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Acid-catalyzed isomerization of caryophyllene in the presence of SiO_2 and Al_2O_3 impregnated with sulfuric acid

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The conversion of caryophyllene upon contact with Al_2O_3 and SiO_2 impregnated with sulfuric acid was carried out, and the components of the resulting mixtures were identified. Having in hands such "standard" mixtures greatly facilitates identification of components of sesquiterpene fractions of essential oils and other mixtures of natural origin. The catalytic activity of silica gel impregnated with sulfuric acid (H^+-SiO_2) in the acid-catalyzed isomerization of caryophyllene is significantly higher than that for H^+-Al_2O_3 and is comparable with the activity of concentrated sulfuric acid.

Key words: sesquiterpenoids, caryophyllene, isomerization, acid catalysis.

Sesquiterpenoids are a very important group of plant metabolites. Although the content of these compounds in natural sources is often low, they play a very important biological role. Among them, caryophyllene, *i.e.*, 1*R*,4*E*,9*S*-4,11,11-trimethyl-8-methylidenebicyclo[7.2.0]undec-4-ene (**1**), takes a special place.[1—8] One of the barriers to practical application of sesquiterpenoids is the insufficient knowledge of their metabolic characteristics.[9] This kind of studies is restrained, in particular, by the lack of simple methods for the obtaining the "standard" mixtures containing various caryophyllene derivatives. The need for these mixtures is substantiated by the fact that sesquiterpenoids, because of the variety of their structures, close retention parameters, and similar mass spectra,[10] represent the group of compounds most complicated for analysis.

In the present work, we describe access to the mixtures of caryophyllene compounds using acid-catalyzed conversions in the presence of Al_2O_3 and SiO_2 impregnated with sulfuric acid. A determining factor influencing the reaction course with these catalysts can be not only the concentration of the reagents on the surface of the adsorbent, but also the nature of the latter. Reactions in the presence of SiO_2 and Al_2O_3 often proceed under mild conditions, they are characterized by higher chemo-, regio- and stereoselectivity of transformations and simple procedures for isolation of products in comparison with similar homogeneous reactions.[11—15]

Results and Discussion

The catalysts were prepared by impregnation of the sorbent (Al_2O_3 or SiO_2) with an aqueous solution of H_2SO_4 and subsequent removal of water; the acid content ranged from 1 to 20 wt.%. The following samples of catalysts were obtained: H^+-$Al_2O_3^{(5\%)}$, H^+-$Al_2O_3^{(20\%)}$, H^+-$SiO_2^{(1\%)}$ and H^+-$SiO_2^{(5\%)}$. The isomerization of caryophyllene **1** was carried out by reacting its solution in hexane with the acid impregnated sorbent at 20 or 68 °C; the contact time of the substrate solution with the catalyst ranged from 1—5 min to 72 h. The individual components were isolated from the product mixtures by a combination of column chromatography on SiO_2 or $AgNO_3/SiO_2$ and preparative gas chromatography.

The acid-impregnated alumina H^+-Al_2O_3 has a low activity with respect to caryophyllene **1** (Table 1, entries *1—8*): when the catalyst with a 5% acid content (H^+-$Al_2O_3^{(5\%)}$) was used, the conversion of caryophyllene **1** after 24 h at 20 °C did not exceed 10% (entry *1*). A complete conversion was reached after increasing the reaction temperature (entry *4*), with a mixture of six alcohols (**2—7**) and eleven hydrocarbons (**8—16**) being formed. The structures of caryolan-1-ol (**2**),[16—18] isocaryolan-8-ol (**3**),[16] clovan-2β-ol (**4**),[19,20] caryophyllen-8β-ol (**5**),[21] caryophyllen-4β-ol (**6**),[22] isocaryophyllene (**8**),[19,23] isomeric dienes **9**, **10**,[23] clovene (**11**),[19,24] 3,8-cyclocaryophyll-4-ene (**12**),[19] isomeric 5,8-cyclocaryophyllenes **13**, **14**,[19] $\Delta^{8,9}$-isocaryolane (**15**),[23] and α-neoclovene (**16**)[19] were established based on the comparison of their mass spectra and linear retention indices with those described in the work.[25] The structure of ginsenol (**7**) was established by the comparison of its NMR spectra with the spectra described in the literature.[26]

Analysis of scientific literature devoted to the study of acid-catalyzed transformations of mono-, sesqui- and diterpenoids shows that the formation of final products is explained by the following processes: (1) intramolecular

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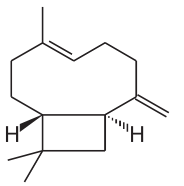

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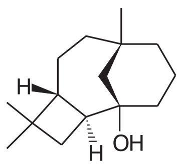

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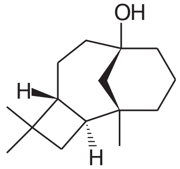

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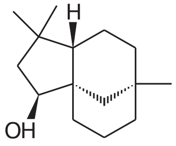

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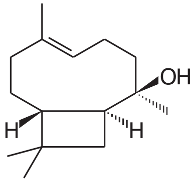

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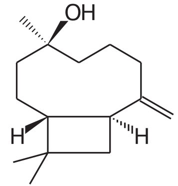

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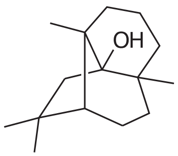

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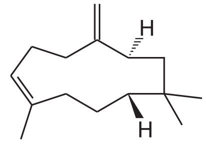

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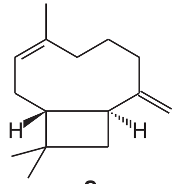

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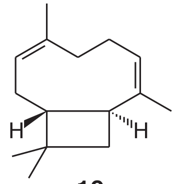

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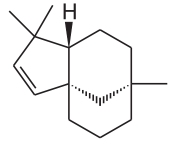

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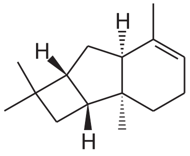

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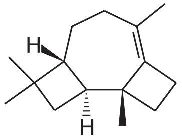

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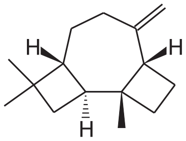

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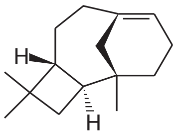

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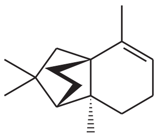

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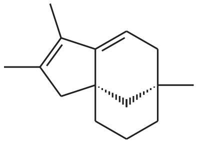

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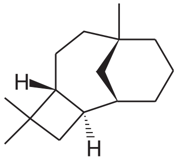

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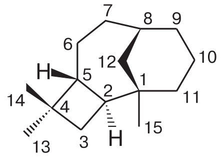

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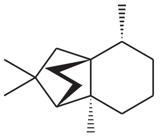

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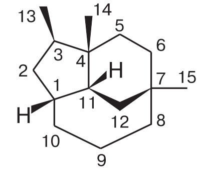

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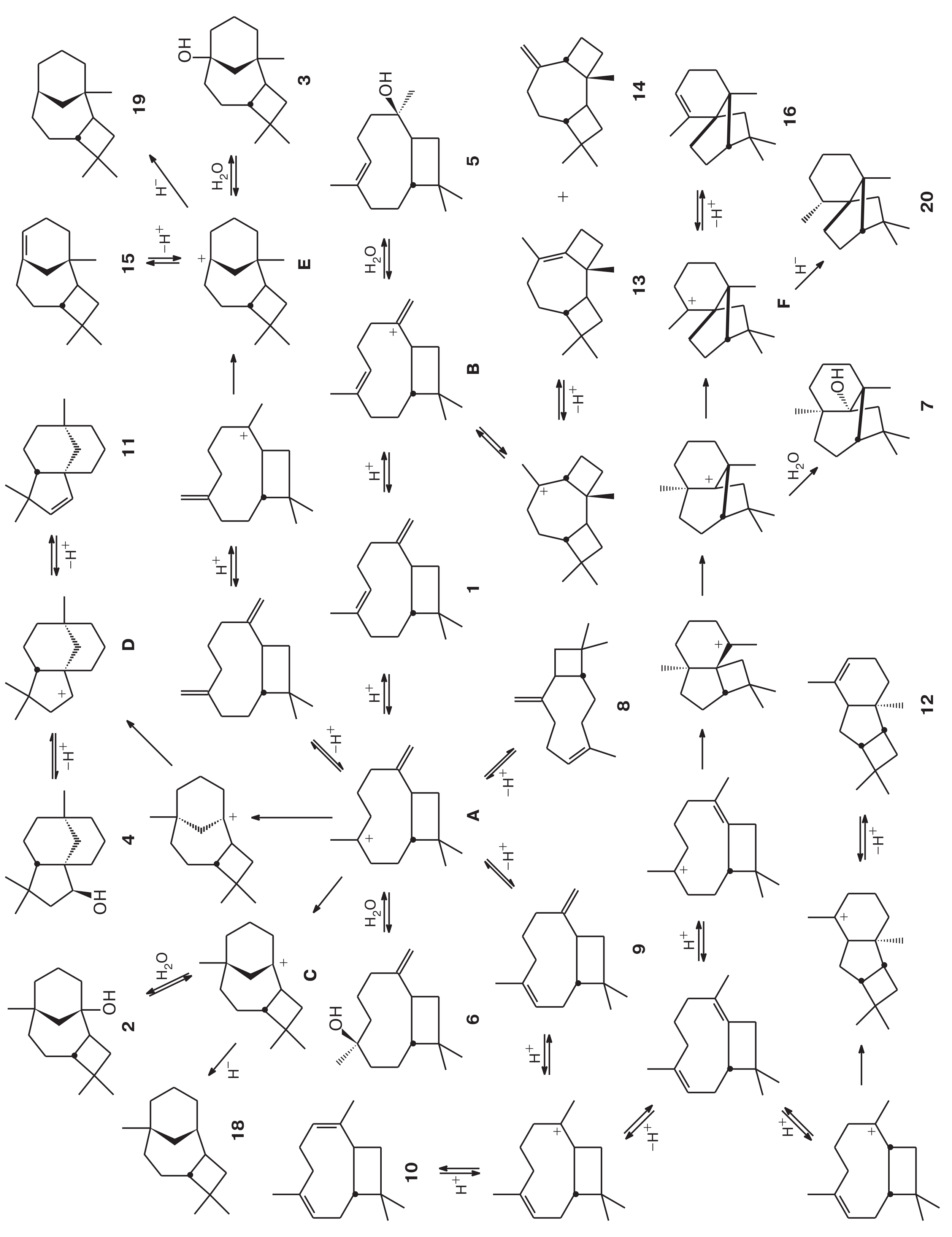
Table 1. Results of isomerization of caryophyllene **1**

Entry	Catalyst	Conditions		Reaction mixture composition (%)																
		t	*T*/°C	**1**	**2**	**3**	**4**	**5, 6**	**7**	**8—10**	**11**	**12**	**13, 14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
1	H^+-$Al_2O_3$$^{(5\%)}$	24 h	20	90.6	5.5	—	—	3.9	—	—	—	—	—	—	—	—	—	—	—	—
2	H^+-$Al_2O_3$$^{(5\%)}$	72 h	20	34.4	33.9	4.7	3.5	7.0	—	7.2	4.1	—	1.6	2.3	—	—	—	—	—	—
3	H^+-$Al_2O_3$$^{(5\%)}$	3 h	68	—	35.5	4.7	2.0	2.4	—	0.9	14.3	9.7	2.4	10.4	11.8	—	—	—	—	—
4	H^+-$Al_2O_3$$^{(5\%)}$	24 h	68	—	45.5	14.5	4.3	3.1	0.5	1.8	12.8	6.3	1.9	1.5	7.8	—	—	—	—	—
5	H^+-$Al_2O_3$$^{(20\%)}$	24 h	20	75.5	13.7	1.7	0.9	1.9	—	2.6	0.8	—	0.9	—	—	—	—	—	—	—
6	H^+-$Al_2O_3$$^{(20\%)}$	72 h	20	15.2	43.9	5.4	4.6	—	—	11.8	8.4	—	3.8	5.1	—	—	—	—	—	—
7	H^+-$Al_2O_3$$^{(20\%)}$	3 h	68	—	39.6	2.0	2.7	3.1	—	18.6	14.0	1.2	4.9	13.0	—	—	—	—	—	—
8	H^+-$Al_2O_3$$^{(20\%)}$	24 h	68	—	57.1	—	—	2.2	—	—	15.1	6.2	—	—	9.0	—	—	—	—	—
9	H_2SO_4—Et_2O	30 min	20	—	44.7	4.0	9.1	2.6	3.9	8.1	8.1	1.0	8.4	3.7	2.5	—	—	—	—	—
10	H_2SO_4—Et_2O	72 h	20	—	48.6	3.9	9.4	2.8	6.4	—	6.0	7.0	—	—	12.7	—	—	—	—	—
11	H_2SO_4—acetone	1 h	20	2.2	38.0	3.4	11.7	4.3	2.8	14.7	4.5	1.1	12.1	—	2.1	—	—	—	—	—
12	H_2SO_4—acetone	3 h	56	—	43.5	5.7	16.7	4.7	6.0	2.1	2.9	6.2	—	—	6.4	—	—	—	—	—
13	H^+-$SiO_2$$^{(1\%)}$	1 min	15	59.6	18.6	1.0	4.0	—	—	2.6	7.1	—	5.9	—	—	—	—	—	—	—
14	H^+-$SiO_2$$^{(1\%)}$	1 h	20	2.0	37.7	3.5	13.2	16.0	—	6.2	4.0	—	8.7	—	—	—	—	—	—	—
15	H^+-$SiO_2$$^{(5\%)}$	5 min	20	—	43.1	—	1.3	1.7	0.8	—	8.5	2.1	—	—	—	8.0	—	—	1.5	—
16	H^+-$SiO_2$$^{(5\%)}$	72 h	20	—	14.7	—	—	—	—	—	—	—	—	—	—	35.1	23.2	2.0	2.3	5.1
17	H^+-$SiO_2$$^{(5\%)}$	3 h	68	—	—	—	—	—	—	—	—	—	—	—	—	41.7	28.0	3.1	2.0	11.1
18	H_2SO_4—hexane	3 h	68	—	—	—	—	—	—	—	—	—	—	—	—	38.7	35.3	—	—	13.9

Scheme 1



cyclizations of unsaturated compounds; (2) rearrangements caused by migration of a hydride ion and/or alkyl groups; (3) reactions involving water (formation of alcohols from the corresponding carbocations); (4) intermolecular reactions of a hydride ion addition to carbocations to form saturated compounds (the reaction medium components may serve as sources of hydride ions); (5) intermolecular reactions of proton elimination from the allylic-type carbocations to form dienes (other compounds present in the reaction medium may act as proton acceptors).

The first stage of the reaction of caryophyllene **1** with the acid catalyst is the competitive protonation of endo- and exocyclic double bonds (Scheme 1). Subsequent deprotonation (or several successive protonation-deprotonation steps) of carbocations **A** and **B** leads to a mixture of dienes **8—10**, while the addition of water gives alcohols **5** and **6**. These reactions are reversible, and the accumulation of these products is observed only at low conversion. In addition, dienes **9** and **10** can be irreversibly consumed in the intramolecular carbocyclization leading to tricyclic olefins **12** and **16**. The cyclization of carbocation **B** gives two isomeric tricyclic alkenes **13** and **14**. The results presented in Table 1 indicate the reversibility of the formation of these products.

In the thermodynamically controlled reaction, carbocation **A** also undergoes carbocyclization, which, depending on the carbocation conformation, results in caryolan-1-ol **2** or clovene **11** as the major products (the content of caryolan-1-ol **2** in the product mixture can reach 50%). Apart from that, carbocation **A** through the intermediate diene bearing two exocyclic bonds can undergo ring closure to isocaryolan-8-ol **3**, with no intermediate diene being detected in the mixture in appreciable amounts.

The general regularities of the reaction carried out in the presence of H^+-Al_2O_3 (see Table 1, entries *1—8*) correspond to those observed in the homogeneous version of the reaction in the H_2SO_4—diethyl ether or H_2SO_4—acetone (entries *9—12*).

The activity of the acid impregnated silica gel H^+-SiO_2 in the reaction with caryophyllene **1** (see Table 1, entries *13—17*) is significantly higher than that of H^+-Al_2O_3: the starting caryophyllene **1** was detected only in the experiments using the catalyst with a low acid content H^+-$SiO_2^{(1\%)}$ (entries *13* and *14*). The set of reaction products obtained with H^+-$SiO_2^{(1\%)}$ does not fundamentally differ from that obtained with H^+-Al_2O_3.

On going to the catalyst with higher acid content H^+-$SiO_2^{(5\%)}$ (see Table 1, entries *15—17*), new components appear in the reaction products: tricyclic diene (1*R*,8*R*)-3,4,8-trimethyltricyclo[6.3.1.0^{1,5}]dodeca-3,5-diene (**17**) and four saturated tricyclic sesquiterpenoids, caryolane (**18**), isocaryolane (**19**), neoclovane (**20**), and (1*R*,3*R*,4*S*,7*S*,11*S*)-3,7,11-trimethyltricyclo[5.3.2.0^{4,11}]-dodecane (**21**). When the contact time of the reaction mixture with the catalyst H^+-SiO_2 is long or when the reaction is carried out at an elevated temperature (entries *16*, *17*), compounds **17—21** become the predominant reaction products.

The structure of compounds **17**[27] and **18**[24] was established based on the comparison of their NMR spectra with the spectra described in the literature. The structure of isocaryolane **19** was established based on the NMR spectroscopy data and confirmed by the synthesis of an authentic sample by the reduction of isocaryolan-9-one (**22**) with hydrazine.[28]

Neoclovane **20** is one of the isomeric products of the catalytic hydrogenation of α-neoclovene. In the synthesis of neoclovane by reduction of two stereoisomeric ketones **25** and **26** with the N_2H_4/KOH system, only isomer **27** is formed. This occurs due to the epimerization of ketones in the alkaline medium to form a more stable ketone **25** with *trans*-arrangement of the methyl groups (Scheme 2).

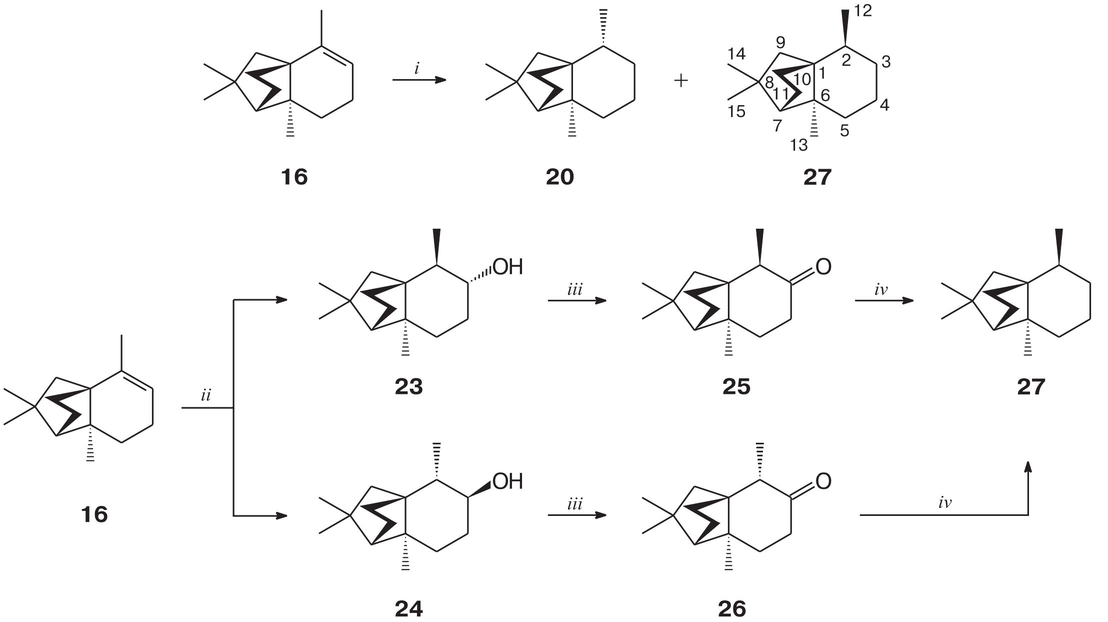
The structure of tricyclic saturated sesquiterpenoid **21** was inferred from the NMR spectroscopy data. The formation of this compound can be ascertained by Scheme 3. The four-membered ring expansion in the cation with the caryolane skeleton **C** to the five-membered ring of the epiclovane skeleton **G** with subsequent expansion of one of its six-membered rings leads to the formation of tricyclo[5.3.2.0^{4,11}]dodecane core **H**. A series of several sequential 1,2-shifts of hydrogen and a methyl group in the latter leads to carbocation **I**, which is an direct precursor of tricycloalkane **21**. Carbocations **H** and **I**, as well as the products of their reactions with nucleophiles, were described previously in the work[17] studied the behavior of 1-substituted caryolanes in superacidic media.

The precursor of tricyclic diene **17** is carbocation **D** with a clovane framework. A series of several successive 1,2-shifts of hydrogen and a methyl group and abstraction of the hydride ion from the intermediately formed olefin lead to allylic ion **J**, the direct precursor of compound **17**[24] (Scheme 4).

In addition to cation **I**, the carbocations with the caryolane (**C**), isocaryolane (**E**), and neoclovane (**F**) cores (precursors of compounds **18—20**) act as the hydride ion acceptors (see Scheme 1).

The higher catalytic activity of H^+-SiO_2 as compared to H^+-Al_2O_3 has already been noted in the literature on the example of sorbents impregnated with phosphoric[29] or phosphotungstic acid.[30] Apparently, this is explained by a weaker interaction of the impregnated acid with the surface of silica gel than with the surface of alumina.[31,32] In addition, a partial solubility of the substrate upon impregnation with a strong mineral acid considerably contributes to the lowering of the activity of H^+-Al_2O_3. For example, when 5% sulfuric acid is used to prepare the catalyst, up to 45% of the impregnated acid is consumed

Scheme 2

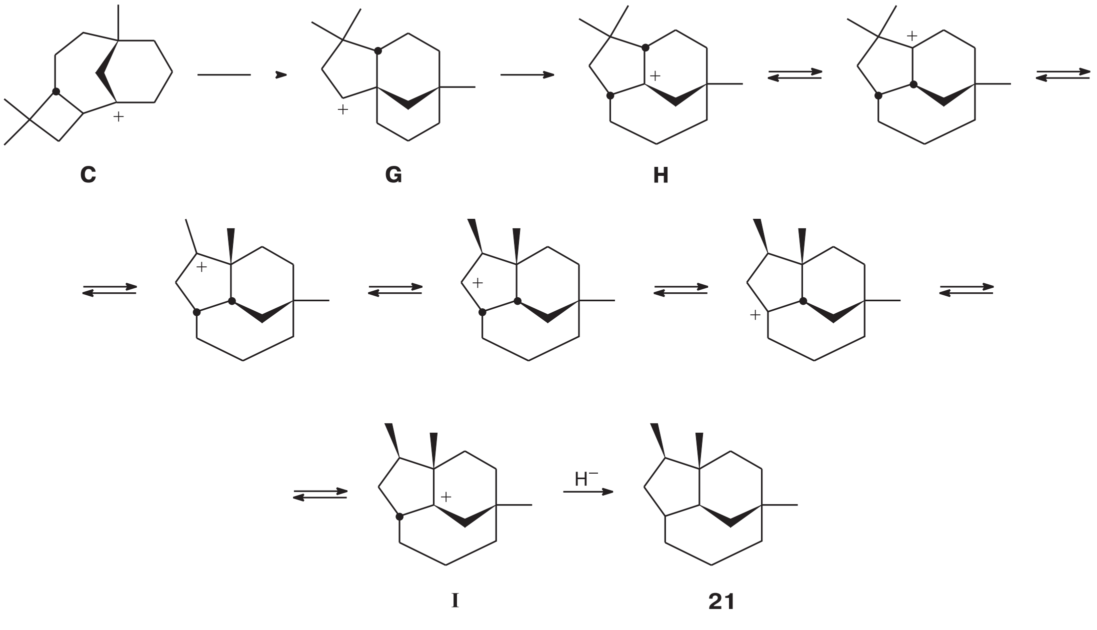


Reagents and conditions: *i*. H_2, Pd/C, EtOAc; *ii*. 1) $BF_3 \cdot Et_2O$, $LiAlH_4$; 2) H_2O_2, NaOH; *iii*. CrO_3, HOAc, H_2O; *iv*. $N_2H_4 \cdot H_2O$, KOH, triethylene glycol.

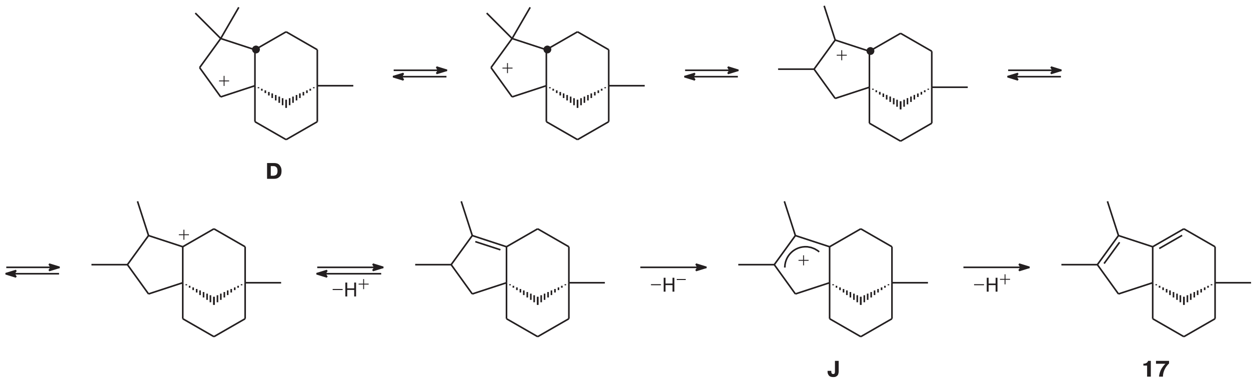
to dissolve Al_2O_3, so that the actual amount of the acid on the sorbent surface is less than 3 wt.%.

The composition of the reaction mixture obtained by the isomerization of caryophyllene **1** in the two-phase system H_2SO_4—hexane (see Table 1, entry *18*) is qualitatively the same observed for the H^+-SiO_2—hexane system (entries *16*, *17*): after 3 h of reflux of the reaction mixture, compounds **17**, **18**, and **21** are the predominant components. A similar behavior in the studied reaction of H_2SO_4 and H^+-SiO_2 confirms the literature data[14,15] on the commensurability of the catalytic activity of concentrated sulfuric acid and H^+-SiO_2.

Scheme 3



Scheme 4



Experimental

(−)-Caryophyllene **1** with a parameter $[\alpha]^{15}_{578}$ −9.78 was obtained by rectification *in vacuo* of the nonphenolic fraction of clove oil. To prepare sorbents impregnated with sulfuric acid, TU 6-09-3916-75 alumina and KSK silica gel with the particle size of 0.002-0.040 mm were used. All solvents were used freshly distilled.

Reaction mixtures were analyzed by chromatography-mass spectrometry using a Hewlett Packard G1081A instrument consisting of an HP 5890 series II gas chromatograph and an HP MSD 5971 mass selective detector (70 eV); an HP5 column (5% of diphenyl- and 95% of dimethylsiloxane): 30 m×00.25 mm×0 0.25 μm; carrier gas helium at a flow rate of 1 mL min^{-1}; the column temperature was programmed as follows: 2 min at 50 °C, temperature increase at a rate of 10 deg min^{-1}, 5 min at 280 °C; temperature of ion source was 173 °C. Data were collected at a rate of 1.2 scan s^{-1} in the mass range of 30—650 a.m.u. A mixture of normal hydrocarbons C_8—C_{24} was added to the test samples as a standard for determining linear retention indices. The identification of the mixture components was based on a comparison of their mass spectra and retention indices with the corresponding data for the reference compounds. The content of the components in the mixture was calculated by the peak areas without correction coefficients.

NMR spectra were recorded on a Bruker DRX-500 spectrometer (500.132 (^{1}H) and 125.758 MHz (^{13}C)) at 25 °C in $CDCl_3$ or in a mixture of $CDCl_3$—CCl_4 (1 : 1) using a sample concentrations of 25—50 mg mL^{-1}. Residual signals of the solvents were used as a reference: δ_H 7.24 ($CHCl_3$) and δ_C 76.90 ($CDCl_3$). Signals were assigned using ^{13}C NMR spectra recorded in a *J*-modulation mode and the following 2D spectra: (1) ^{1}H—^{1}H homonuclear correlation, (2) ^{13}C—^{1}H heteronuclear correlation on direct spin-spin coupling constants (J = 135 Hz), and (3) ^{13}C—^{1}H heteronuclear correlation on indirect spin-spin coupling constants (J = 10 Hz).

Optical rotation angles were measured on a Polamat A polarimeter at λ = 578 nm.

Components of the mixtures were separated by (1) column chromatography on KSK silica gel with a particle size of 0.140—0.315 mm activated at 130 °C for 6 h, (2) column chromatography on silica gel impregnated with 10% $AgNO_3$, and (3) preparative gas chromatography on a 15% OV-101/Chromaton N-AW-DMCS or 15% Carbowax 600/Chromaton N-AW-DMCS column, 4.5 m×1.6 mm, carrier gas nitrogen at a flow rate of 60 mL min^{-1}, column temperature of 150—200 °C.

Analytical TLC was performed on Sorbfil pre-coated plates; the spots were visualized by spraying the plates with an ethanolic solution of vanillin (0.5 g of vanillin and 5 mL of concentrated H_2SO_4 in 100 mL of EtOH).

Preparation of H^+-Al_2O_3 catalysts (general procedure). The H^+-$Al_2O_3^{(5\%)}$ catalyst with 5% content of acid was obtained by the addition of 5% aqueous H_2SO_4 (10.0 g) to Al_2O_3 (10.0 g). The mixture was stirred at room temperature for 30 min. Water was evaporated on a rotary evaporator. The resulting catalyst was dried at 130 °C for 10 h. The H^+-$Al_2O_3^{(20\%)}$ catalyst with 20% content of acid was prepared similarly using 20% aq. H_2SO_4.

Preparation of H^+-SiO_2 catalysts (general procedure). The H^+-$SiO_2^{(5\%)}$ catalyst with 5% content of acid was obtained by the addition of 2.5% aq. H_2SO_4 (20.0 g) to SiO_2 (10.0 g). The mixture was stirred at room temperature for 30 min. Water was evaporated on a rotary evaporator. The resulting catalyst was dried at 130 °C for 10 h. The H^+-$SiO_2^{(1\%)}$ catalyst with 1% content of acid was prepared similarly using 0.5% aq. H_2SO_4.

Isomerization of caryophyllene (1) on H^+-Al_2O_3 or H^+-SiO_2 (general procedure). A solution of caryophyllene **1** (25.0 mg, 0.122 mmol) in hexane (0.8 mL) was applied to a chromatographic column (5 mm in diameter) containing H^+-Al_2O_3 or H^+-SiO_2 (0.50 g). After standing at 20 °C for a control time, the column was washed with hexane (5 mL) and EtOAc (5 mL) (in the case of H^+-Al_2O_3) or acetone (5 mL) (in the case of H^+-SiO_2). The experiments in which the contact time of the solution of compound **1** with the catalyst was over 24 h, as well as the experiments at elevated temperature, were carried out in a flat-bottom flask with stirring (the solvent volume 2.5 mL). The results of the experiments are presented in Table 1.

The isomerization of caryophyllene **1** in the H_2SO_4—acetone (H_2SO_4—diethyl ether) system was carried out similarly to the described procedure.**[19]**

Isomerization of caryophyllene (1) in the H_2SO_4—hexane system (general procedure). Sulfuric acid (0.5 mL, 9.33 mmol) was added to a solution of caryophyllene **1** (50.0 mg, 0.245 mmol) in hexane (2 mL). The mixture was refluxed with vigorous stirring for 3 h. The organic solution was separated, the residue was diluted with water (2 mL), extracted with hexane (3×1 mL) and diethyl ether (3×1 mL). The combined organic fractions were washed with water and dried with $MgSO_4$.

Isocaryolane (19). A mixture of isocaryolan-9-one **22** (54 mg, 0.24 mmol) obtained by isomerization of caryophyllene oxide on H^+-SiO_2,[33] hydrazine hydrate (250 μL, 5.14 mmol), and KOH (100 mg, 1.78 mmol) in triethylene glycol (2 mL) was refluxed at 130 °C for 1 h. Then, water and excessive hydrazine hydrate were evaporated. The residue was heated at 180—190 °C for 5 h. The reaction mixture was diluted with water (3 mL), extracted with hexane (4×2 mL), the combined extracts were washed with water (3×1 mL) and dried with $MgSO_4$. A light yellow oil (34 mg) was obtained after evaporation of the solvent. Purification by column chromatography (SiO_2, eluent hexane) gave isocaryolane **19** (26 mg) as a colorless oil. ^1H NMR ($CDCl_3$—CCl_4 (1 : 1)), δ: 0.74 (s, 3 H, $C(15)H_3$); 0.96 (s, 3 H, $C(14)H_3$); 0.98 (s, 3 H, $C(13)H_3$); 1.61 (m, 1 H, H(5)); 1.98 (m, 1 H, H(8)); 2.05 (dt, 1 H, H(2), *J* = 11.4 Hz, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$—CCl_4 (1 : 1)), δ: 19.7 (t, C(10)); 20.9 (q, C(13)); 26.0 (t, C(6)); 27.9 (q, C(15)); 30.1 (t); 30.8 (q, C(14)); 31.4 (s, C(1)); 32.2 (d, C(8)); 32.9 (t); 34.0 (s, C(4)); 36.7 (t, C(3)); 39.6 (t); 41.5 (t); 41.8 (d, C(2)); 47.6 (d, C(5)).

α-Neoclovene (16). A solution of isocaryophyllene **8** (1.0 g, 4.9 mmol) in diethyl ether (5 mL) was added dropwise to a solution of H_2SO_4 (5.0 g) in diethyl ether cooled to 0 °C with vigorous stirring. The reaction mixture was maintained at this temperature for 1 h and neutralized with 15% aq. NaOH. The organic layer was separated, the aqueous layer was extracted with diethyl ether (4×5 mL), the combined organic fractions were washed with water (3×5 mL) and dried with anhydrous $MgSO_4$. Evaporation of the solvent gave 1.0 g of a residue. The hydrocarbon fraction (652 mg) was separated from the mixture by column chromatography (SiO_2, eluent hexane, then EtOAc). α-Neoclovene **16** (235 mg) was separated from the mixture of hydrocarbons by preparative gas chromatography (a 15% OV-101/Chromaton N-AW-DMCS column, column temperature 150 °C).

Reduction of α-neoclovene (16) with hydrogen was carried out according to the procedure described in the work,[34] which resulted in a mixture of two isomeric neoclovanes with the linear retention indexes of 1464 and 1482. The mass spectra of the neoclovanes obtained agree with those described earlier.[35]

Hydroboration—oxidation of α-neoclovene (16). To a stirred solution of α-neoclovene **16** (100 mg, 0.29 mmol) in anhydrous diethyl ether (6 mL) cooled to 0 °C, $BF_3 \cdot Et_2O$ (100 μL, 0.81 mmol) was added followed by addition of $LiAlH_4$ (40 mg, 1.05 mmol) in small portions. The mixture was kept at this temperature for 2 h, followed by addition of 3 *M* aq. NaOH (0.8 mL) and H_2O_2 (0.1 mL, 0.98 mmol) and stirring at 20 °C for 3 h. The organic layer was separated, washed with saturated aq. $FeSO_4$ (1 mL), 0.5 *M* aq. HCl (1 mL), and water (2×1 mL), dried with anhydrous $MgSO_4$. Evaporation of the solvent gave 94 mg of a mixture of alcohols as a colorless oil. The mixture of alcohols was separated by column chromatography (SiO_2, gradient elution with a mixture of hexane—CH_2Cl_2 (100 : 0→0 : 100)) to obtain alcohol **23** (39.5 mg, 36%) and alcohol **24** (18.8 mg, 17%) (m.p. 140—142 °C). The NMR spectra of these alcohols agree with those described in the literature.[34]

Oxidation of alcohols 23 and 24. A solution of CrO_3 (34 mg, 0.34 mmol) in a mixture of AcOH (200 μL) and water (100 μL) was added dropwise to a solution of alcohol **23** (31 mg, 0.14 mmol) in AcOH (1.7 mL). The mixture was maintained at 16 °C for 10 h, diluted with water (1.5 mL), and extracted with hexane (6×1.5 mL). The combined extracts were washed with aq. $NaHCO_3$ (4×1 mL) and water (3×1 mL), dried with anhydrous $MgSO_4$. Ketone **25** (28 mg, 91%) was obtained after evaporation of the solvent.

Ketone **26** (15.0 mg, 82%) was obtained similarly from alcohol **24** (18.5 mg).

(1*R*,2*S*,6*S*,7*S*)-2,6,8,8-Tetramethyltricyclo[5.2.2.0^{1,6}]undecane (27), neoclovane. A mixture of ketone **25** (10.5 mg, 0.05 mmol), $N_2H_4 \cdot H_2O$ (50 μL, 1.03 mmol), KOH (40 mg, 0.71 mmol), and triethylene glycol was heated at 180—190 °C for 4 h. After cooling, the mixture was diluted with water (2 mL) and extracted with hexane (6×1 mL). The combined extracts were washed with water (3×1 mL) and dried with anhydrous $MgSO_4$. Tricycloalkane **27** (6.0 mg, 61%) was obtained after evaporation of the solvent. ^1H NMR ($CDCl_3$), δ: 0.71 (d, $C(12)H_3$, $J_{12,2}$ = 6.8 Hz); 0.99 (s, $C(14)H_3$); 1.03 (s, $C(13)H_3$); 1.12 (d, H(9), $J_{9,9'}$ = 12.0 Hz); 1.16 (s, $C(15)H_3$); 1.40 (dd, H(9′), $J_{9',9}$ = 12.0 Hz, $J_{9',10}$ = 3.3 Hz); 1.44 (ddq, H(2), $J_{2,3\alpha}$ = 4.8 Hz, $J_{2,3\beta}$ = 11.5 Hz, $J_{1,12}$ = 6.8 Hz). ^{13}C NMR ($CDCl_3$), δ: 17.8 (q, C(12)); 18.7 (q, C(13)); 21.4 (t, C(11)); 22.0 (t, C(4)); 25.4 (t, C(10)); 29.5 (t, C(3)); 29.8 (t, C(5)); 31.7 (q, C(14)); 31.8 (q, C(15)); 32.2 (d, C(2)); 36.4 (s, C(8)); 49.7 (s, C(6)); 50.3 (t, C(9)); 51.5 (s, C(1)); 55.5 (d, C(7)). MS, *m/z* (I_{rel} (%)): 206 $[M]^+$ (25), 191 (58), 178 (13), 177 (10), 164 (13), 163 (84), 151 (20), 150 (73), 149 (20), 136 (20), 135 (52), 124 (37), 123 (53), 122 (43), 121 (47), 110 (17), 109 (86), 108 (33), 107 (79), 105 (14), 97 (17), 96 (26), 95 (63), 94 (84), 93 (65), 91 (35), 83 (16), 82 (70), 81 (100), 80 (15), 79 (44), 77 (27), 69 (51), 67 (45), 65 (10), 55 (46), 53 (18), 43 (13), 41 (55), 39 (16).

Neoclovane **27** (8.8 mg, 65%) was obtained by the reduction of ketone **26** (14.5 mg) by a similar procedure.

(1*R*,3*R*,4*S*,7*S*,11*S*)-3,7,11-Trimethyltricyclo[5.3.2.0^{4,11}]dodecane (21). $[\alpha]^{14}_{578}$ –6.18 (*c* 4.85, CCl_4). ^1H NMR ($CDCl_3$), δ: 0.81 (d, $C(13)H_3$, $J_{13,3}$ = 6.8 Hz); 0.83 (s, $C(15)H_3$); 0.91 (s, $C(14)H_3$); 2.32 (ddddd, H(1), *J* = 3.0 Hz, *J* = 4.8 Hz, *J* = 9.1 Hz, *J* = 9.1 Hz, *J* = 11.9 Hz). ^{13}C NMR ($CDCl_3$), δ: 12.4 (q, C(13)); 23.0 (t, C(9)); 23.9 (q, C(14)); 26.4 (t, C(5)); 31.2 (t, C(10)); 33.3 (s, C(7)); 35.1 (t, C(12)); 35.2 (t, C(6)); 35.9 (q, C(15)); 36.7 (t, C(2)); 37.4 (d, C(1)); 40.1 (s, C(4)); 44.3 (d, C(3)); 44.8 (t, C(8)); 47.4 (d, C(11)). MS, *m/z* (I_{rel} (%)): 206 (48), 192 (15), 191 (97), 177 (16), 164 (25), 163 (80), 150 (10), 149 (31), 137 (20), 136 (12), 135 (39), 123 (13), 122 (16), 121 (47), 120 (5), 119 (5), 111 (10), 110 (11), 109 (71), 108 (31), 107 (70), 106 (7), 105 (8), 97 (7), 96 (33), 95 (95), 94 (17), 93 (55), 92 (9), 91 (32), 83 (13), 82 (22), 81 (70), 80 (11), 79 (36), 78 (8), 77 (28), 69 (35), 68 (24), 67 (64), 65 (12), 57 (9), 56 (5), 55 (68), 54 (5), 53 (29), 51 (5), 43 (24), 42 (8), 41 (100), 40 (8), 39 (29), 32 (19).

Evaluation of the solubility of the sorbent during the preparation of the catalyst. A freshly prepared H^+-$Al_2O_3^{(5\%)}$ catalyst (2.5 g) was washed with water (10×10 ml) until neutral pH of the washings was reached. The washings were concentrated *in vacuo* to a volume of 50 mL. In the concentrate obtained, the concentration of Al^{3+} was determined by a known procedure,[36] as well as the concentration of H^+: $C(Al^{3+})$ = 0.0075—0.0082 mol L^{-1} (which corresponds to the consumption of H_2SO_4 43—47%), $C(H_2SO_4)$ = 0.0135—0.0140 mol L^{-1} (52—54% from the theoretical). In a similar procedure with H^+-$SiO_2^{(5\%)}$, no silicon ions were detected in the solution, with $C(H_2SO_4)$ = 0.0210—0.0260 mol L^{-1} (80—100% from the theoretical).

The linear retention indices of caryophyllene (1) and its isomerization products 2—20 are as follows (in ascending order): 1360 (**11**), 1367 (**13**), 1371 (**14**), 1380 (**12**), 1408 (**18**), 1412 (**8**), 1415 (**19**), 1415 (**15**), 1422 (**1**), 1434 (**10**), 1451 (**9**), 1451 (**16**), 1455

(**17**), 1482 (**20**), 1576 (**2**), 1581 (**5**), 1583 (**3**), 1605 (**6**), 1630 (**7**), 1635 (**4**).

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