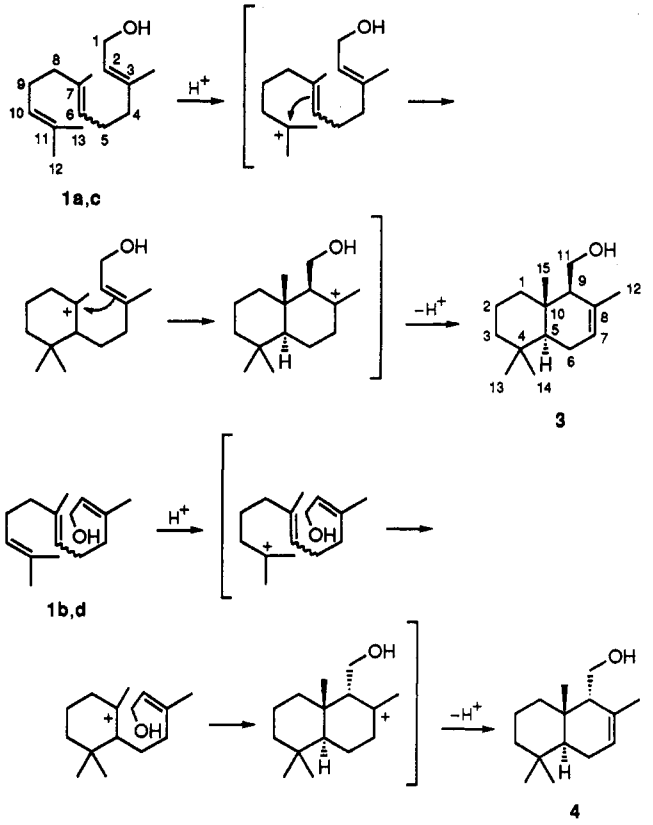
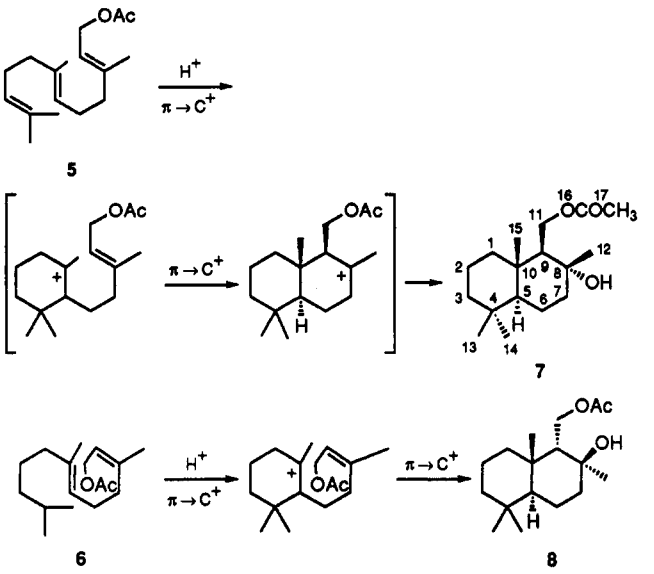
Scheme 1



Scheme 2



synthesis of **3** *via* the degradation of diterpenoids;[10] it is also very important for studying the biogenesis of various terpenoids.

Alcohol **3** has been used as a starting material in syntheses of biologically active drimanes,[11] and it has usually been obtained by multistep synthesis.[12] The formation of the drimane skeleton from farnesyl pyrophosphate is supposed to occur in biogenetic schemes.[3] However, it has not been possible to obtain these compounds from alcohol **1** in ordinary acids.[5-7]

The dissolution of the *cis,cis* isomer **1d** in a HSO_3F–SO_2FCl system at −110 °C and quenching with a CH_3OH–$(C_2H_5)_2O$ mixture resulted in the formation of **4** as the major product (GC). Compound **4** was identified as *epi*-drimenol on the basis of its ^1H and ^{13}C NMR spectra and comparisons with the published data.[8] A mixture of **1b** and *trans,cis*-farnesol (**1c**) cyclizes under the same conditions to produce a mixture of the alcohols **3** and **4**; a similar result was obtained for a mixture of all the four isomers **1a–d**. The cyclization of isomer **1b** in a HSO_3F–2-nitropropane mixture at −80 to −82 °C produced alcohol **4** in ~60% yield.

As can be concluded from Scheme 1, the configuration of the C(6)–C(7) double bond does not affect the stereochemical course of the reaction, and the bicyclic skeleton of the product **3** always has the trans A/B ring junction. This phenomenon may be related to the low nucleophilicity of the C(2)–C(3) double bond, which is due to the influence of the hydroxyl group. Therefore, conformational inversion of the C(7) cation proceeds faster than cyclization with participation of the C(2)–C(3) double bond (compare with ref 13). Another possibility is that the cyclization proceeds *via* one or more monocyclic olefin intermediates (analogous to **10**), so that the *trans* stereochemistry is established in the second cyclization step (see ref 3b). Opposite results were obtained for the cyclizations of *trans*- and *cis*-geranylacetones[1] under similar conditions, since the interaction of the cationic center with the highly nucleophilic carbonyl group proceeds faster than the conformational interconversions. Conversely, the configuration of the C(2)–C(3) double bond in the isomers **1a–d** determines the configuration of the C(9) substituent in the bicyclic products **3** and **4**, and the reaction can thus be considered to be a stereospecific process.

The cyclization of the *trans,trans*- (**5**) and *cis,trans*-farnesyl acetates (**6**) in a HSO_3F–1-(or 2)nitropropane system at −80 to −82 °C proceeds similarly, producing hydroxy acetates **7** and **8**, respectively (Scheme 2).

These cyclization reactions may be terminated by participation of the acetoxy group, producing stable lactonium ions. Compound **7** was identified by comparison of its spectral characteristics with data previously obtained for the optically active isomer.[12] Evidence for the skeletal structure and the configuration of **8** was obtained in the following way. Dehydration of **8** ($POCl_3$–C_5H_5N) gave alcohol **4**. The high rate of dehydration indicates the axial orientation of the hydroxyl group,[13a] hence, the OH and CH_2OAc groups have the *trans*-diaxial orientation. Compound **7** was not dehydrated under the same conditions.

The cyclization of **1a** in a HSO_3F–SO_2FCl mixture at −110 °C led to a small amount of a monocyclic methyl ether. ^1H and ^{13}C NMR spectral analysis indicated the structure to be 1,3-dimethyl-2-(hydroxymethyl)-1-(4′-methoxy-4′-methylpentyl)cyclohex-3-ene (**9**), presumably produced during the methanol quench (Scheme 3).

The cyclization of the acetate **5** produced a minor amount of a monocyclic acetate (**10**). GC analysis of the reaction mixture provided evidence that **10** is an intermediate product in the process of conversion of **5** to **7**. After 1 min, the reaction mixture contained 70% of **10**

(10) Vlad, P. F.; Kryshtal, G. V.; Lazurevskii, G. V. *Zh. Org. Khim.* **1967**, *37*, 2187–2190 (Russ).
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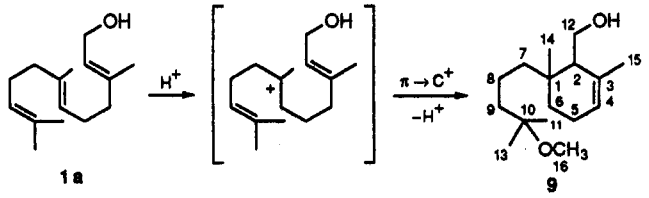
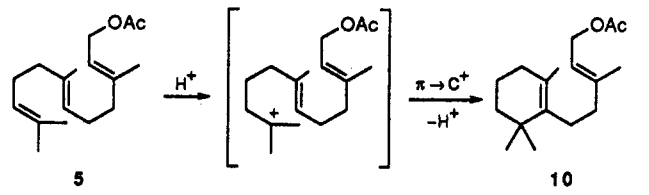
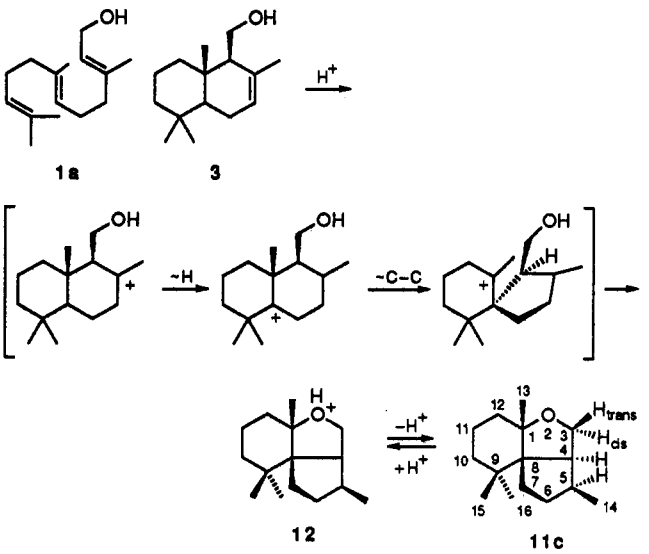
Scheme 3



Scheme 4



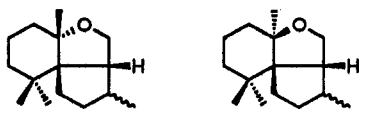
Scheme 5



and 22% of **7**, while after 10 min the percentages were 7% and 70%, respectively (Scheme 4).

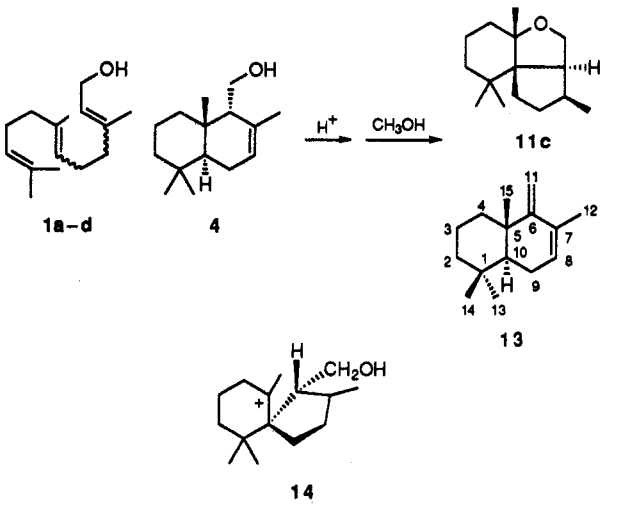
In contrast, when alcohol **1a** was dissolved in HSO_3F–SO_2FCl at −110 °C and the solution warmed to −70 to −60 °C followed by quenching with a CH_3OH–$(C_2H_5)_2O$ mixture, the main product was **11c**. Its structure was established by the ^1H and ^{13}C NMR data and the 2D spectrum of the ^{13}C–^{13}C correlation, based on the biquantum coherency (2D-INADEQUATE). The cyclization of **3** under the same conditions also led to **11c**. A feasible cyclization mechanism is given in Scheme 5. Another possibility is cleavage of ring B to form a monocyclic intermediate followed by reprotonation of the C(8)–C(3) double bond and cyclization.

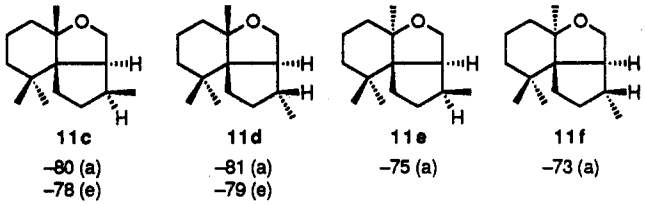
The α-configuration of the hydrogen atom at C(4) and the β-configuration of the methyl at C(1) were revealed by considering the relative stereochemistry of the initial alcohol **3**. Structures **11a** and **11b** with the β-configuration of H(4) must be extremely unstable and the Dreiding models of the compounds cannot be constructed.



Dreiding models of the structures **11c–f** with 4α-H can be easily constructed. The enthalpies of formation ($\Delta H_f°$, kcal/mol) were calculated for these structures by the MM2 program.[14a]

Scheme 6





Two stable conformations can be found for stereoisomers **11c,d**, where the cyclohexane ring has a chair form and the angular C(13)H_3 group has an axial or equatorial position. Only one stable conformation with the axial position of C(13)H_3 can be found for each of the stereoisomers **11e,f**. The resonance frequency of C(13)H_3 (25.4 ppm) in the ^{13}C NMR spectrum corresponds to the axial position of the methyl group.[15] The coupling constant $J_{H(4),H(5)}$ (5.5 Hz) was established from the 2D ^1H–^1H NMR spectrum. Measurements on Dreiding models provided estimates for the values of the dihedral angle for the *cis* (~40°) and *trans* configuration (~100°) of H(4) and H(5); hence, according to the Karplus curve, the *cis* configuration can be assigned to the atoms H(4) and H(5). Structure **11c** can be considered to be the most favorable on the basis of both the NMR spectral data and the data of molecular mechanics calculations.

Alternatively, when alcohols **1a–d** or alcohol **4** were dissolved in a HSO_3F–SO_2FCl system at −110 °C and the reaction mixture was warmed to −60 °C and then quenched with a CH_3OH–$(C_2H_5)_2O$ mixture, two main products resulted (Scheme 6): the ether **11c** and 1,1,5β,7-tetramethyl-6-methylene-10αH-1,2,3,4,5,6,9,10-octahydronaphthalene (**13**).

Examination of Dreiding models convinced us that the cyclization of ion **14** leading to the oxide **11c** is unlikely. Another scheme can be proposed to explain the mechanism of the process (Scheme 7).

(14) (a) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982; ACS Monograph, Vol. 177. (b) Muller, P. M.; Blanc, J.; Mareda, J. *Chimia* **1985**, *39*, 234–235 and references therein.

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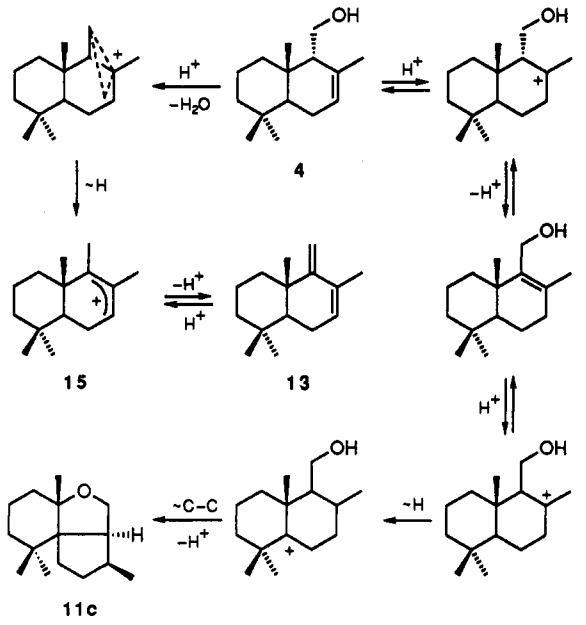
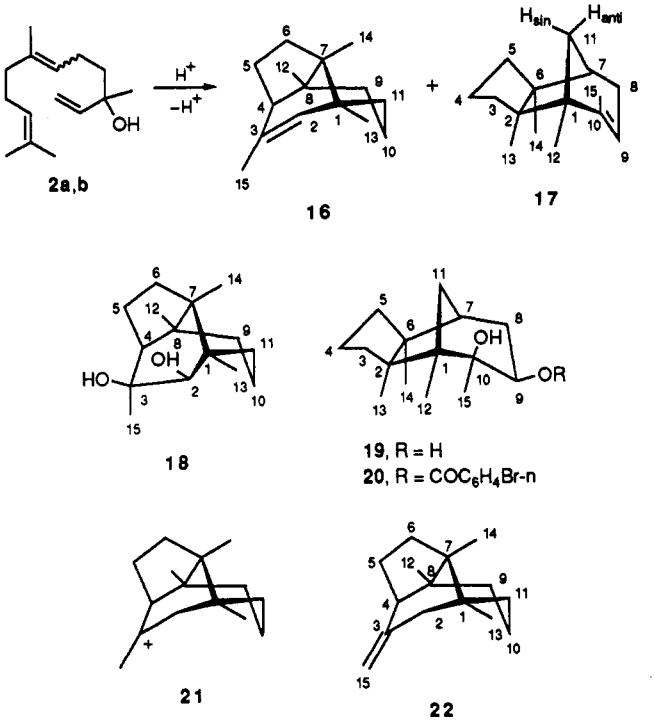
Scheme 7



Scheme 8



The protonation of the compounds **11c** and **13** in HSO_3F–SO_2FCl at −110 °C produced the ions **12** and **15**, respectively. The structures of **12** and **15** were established from their ^1H NMR spectra.

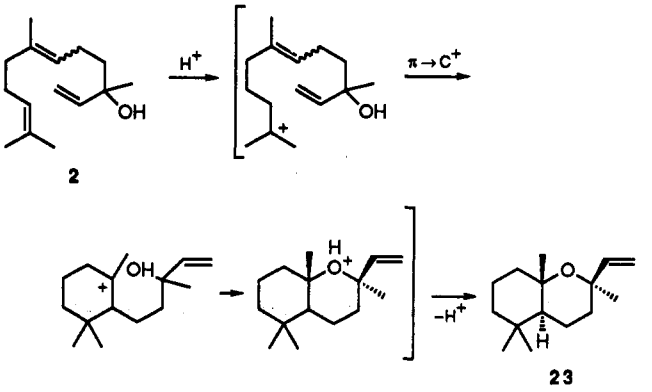
The cyclization of the *trans*- (**2a**) and *cis*-nerolidols (**2b**) in a HSO_3F–SO_2FCl system at −110 °C, followed by quenching with CH_3OH–$(C_2H_5)_2O$, gave a complex reaction mixture. The main products were isolated by passing the mixture through a SiO_2 column and then identified by their ^1H and ^{13}C NMR spectra as the tricyclic olefins **16** and **17**. The oxidation of **16** and **17** by OsO_4 produced the diols **18** and **19**, respectively. According to X-ray crystallographic analysis of diol **18** and mono-*p*-bromobenzoate of diol **19** (**20**), compounds **16** and **17** were assigned the structures 1,3,7,8-tetramethyltricyclo[5.4.0.$0^{4,8}$]undec-2-ene and 1,2,6,10-tetramethyltricyclo[5.3.1.$0^{2,6}$]undec-9-ene, respectively (Scheme 8).

The signals in the ^1H and ^{13}C NMR spectra of compounds **16** and **17** were identified by 2D spectra of the ^{13}C–^1H correlations on the direct and remote constants of the spin–spin coupling.

Aside from the isomers **16** and **17**, the products **22** and **23** were isolated from the reaction mixture. Evidence for the structure of **22** as 1,7,8-trimethyl-3-methylenetricyclo-[5.4.0.$0^{4,8}$]undecane was obtained from its ^1H and ^{13}C NMR spectra. The structure was also confirmed by the fact that both compounds **16** and **22** formed the same ion **21** (^1H, ^{13}C) in superacid; this ion was quenched, yielding predominantly the olfein **16**. The structure of the oxide **23** was identified (by comparing the data from the ^1H and ^{13}C NMR spectra with the published data[16]) as 1,3,7,7-tetramethyl-3-vinyl-2-oxabicyclo[4.4.0]decane.

The decrease of the molar ratio HSO_3F:**2** from ~20:1 down to ~5:1 increased the yield of **23** significantly (to 80%). This fact is completely consistent with the suggested mechanism of formation of **23**. The oxide **23** is known to be a natural, biologically active compound, which has been obtained so far only *via* a multistep synthesis.[17] In the present work, it was obtained in a single-step biomimetic synthesis, using the natural alcohol **2** as the starting substance (Scheme 9).

Scheme 9



Computer-Assisted Elucidation of Mechanisms of the Carbocationic Rearrangements

Rearrangements of the alcohol **2** to the isomers **16**, **17**, and **22** cannot be explained using schemes including three–four steps. Therefore, we applied our ICAR program which was specially designed for elucidating mechanisms of carbocationic rearrangements.[18] Let us briefly consider the main principles of the program operation.

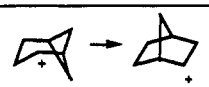
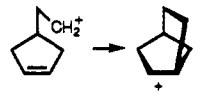
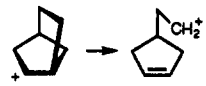
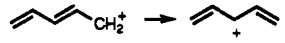
The program is based on the exhaustive enumeration of possible transformations for the starting cationic structure. Every transformation belongs to one of the four basic types which are presented in Table 1. During the generation of transformations for the initial cationic structure, a reasonable and effective selection of results

(16) Baker, R.; Evans, D. A.; McDowell, P. G. *Tetrahedron Lett.* **1978**, *42*, 4073–4076. (b) Lombardi, P.; Cookson, R. C.; Weber, H. P.; Renold, W.; Hauser, A.; Schulte-Elte, K. H.; Willhalm, B.; Thommen, W.; Ohloff, G. *Helv. Chim. Acta* **1976**, *59*, 1158–1168.

(17) Kametani, T.; Fukumoto, K.; Kurobe, H.; Nemoto, H. *Tetrahedron Lett.* **1981**, *22*, 3653–3656.

(18) Gordeeva, E. V.; Shcherbukhin, V. V.; Zefirov, N. S. *Tetrahedron Computer Methodology* **1990**, *3* (6B), 429–443.

Table 1. Basic Types of Carbocationic Rearrangements

type	sample of reaction
shift of σ-bond	
addition to multiple bond	
β-fragmentation	
allylic[a] "rearrangement"	

[a] Chemical structures are represented in the computer as graphs. Therefore, two boundary Lewis structures of the same carbocationic intermediate are distinguished by the computer and their mutual interconversion or resonance is always interpreted as "rearrangement".

is performed by an expert-like system. The empirical knowledge, interpreted by the chemist as "common sense", is formalized and accumulated in the form of rules in an external database. Rules are written in a user-friendly manner; they can be easily recognized, checked, and modified by the user. This versatile approach enables facile and interactive customization of the program for solving a specific chemical problem.

The main goal of the program operation is to construct a tree of rearrangements, which can be interpreted as a set of multistep rearrangements leading to the starting cationic structure. As the first step, the program generates structures that can be produced by one-step rearrangements of the starting cation. All structures that are obtained at the first step are subsequently involved in the procedure, in order to obtain all the possible variants of two-step carbocationic transformations. Successive repetition of this operation results in a multistep tree of rearrangements. Transformations of redundant structures and of those which are eliminated by empirical criteria are not performed by the ICAR program. After the tree of rearrangements had been constructed, the multistep rearrangement pathways between two specified cations in the tree can be searched.

In the present work, we did not try to perform an exhaustive investigation of the possible mechanisms. We restricted the task to searching for the shortest pathways, which are generally the most reasonable ones. The allylic cation, which is formed *via* the elimination of the hydroxyl group from the structure **2**, was taken as the starting structure, and its tree of rearrangements was constructed. Each of the final structures **16**, **17**, and **22** can be considered as resulting from the quenching of a pair of different cations: C(3), C(2) cations for **16** and **22**; C(10), C(9) cations for **17**. Despite the relatively lower stability of the secondary cations (C(2) and C(9)) in comparison with the tertiary cations (C(3) and C(10)), rearrangements with the participation of the four final cationic structures were taken into account.

An essential step that precedes the construction of a rearrangement tree consists of the development of the selection criteria. That task requires detailed analysis of experimental conditions to establish which transformations can be considered to be less probable and therefore can be eliminated. Very loose criteria result in the generation of many unreasonable solutions, while excessive restrictions can eliminate promising mechanisms. The following criteria were used in the present work: (a) Only 1,2-shifts of C–C and C–H bonds were considered to be possible. Rearrangements that proceed as 1,3-shifts of a C–H bond were discarded. (b) Since intramolecular rearrangements were of major interest, only the transformations that did not result in fragmentation of the whole structure were accepted. (c) Rearrangements producing unstable primary cations, vinylic cations, or structures containing strained three- and four-membered rings were eliminated. (d) The rarely observed processes of β-fragmentation resulting in the formation of mono- or disubstituted double bonds ($RCH{=}CH_2$, $R^1R^2C{=}CH_2$) were discarded. (e) The 1,2-shifts of a σ-bond in stable allylic cations were forbidden.

The result of ICAR operation is a series of possible rearrangement mechanisms. For transformations of nerolidol **2**, we obtained the four shortest routes leading to olefins **16** and **22** and seven routes leading to olefin **17**. The problem is to select the most probable mechanism. The probability of a rearrangement mechanism is determined by the "total" barrier on the route from the initial to the final cations. The barrier of the specific 1,2-shift of the migrant depends on several factors: (a) the charge at the carbonium center, (b) the difference between the thermodynamic stabilities of the ions that are rearranged and formed ($\Delta\Delta H_f$), and (c) structural factors, e.g., the dihedral angle φ between the vacant carbocation orbital and the migrating bond. The thermodynamic factor was applied by Schleyer,[19] while the orbital factor was introduced later by Osawa.[20] For ions with a localized charge, these two factors are of major importance.

For a rough selection of favorable routes, we used only the thermodynamic factor, which was considered as the maximum increase in the enthalpy of formation between two successive cationic intermediates. The MM2 program with a force field[14b] was applied to evaluate the $\Delta\Delta H_f$ values. Thus, we selected two mechanisms presented in Schemes 10 and 11. The differences between the enthalpies of formation ($\Delta\Delta H_f$, kcal/mol) are given under the arrows.

More detailed consideration of these mechanisms requires an estimation of the $\Delta G^{\ddagger}$ values for 1,2-shifts, i.e., the inclusion of both the thermodynamic and the orbital factor into consideration. These factors often give contradictory forecasts, and therefore are difficult to use. It has been suggested in ref 21a that the internal barrier ($\wedge$) of the 1,2-shift depends on the orbital factor ($\wedge = \wedge_0/\cos\varphi$), while the thermodynamics of the 1,2-shift may be evaluated using the Marcus equation ($\Delta G^{\ddagger} = \wedge(1-\Delta\Delta H_f/4\wedge)^2$). We used this method to estimate the barrier values for most 1,2-shifts. These values ($\Delta G^{\ddagger}$, kcal/mol) are indicated in parentheses.

Evidently, in the range of φ angles at about 90°, we will obtain overestimated $\wedge$ values. Therefore, we made an attempt to find the relations that would allow them to conduct a quantitative determination of $\Delta G^{\ddagger}$ values.[21b] The new approach models the transition state for the

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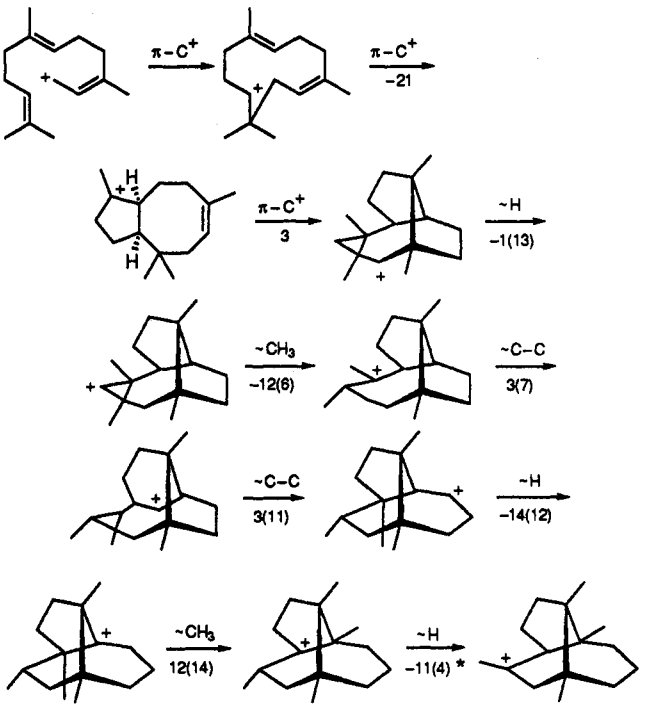
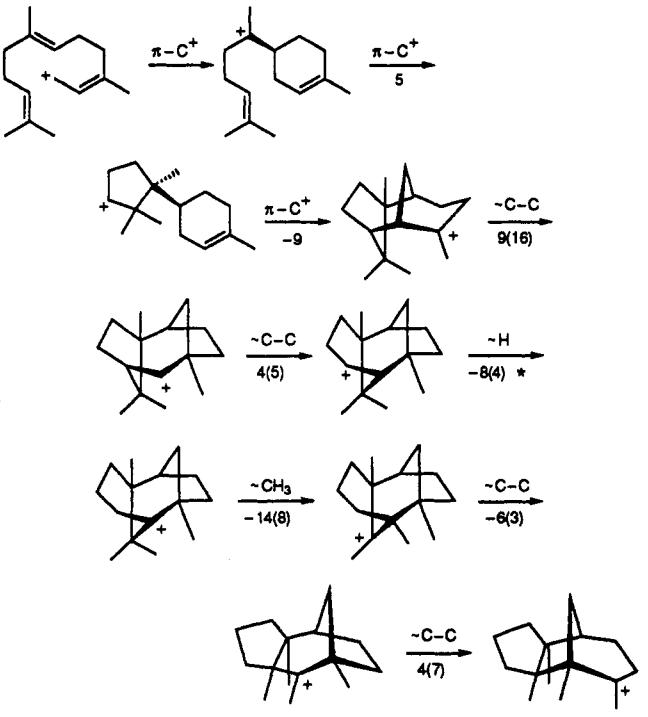
Scheme 10



Scheme 11



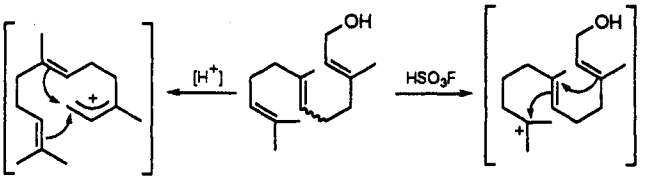
degenerate 1,2-shift of the H atom and the CH_3 group as the neutral olefin that is formed by the elimination of the migrant group from the cationic frame. The correlations obtained in ref 21b are

$$\Delta G^{\ddagger}(H) = 24.26 + 0.122[\Delta H_f(\text{olefin}) - \Delta H_f(R^+)]$$

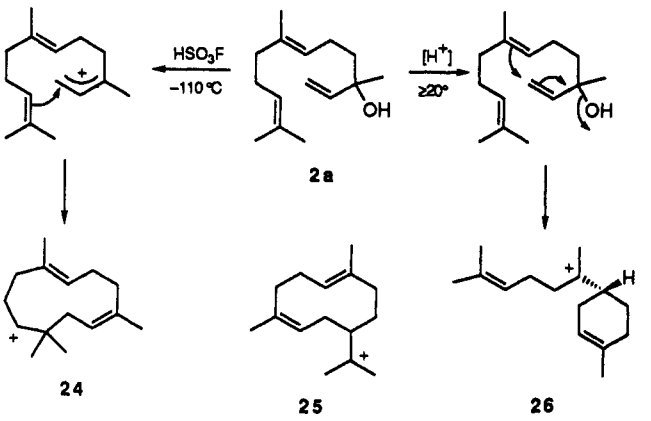
$$\Delta G^{\ddagger}(CH_3) = 30.01 + 0.160[\Delta H_f(\text{olefin}) - \Delta H_f(R^+)]$$

The nondegenerate character of the 1,2-shift can be considered using the above-mentioned Marcus equation. The correlations are inapplicable to Wagner–Meerwein rearrangements. Therefore, we have used them to recalculate the barriers of several crucial 1,2-shifts that determine the "total" barrier of the whole multistep rearrangement. These values are marked by asterisks in Schemes 10 and 11.

Scheme 12



Scheme 13



The application of this analysis led to quite acceptable "total" barrier heights: about 18 kcal/mol for both mechanisms. Verification of these mechanisms is an interesting problem, which can be reached by performing additional experiments, e.g., isotope labeling, trapping of intermediates, etc.

Discussion

The single-step rearrangement of the widespread natural alcohols **1** and **2** was performed for the first time to produce a well-known set of various natural compounds and a set of caged structures with new types of skeletons. It is interesting to compare the results obtained for rearrangements of **1** and **2** in superacids and in common acids in order to clarify the dependence of the preferred direction of the carbocationic rearrangements on the nature of the acidic catalyst. The different behavior of alcohol **1** in superacids as compared to common acids is related to the different formation site of the cationic center (Scheme 12). This phenomenon may be characteristic for unsaturated primary alcohols.

Contrasting results were demonstrated in experiments with alcohol **2**. The cationic center is always formed *via* the elimination of the tertiary allylic hydroxyl group, irrespective of the nature of the acidic environment. However, the cyclization process may occur with the participation of different π-bonds.

If the reaction is performed in a superacid at low temperature (−110 °C), conformational control promotes the interaction of the molecular chain ends, leading to ion **24** (Scheme 13). This ion is evidently less strained than germacrylic ion **25**. In contrast, the cyclization of **2** in a weak acid at normal temperature is not influenced by conformational factors and produces the more stable tertiary bisabolylic ion **26**. Experiments with models also demonstrated that the formation of this ion requires that

Table 2. ^{13}C NMR Spectra (δ, TMS) of Compounds 1a, 1d, 2a, 2b, 3, 4, 7, 9, 11, 13, 16, 17, 22, and 24[a,b]

	Sequential numbers of carbon atoms														
no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1a	58.91 t	123.71[e] d	138.83 s	39.55 t	26.20 t	123.58[g] d	134.97 s	39.43 t	26.55 t	124.26 d	130.87 s	25.58 q	17.57 q	15.89 q	16.12 q
1d	58.51 t	124.16 d	138.73 s	31.77 t	25.60 t	124.79[g] d	135.59 s	32.11 t	26.45 t	124.50[g] d	131.14 s	23.31[f] q	17.57 q	26.20 q	23.22[f] q
2a	111.50 t	144.97 d	73.23 s	41.96 t	22.57 t	124.19 d	135.16 s	39.57 t	26.51 t	124.19 d	131.02 s	25.58 q	17.56 q	15.89 q	27.75 q
2b	111.50 t	144.91 d	73.11 s	42.23 t	22.37 t	124.94[e] d	135.19 s	31.76 t	26.36 t	124.17[e] d	131.20 s	25.58 q	17.47 q	23.24 q	27.65 q
3	39.86 t	18.74 t	42.17 t	32.91 s	49.88 d	23.66 t	123.88 d	132.88 s	57.27 d	36.03 s	60.73 t	21.92 q	33.38 q	22.07 q	14.88 q
4	36.71 t	18.71 t	42.64 t	32.94 s	43.38 d	23.96 t	124.47 d	131.29 s	57.60 d	36.05 s	61.16 t	22.90 q	33.12 q	22.10[e] q	21.67[e] q
7[c]	39.72 t	18.37 t	41.73 t	33.19 s	55.73 d	20.28 t	43.95 t	72.45 s	59.99 d	38.07 s	62.42 t	24.57 q	33.47 q	21.55 q	15.78 q
9	34.39 s	50.69 d	131.79 s	124.60 d	22.69 t	30.32 t	39.64 t	17.72 t	40.74 t	74.44 s	25.04 q	61.33 t	25.04 q	24.29 q	22.88 q
11	84.33 s		72.27 t	54.85 d	44.86 d	37.76 t	31.83 t	64.17 s	35.26 s	38.74 t	18.80 t	34.44 t	25.41 q	20.03 q	30.74 q
13[d]	33.28 s	42.16 t	19.00 t	37.67 t	41.15 s	158.15 s	131.16 s	126.34 d	24.23 t	48.64 d	103.57 t	20.41 q	32.82 q	22.03[e] q	20.99[e] q
16	44.52[e] s	126.15 d	139.78 s	53.25 d	32.79[f] t	32.85[f] t	41.90[e] s	43.64 s	32.79[f] t	20.95 t	31.76[f] t	26.45 q	23.93 q	15.12 q	21.89 q
17	46.98 s	58.17 s	39.72 t	23.84 t	46.55 t	52.07 s	44.48 d	31.14 t	119.96 d	143.56 s	39.12 t	17.68 q	18.86 q	22.59 q	22.04 q
22	34.27[e] s	27.84 t	161.99 s	38.33 d	25.55[f] t	41.08[f] t	41.28[e] s	37.33[e] s	37.04[f] t	19.48 t	36.55[f] t	27.57 q	25.63 q	15.21 q	103.70 t
24	76.03 s		73.38 s	35.03 t	16.86 t	54.31 d	33.36 s	41.51 t	20.07 t	41.65 t	147.75 d	109.35 t	32.73 q	20.86 q	32.39 q

[a] The values of the chemical shifts denoted with the same letters may be exchanged within the row. [b] δ(C(16)): 170.96 s (7), 48.93 q (9), 25.92 q (11), 22.60 q (24). [c] δ(C(17)): 21.15 q. [d] In $CDCl_3$.

the two π-systems should approach each other with a strong eclipsing of bonds (compare with ref 2 and 3).

In our previous work we have compared the rearrangements of the tertiary allylic alcohol manool in superacids and in various Brönsted acids.[15] In both cases, the cationic center is formed *via* the elimination of the hydroxyl group, and all subsequent transformations proceed in a similar way but with different deepness. Rearrangements of alcohol **2** reveal the strong dependence of the predominant direction on the nature of the catalyst, since different internal nucleophiles are involved in the cyclization process. It should be noticed that the molar ratio superacid:alcohol **2** substantially affects the ratio of the carbocyclic products to heterocyclic products. The terminal carbon–carbon bond is protonated easier if we use the lower ratio (5:1), while the higher ratio (20:1) promotes the heterolysis of the C–O bond. Therefore, the carbocationic center is formed in different parts of the acyclic molecule, and the nature of the internal nucleophiles is also different (compare with ref 22).

We have mentioned above that **1** and **2** rearrange in formic acid and produce α-bisabolol as the main product.[5,6] Our experiments demonstrated that transformations of this compound in HSO_3F–SO_2FCl at −110 °C resulted in products that were different[23] from the substances described in the present work. However, rearrangements of **1** and α-bisabolol catalyzed by boron fluoride etherate gave the same set of products.[7] A reason for this phenomenon rests in the ability of the Lewis acid to generate a carbocation *via* the elimination of a hydroxyl group.

Experimental Section

The spectra of the carbocationic salts were recorded with the use of TMS as an external standard or CH_2Cl_2 (δ 5.33) as an internal standard. For solutions of the neutral compounds in $CDCl_3$–CCl_4 (volume ratio 1:1), we used the signal of $CHCl_3$ (δ 7.24). The ^1H NMR spectra of **7** and **8** were recorded in CCl_4. The ^{13}C NMR spectra were recorded at 50.32 MHz; for acidic solutions, we used TMS as an external standard or CD_2Cl_2 (δ 53.3) as an internal standard. NMR spectra of neutral compounds were recorded using $CDCl_3$ (δ 76.90) as an internal standard. The ^{13}C NMR spectral data for neutral compounds are given in Table 2. The signals were assigned (i) according to the values of residual splittings with the off-resonance radiation of protons or (ii) by recording the differential spectra, *J*-modulated with the long-range spin–spin interaction (LRJMD).[24]

The purity of the initial substances was monitored, and the reaction products were analyzed by GC on (i) a glass capillary column 51000 × 0.3 mm, poly(dimethyl(methylvinyl)siloxane) containing 0.5% of vinyls as the stationary phase; phase analogous to SE-31, the carrying gas (He) velocity 3 mL/min, temperature 110-140 °C, flame ionization detector; (ii) a glass column 1500 × 3 mm, 5% SE-30 phase on chromatone N-AW-DMCS (100-160 μm), program in the range of 140–180 °C, velocity 15 deg/min. According to GC data, all products were individual compounds.

The starting materials and the products were separated by flash chromatography[25] on SiO_2 (40-100 μm) or on SiO_2 containing 20% of $AgNO_3$. To prepare the solutions of the ion salts, we used twice-distilled HSO_3F (bp 158-161 °C). The diluent SO_2FCl was purified by passage through H_2SO_4. The solutions of the salts were prepared and quenched with the CH_3OH–$(C_2H_5)_2O$ mixture (volume ratio 5:2) as described previously.[26] Alcohols **1a** and **2b** as well as the mixture of isomers **1a-g** were purchased from Fluka; the mixture **2a** and **2b** was obtained from Firmenich. The spectral characteristics of all the substances satisfy those described in the literature.[27] The alcohol **2a** was isolated from the oleoresin *Abies nephrolepis* Maxim. The purified product had $[\alpha]^{21}_D$ −2.66°.[28]

Most of obtained compounds were liquids, except **18** and **20**. Elemental compositions were established using high-resolution mass spectroscopy.

Drimenol (3). (i) A solution of alcohol **1a** (0.5 g, 2.25 mmol) in SO_2FCl (3.1 mL) was mixed with HSO_3F (2.70 g, 27 mmol) in a SO_2FCl (3.1 mL) solution at −115 °C, the reaction was quenched with a mixture of CH_3OH (30 mL) and $(C_2H_5)_2O$ (12 mL), and the solution was washed with a saturated solution of Na_2CO_3 (100 mL) at 0 °C. Extraction by diethyl ether gave 0.47 g of crude product. The product was chromatographed (hexane/diethyl ether with ether content increasing from 1 to 30%) on a SiO_2 column to give (a) 0.13 g (28%) of alcohol **3** [^1H NMR δ 0.82 s, 0.85 s, 0.87 s, 1.74 w s, 1.80 m, 3.67 dd (J = 11 and 5 Hz), and 3.79 dd (J = 11 and 3 Hz), 5.47 w d (J = 5 Hz), 0.92-2.06 m; IR (CCl_4, 1%, d = 0.4) 3450, 3627, 1664, 834 cm^{-1}] and (b) 0.005 g (1%) of alcohol **9** [^1H NMR δ 0.96 s (C(14)H_3), 1.10 s (C(11)H_3,

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C(13)H_3), 1.65 m (H(2)), 1.70 m (C(15)H_3), 1.91 m (2H(5)), 3.12 s (OCH_3), 3.69 d (J = 3 Hz, 2H(12)), 5.54 m (H(4)), 1.11–1.60 m ($4CH_2$).

(ii) A solution of HSO_3F (0.70 g, 7 mmol) in SO_2FCl (1.6 mL) was added to alcohol **1a** (0.12 g, 0.54 mmol) in CH_2Cl_2 (0.5 mL) at −115 to −110 °C. "Quenching" with the mixture of CH_3OH (10 mL) and $(C_2H_5)_2O$ (4 mL) gave 0.1 g (72%) of the crude product **3** (GC).

(iii) A solution of HSO_3F (0.67 g, 6.7 mmol) in 1-nitropropane (1.0 mL) was added to alcohol **1a** (0.15 g, 0.67 mmol) in 1-nitropropane (1.5 mL) at −85 to −80 °C. After 7 min of stirring, a solution of $(C_2H_5)_3N$ (1.3 mL) in petroleum ether (2.0 mL) was added. The reaction mixture was diluted with water, extracted with petroleum ether, washed with water until the washes were neutral, dried, and filtered. The solvent was removed, and 0.15 g of crude product was obtained. The product was chromatographed (petroleum ether/ethyl acetate, 9:1) on a column containing SiO_2 (3 g with 20% of $AgNO_3$) to give **3** (0.07 g, 58%).

***epi*-Drimenol (4).** (i) A solution of alcohol **1d** (0.12 g, 0.54 mmol) in CH_2Cl_2 (0.6 mL) was added to HSO_3F (0.7 g, 7 mmol) in SO_2FCl (1.6 mL) at −115 °C. The quenching was done with a mixture of CH_3OH (10 mL) and $(C_2H_5)_2O$ (4 mL). The crude product (0.12 g) was chromatographed (hexane/$(C_2H_5)_2O$ with gradient 1-30%) on a SiO_2 column to give alcohol **4** (0.012 g, 10%): ^{1}H NMR δ 0.84 s, 0.87 s, 0.88 s, 1.71 w s, 3.68 m, 3.70 m, 5.54 w d (J = 4 Hz), 1.15-2.08 m.

(ii) A solution of HSO_3F (0.16 g, 1.6 mmol) in 2-nitropropane (0.2 mL) was added to alcohol **1b** (0.035 g, 0.16 mmol) in 2-nitropropane (0.5 mL) at −80 to −82 °C and the resulting solution was stirred at this temperature for 55 min. The reaction mixture, to which a solution of $(C_2H_5)_3N$ (0.4 mL) in petroleum ether (0.1 mL) was added, was then diluted with water. The aqueous phase was extracted with petroleum ether, and the extract was washed with water. The product (0.12 g) was chromatographed (petroleum ether/ethyl acetate, 9:1) on a SiO_2 column (1 g of SiO_2 containing 20% of $AgNO_3$) to give alcohol **4** (0.019 g, 63%).

A mixture of alcohols **3** and **4** was prepared by adding the alcohols **1a-d** (0.6 g, 2.7 mmol) in CH_2Cl_2 (1.5 mL) to a solution of HSO_3F (2.70 g, 27 mmol) in SO_2FCl (6.2 mL) at −115 to −110 °C. The quenching with a mixture of CH_3OH (30 mL) and $(C_2H_5)_2O$ (12 mL) produced crude product (0.5 g), which consisted of alcohols **3** and **4** (≈1:1, GC). The product was chromatographed on a SiO_2 column to give alcohol **4** (0.06 g, 0.27 mmol) and alcohol **3** (0.04 g, 0.18 mmol).

Hydroxy Acetate 7 and Acetate 10. A mixture of HSO_3F (0.32 g, 3.2 mmol) in 1-nitropropane (1 mL) was added to a solution of acetate **5** (0.08 g, 0.30 mmol) in 1-nitropropane (1 mL) at −80 to −85 °C. After 30 min of stirring, a solution of $(C_2H_5)_3N$ (0.57 mL) in petroleum ether (1 mL) was added. The reaction mixture was diluted with water (10 mL), extracted with petroleum ether, and washed with water until the washes were neutral. The solvent was removed, and 0.08 g of crude product was obtained. The product was chromatographed (petroleum ether/ethyl acetate, 19:1) on a column containing SiO_2 (2 g) to give **10** (0.0013 g, 2%). Chromatography with the same solvents (4:1) gave **7** (0.056 g, 67%): ^{1}H NMR δ 0.79 s, 0.87 s, 1.23 s, 1.95 s, 3.68 w s, 4.23 m; IR (CCl_4, 5%, d = 0.1) 3600, 3500, 1732, 1384, 1323, 1236 cm^{-1}.

Hydroxy Acetate 8. A mixture of HSO_3F (0.22 g, 2.2 mmol) in 2-nitropropane (0.2 mL) was added to a solution of acetate **6** (0.06 g, 0.22 mmol) in 2-nitropropane (0.5 mL) at −80 to −85 °C. After 1 h of stirring of $(C_2H_3)_3N$ (0.4 mL) in petroleum ether (0.1 mL) was added. The reaction mixture was diluted with water and extracted with petroleum ether. Chromatography on a column with 1.5 g of SiO_2 (petroleum ether/ethyl acetate, 4:1) gave **8** (0.04 g, 62%): ^{1}H NMR δ 0.80 s, 0.86 s, 0.97 s, 1.08 s, 1.95 s, 3.61 w s, 4.25 m; IR (CCl_4, 5%, d = 0.1) 3600, 3495, 1735, 1377, 1360, 1230 cm^{-1}.

1,5,9,9-Tetramethyl-2-oxatricyclo[6.4.0.0^{4,5}]dodecane (11) and 1,1,5,7-Tetramethyl-6-methylene-1,2,3,4,5,6,9,10-octahydronaphthalene (13). A mixture of alcohols **1a-d** (0.27 g, 1.22 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of HSO_3F (1.40 g, 14.0 mmol) in SO_2FCl (3.2 mL) at −115 °C and warmed to −70 °C. After 3 min, the reaction was quenched with a mixture of CH_3OH (20 mL) and $(C_2H_5)_2O$ (8 mL). The product was chromatographed on a SiO_2 column (hexane/diethyl ether with gradient 1-10%) to give **11** (0.03 g, 11%) and **13** (0.005 g, 2%). **11**: ^{1}H NMR δ 0.94 s, 0.95 s, 1.00 d (J = 7 Hz), 1.24 s, 1.97 m, 2.06 ddd (J = 8, 5.5, and 3.5 Hz), 3.44 dd (J = 9 and 3.5 Hz), 3.99 dd (J = 9 and 8 Hz), 1.10–1.88 m; IR (CCl_4, 1%, d = 0.4) 2960, 2880, 1470, 1380, 1055 cm^{-1}; MS m/z 222 (1), 208 (11), 207 (79), 138 (100), 137 (39), 109 (30), 96 (40), 95 (38), 81 (24), 69 (26), 55 (23), 43 (48), 41 (27). **13**: ^{1}H NMR δ 0.84 s, 0.90 s, 0.94 s, 1.77 m, 4.77 s, 4.81 w s, 5.65 m, 1.12–2.15 m.

The compound **11** was also obtained by mixing **1a** (0.01 g, 0.05 mmol) in CH_2Cl_2 (0.3 mL) and a solution of HSO_3F (0.174 g, 1.74 mmol) in SO_2FCl (0.4 mL) at −115 °C. The mixture was warmed to −70 °C and the reaction was quenched with a solution of CH_3OH (5 mL) in $(C_2H_5)_2O$ (2 mL). GC analysis revealed no byproducts.

Salt of Ion 12. Ether **11** (0.007 g, 0.03 mmol) in CD_2Cl_2 (0.1 mL) was mixed with a solution of HSO_3F (0.174 g, 1.74 mmol) in SO_2FCl (0.4 mL) at −115 °C. The ^{1}H NMR spectrum was not changed in the temperature range of −110 to −50 °C: ^{1}H NMR (−50 °C) δ 1.08 s, 1.10 s, 1.16 d (J = 7 Hz), 1.80 s, 4.50 dd (J = 9 and 3.5 Hz), 4.84 dd (J = 9 and 8 Hz), 1.24–2.67 m.

Salt of Ion 15. Diene **13** (0.01 g, 0.05 mmol) in CD_2Cl_2 (0.15 mL) was mixed with a solution of HSO_3F (0.174 g, 1.74 mmol) in SO_2FCl (0.4 mL) at −115 °C: ^{1}H NMR (−110 °C) δ 1.02 s, 1.10 s, 1.31 s, 2.24 s, 2.93 s, 9.00 s.

1,3,7,8-Tetramethyltricyclo[5.4.0.0^{4,8}]undec-2-ene (16), 1,2,6,-10-Tetramethyltricyclo[5.3.1.0^{2,6}]undec-9-ene (17), and 1,7,8-Trimethyl-3-methylenetricyclo[5.4.0.0^{4,8}]undecane (22). A solution of alcohol **2** (0.5 g, 2.25 mmol) in SO_2FCl (3.0 mL) was added to HSO_3F (2.65 g, 26.5 mmol) in SO_2FCl (3.0 mL) at −115 °C and the reaction was quenched with a mixture of CH_3OH (20 mL) and $(C_2H_5)_2O$ (8 mL). The crude product was chromatographed (hexane) on a column of Al_2O_3 and rechromatographed (hexane/diethyl ether with a gradient of 1–10%) on a column of SiO_2 containing 20% of $AgNO_3$; the final products were olefins **16** (0.032 g, 7%), **17** (0.012 g, 3%), and **22** (0.009 g, 2%). **16**: ^{1}H NMR δ 0.75 s, 0.87 s, 0.89 s, 1.65 d (J = 1.5 Hz), 4.41 w s, 1.17–2.06 m. **17**: ^{1}H NMR δ 0.80 s, 0.85 s, 0.92 s, 1.47 d (J = 11 Hz), 1.83 dd (J = 11 and 5.5 Hz), 1.60 m, 1.72 m, 2.00 m, 5.09 m, 1.30–1.56 m. **22**: ^{1}H NMR δ 0.75 s, 0.90 s, 1.00 s, 1.79 m, 2.20 m, 4.58 d, 4.79 d (J = 1.5 Hz), 1.10–1.75 m.

1,3,7,7-Tetramethyl-3-vinyl-2-oxabicyclo[4.4.0]decane (23). A solution of alcohol **2** (0.1 g, 0.45 mmol) in CH_2Cl_2 (0.15 mL) was added to HSO_3F (0.45 g, 4.5 mmol) in SO_2FCl (1.04 mL) at −115 °C and the reaction was quenched with mixture of CH_3OH (10 mL) and $(C_2H_5)_2O$ (4 mL). The product was chromatographed (hexane/diethyl ether with a gradient of 1–30%) to give olefin **16** (0.013 g, 14%), olefin **17** (0.007 g, 8%), and compound **23** (0.007 g, 7%). **23**: ^{1}H NMR δ 0.70 s, 0.87 s, 1.12 s, 1.20 s, 4.89 dd (J = 11 and 1 Hz), 4.95 dd (J = 18 and 1 Hz), 6.00 dd (J = 18 and 11 Hz), 1.15–1.82 m.

1,3,7,8-Tetramethyltricyclo[5.4.0.0^{4,8}]undecane-2,3-diol (18). The reaction of olefin **16** (0.08 g, 0.39 mmol) with OsO_4 (0.096 g, 0.39 mmol) in diethyl ether was performed as described in the literature.[29] Chromatography (hexane/diethyl ether with a gradient of 1–90%) on SiO_2 gave diol **18** (0.044 g, 45%), mp 169.5–171 °C (from CCl_4): ^{1}H NMR ($(CD_3)_2CO$) δ 0.86 s, 0.87 s, 0.93 s, 1.54 s, 4.59 s, 1.10–2.30 m; IR (CCl_4, 5%, d = 0.1) 3620, 3460, 2980, 1380, 1060 cm^{-1}.

1,2,6,10-Tetramethyltricyclo[5.3.1.0^{2,6}]undecane-9,10-diol (19). The reaction of olefin **17** (0.074 g, 0.36 mmol) with OsO_4 (0.08 g, 0.31 mmol) was performed as described above to give diol **19** (0.043 g, 51%): ^{1}H NMR δ 0.87 s, 0.95 s, 0.96 s, 1.26 s, 3.58 m, 1.17–2.00 m; IR (CCl_4, 1%, d = 0.4) 3640, 3585, 2960, 1385, 1080, 1040 cm^{-1}.

A solution of *p*-bromobenzoyl chloride (0.16 g, 0.73 mmol) in dry pyridine (5 mL) was added to diol **19** (0.004 g, 0.02 mmol) and boiled during 2 min to give benzoate **20**, mp 176.5–177.5 °C (from CCl_4): IR (CCl_4, 5%, d = 0.4) 3615, 1725, 1270 cm^{-1}.

Salt of Ion 21. The salt was obtained from **16** (0.11 g, 0.54 mmol), HSO_3F (0.78 g, 7.8 mmol), and SO_2FCl (1.8 mL) at −115 °C: ^{1}H NMR (−100 °C) δ 1.05 s, 1.23 s, 1.33 s, 3.87 m, 1.10–3.40 m; ^{13}C NMR (−110 °C) δ 289.44 s, 81.46 d, 55.82 t, 55.04 s, 45.14 s, 44.83 s, 39.44, 35.54, 30.95, and 30.76 all t, 36.22 q, 23.80 t, 23.38 q, 22.29 q, 13.51 q. The salt was also generated from olefin **22**

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Table 3. Crystallographic Characteristics of Compounds 18 and 20

parameter	18	20
a, Å	7.886 (2)	6.685 (2)
b, Å	8.743 (2)	11.033 (2)
c, Å	19.494 (5)	14.078 (3)
α, deg	90	84.13 (2)
β, deg	90.44 (2)	84.68 (2)
γ, deg	90	74.13 (2)
space group	$P2_1/c$	$P\bar{1}$
z	4	2
d_{calc}, g/cm^3	1.18	1.41
μ, cm^{-1}	0.71	20.69
fw	238.37	421.37
V, Å^3	1344.0 (1.0)	991.2 (0.5)
solution	direct method	Patterson method
Brutto formula	$C_{15}H_{26}O_2$	$C_{22}H_{29}O_3Br$
no.	995	2417
$2\theta_{max}$, deg	40	50
R	0.132	0.069
R_w	0.132	0.073

(0.025 g, 0.12 mmol) in CD_2Cl_2 (0.15 mL) and HSO_3F (0.35 g, 3.5 mmol) in SO_2FCl (0.8 mL) at −115 °C. The quenching of the salt solution with a mixture of CH_3OH and $(C_2H_5)_2O$ predominantly yields olefin **16** (GC).

X-ray Crystallographic Analysis. Crystallographic characteristics of compounds **18** and **20** are given in Table 3. The crystals of diol **18** usually join together according to the rule $c_1^* = c_2^*$, $b_1^* = -b_2^*$. For the routine investigation, we used a joined crystal with the ratio of intensities ~1:2.6. The intensities of reflections were measured by the $2\theta/\theta$ scan method. The structure of diol **18** was elucidated by direct methods. The heavy atom method was used to interpret the structure of the benzoate **20**. The structures were refined by the least-squares method in anisotropic–isotropic approximation. The positions of the hydrogen atoms were obtained geometrically.

The six-membered rings of diol **18** are found to have the chair form, while the five-membered ring has the envelope form with the C(8) atom deviating (0.74 Å) from the plane of the four other atoms. A search in the Cambridge Structural Database[30] (CSD) failed to reveal any derivatives of tricyclo[5.4.0.0^{4,8}]undecane. However, it is possible to compare the distance between C(3) and C(10) in diol **18** (3.31 Å) with the similar distance in bicyclo[3.3.1]nonane (3.06 Å).[31] This comparison demonstrates a substantial planarity of the six-membered rings in diol **18** along the line C(3)–C(10). The possible reason for this phenomenon is the repulsion between the methyl group C(15)H_3 and the methylene group C(10)H_2, since the distance between C(15) and C(10) (3.21 Å) is substantially shorter than the van der Waals contact (3.42 Å).[32]

To discuss the structure of benzoate **20**, we performed a search for tricyclo[5.3.1.0^{2,6}]undecane derivatives in the CSD and found the structure of the α-cariophyllene alcohol *p*-bromobenzenesulfonate.[33] This compound and molecule **20** have similar geometries. The out-of-plane deviations of the atoms C(4) and C(11) in the five-membered rings are equal to 0.64 and 0.73 Å, respectively. The C(9) and C(11) atoms deviations from the plane of C(1), C(7), C(8), and C(10) are equal to −0.57 and 0.87 Å. The same parameters in the molecule of ester **27** are equal to 0.65, 0.71, −0.62, and 0.80 Å. The lengths of the bond C(1)–C(2) in **20** and the bond C(2)–C(6) in **27** also increase in a similar way.

Molecules of diol **18** are connected with hydrogen bonds of the type O–H···O, forming endless chains along the *b* axis; the distances OH(1)···OH(2) (x, y, z) and OH(1)···OH(2) (1-x, y-$^1/_2$, $^1/_2$-z) are equal to 2.45 and 2.73 Å, respectively. The bifurcated hydrogen bond is observed in the crystal of benzoate **20**; it combines molecules into centrosymmetrical dimers with the distances OH···O(1) (x, y, z) = 2.723 Å and OH···OH (2-x, -y, 1-z) = 2.971 Å.

Supplementary Material Available: X-ray data, PLUTO drawings of **18** and **20**, and puckering parameters for five- and six-membered rings[34] (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information. For an IBM PC version of the ICAR program, please contact Prof. Steve R. Heller, Research Leader Model and Database Coordination Lab., Agricult. Research Service, BARC-W, Beltsville, MD 20705. The authors have deposited atomic coordinates for compounds **18** and **20** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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