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Acid-Catalyzed Cyclization of Terpenes Under Homogeneous and Heterogeneous Conditions as Probed Through Stereoisotopic Studies: A Concerted Process with Competing Preorganized Chair and Boat Transition States

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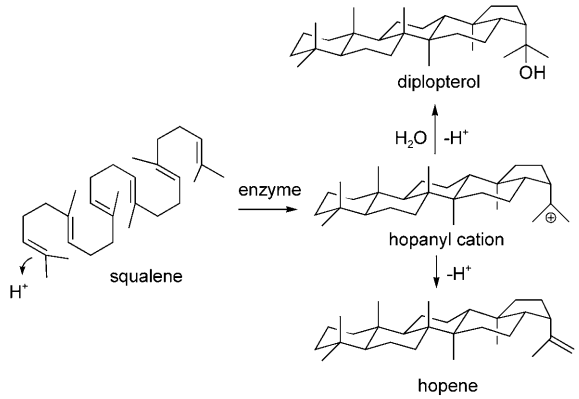
Abstract: Based on stereoisotopic studies and β-secondary isotope effects, we propose that the acid-catalyzed cyclization of geranyl acetate proceeds through a concerted mechanism. Under heterogeneous conditions (zeolite Y confinement), a preorganized chairlike transition state predominates, whereas under homogeneous conditions the boat- and chairlike transition states are almost isoenergetic. For the case of farnesyl acetate, we propose that under homogeneous conditions a concerted dicyclization occurs with a preorganized boat–chair transition state competing with the chair–chair transition state. Under zeolite confinement conditions, the chair–chairlike dicyclization transition state is highly favorable. The preference of chairlike transition states within the cavities of zeolite Y is attributed to a transition state shape selectivity effect.

Keywords: heterogeneous catalysis · homogeneous catalysis · isotope effects · reaction mechanisms · terpene cyclization

Introduction

The remarkable product variety and stereocontrol in the enzyme-catalyzed cyclization of polyene terpenes has fascinated chemists for over half a century.[1] An array of polycyclic natural products is derived from protonation of a suitable double bond proximal to an acidic amino acid residue (initiation) and termination of the (poly)cyclization occurs by a suitable basic amino acid residue within the enzyme cavity. An impressive example is the cyclization of squalene by squalene–hopene cyclase, which yields the pentacyclic hopene and diplopterol via a hopanyl cation. Within a single step, nine stereocenters are generated in a totally diastereoselective manner (Scheme 1).[2] The enzyme cavity provides ideal stereochemical restrictions for the polyene to adopt the all-pre-chair conformation required for the stereospecific formation of the pentacyclic hopanyl skeleton.



Scheme 1. The enzymatic cyclization of squalene to hopene and diplopterol.

Numerous attempts to replicate this fascinating one-step polycyclization in squalene by chemical means (acid catalysis) have been unsuccessful. For smaller acyclic terpenes (geranyl, farnesyl, geranylgeranyl), some efficient cyclization protocols are known. The most acceptable methodology

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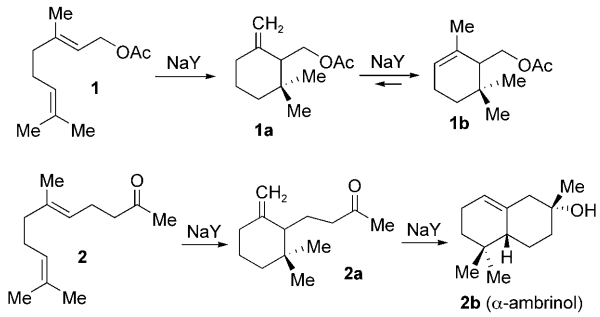
makes use of strong Brønsted acids,[3] such as halosulfonic acids. Although the reaction is formally considered as catalytic, the acid is used in multimolar equivalents relative to the reacting substrate. Furthermore, the temperature has to be maintained at −78 °C, or even lower. Formation of a six-membered carbocyclic ring by the intramolecular nucleophilic attack of a C=C double bond to a carbocation is highly exothermic and requires a very low activation energy. An acyclic terpene, which is conformationally mobile, may cyclize upon protonation under several diastereoselective modes of low activation energy as well. Therefore, a variety of isomeric products may be formed, unless the reaction temperature is kept very low. Upon increasing the reaction temperature, the product selectivity drops substantially,[4] as various diastereoselective or other isomeric cyclization pathways also compete. Apart from diastereoselection, another significant issue in the non-enzyme-catalyzed cyclization of terpene polyenes is enantiocontrol. Yamamoto and co-workers have significantly contributed to this field by using a combination of a chiral Brønsted acid and a Lewis acid as a catalyst.[5] Ishihara and co-workers achieved high enantiocontrol in polyene cyclization promoted by a "chiral" electrophilic halogen.[6] Moreover, Loh and Zhao reported an asymmetric polyene cyclization methodology using a combination of a chiral acetal and a Lewis acid as initiating electrophile.[7]

Recently, we examined the efficiency of acidic porous materials (zeolites)[8] as hosts and catalysts for the cyclization of polyene terpenoids. Zeolites are mixed aluminosilicates, which catalyze reactions by confining the substrates within "active site" cavities.[9] Our concept postulated that the zeolite cavity would provide the necessary acidic sites for initiating the cationic cyclization, whereas substrate confinement would decrease its conformational mobility and provide stereocontrol. We chose faujasites (zeolites HY and NaY) as possible catalysts. They possess a three-dimensional framework that consists of supercages, the interior diameter of which is approximately 13 Å. The supercages are interconnected by four "windows" that are tetrahedrally distributed around each cage and have a pore entrance diameter of around 7.5 Å. The dimensions of the cavities are ideal to host relatively big organic molecules, even steroids.[10] Zeolite NaY was our first choice because it is known to contain Brønsted and Lewis acidic sites.[11] The catalytic activity of zeolite Y has been attributed to synergistic Brønsted and Lewis acidity.[12] We were pleased to find that small acyclic terpenes undergo a clean cyclization reaction under essentially mild and environmentally friendly conditions (Scheme 2).[13] Furthermore, NaY promotes the selective monocyclization of epoxy polyene terpenoids,[14] as a unique methodology for the synthesis of a series of incompletely cyclized naturally occurring terpenols.[15] For example, geranyl acetate (**1**) forms at the initial reaction stages primarily γ-cyclogeranyl acetate (**1a**), which on prolonged reaction time isomerizes to the thermodynamically more stable α-cyclogeranyl acetate (**1b**). A remarkable result among those studies was the cyclization of geranylacetone (**2**)[13] and its derivatives,[16] which provide a direct one-pot cascade route to the synthesis of α-ambrinol (**2b**); a valuable compound in the fragrance industry. A unique tandem dicyclization pathway was also uncovered for the case of farnesal adsorbed within NaY.[17] The ability of NaY to promote terpene cyclization was also reported immediately after our publication by Yu and co-workers.[18]



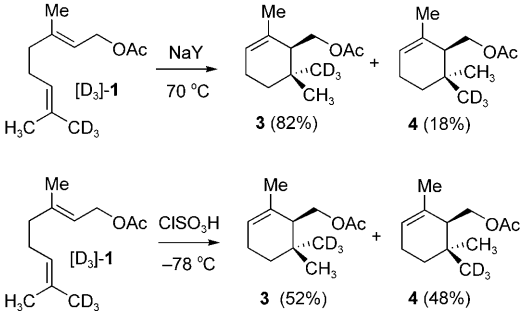
Scheme 2. Zeolite NaY promoted cyclization of small terpenoids.

Although the mechanism of epoxy terpene cyclization under Brønsted,[19] Lewis acid[20] or zeolite[15] catalysis is well established to proceed through a concerted pathway, the mechanism of the acid-catalyzed cyclization of polyene terpenes is still not fully understood.[1d] The abundant stereochemical studies of the past often contradict each other,[1c] rather than merging upon accepting a concerted mechanism. Yet, the nature of the transition states is still only hypothesized. From a theoretical point of view, Rajamani and Gao applied a combined quantum mechanics/molecular mechanics (QM/MM) approach and presented discrete formation of incompletely cyclized carbocationic intermediates en route from squalene to hopenes.[21] On the other hand, DFT calculations by Hess and Smentek on a terpenoid fragment of squalene supported a concerted mechanism for the A–B ring formation.[22] Later on, Matsuda and co-workers reported systematic errors in the DFT method as a tool to calculate the energetics and transition states of polyene cyclization.[23] It is important to emphasize herein that all theoretical calculations deal with the cyclization of a tertiary carbocation (resulting from protonation of the terminal double bond), which would not exist as an intermediate in a concerted polycyclization process.

Prompted by our studies on the zeolite Y promoted cyclization of terpenoids, we undertook a mechanistic investigation of the cyclization of geranyl and farnesyl acetate under heterogeneous (zeolite NaY or HY confinement) and homogeneous ($ClSO_3H$, solvent) conditions. These studies are based on stereoisotopic labeling of the reacting substrates and kinetic β-secondary isotope effects, and support a concerted mechanism for the monocyclization (geranyl acetate) or dicyclization (farnesyl acetate) of small acyclic polyene terpenes.

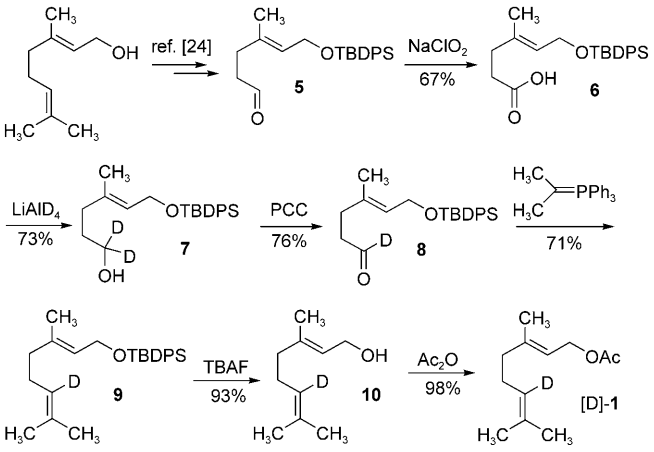
Results and Discussion

Cyclization of geranyl acetate: So far, we have shown that in the cyclization of labeled 8,8,8-[D_3]-geranyl acetate ([D_3]-**1**) a significant difference was found regarding the stereochemical disposition of the *gem*-dimethyl group in the cyclized α- or γ-cyclogeranyl acetate on going from homogeneous ($ClSO_3H$, 2-nitropropane, −78 °C) to heterogeneous (zeolite NaY) conditions (Scheme 3).[24] Under homogeneous conditions the diastereomeric products **3** and **4** are formed in almost equimolar amounts, with **3** slightly prevailing, whereas under heterogeneous conditions **3** substantially predominates over **4**. Although we postulated that within the zeolite cavities an initially formed tertiary carbocation possibly undergoes cyclization at a faster rate than the rotation around the terminal Me_2C^+–C bond, we also considered the possibility of cyclization through competing chair and boat transition states. In addition, a question was raised: is the cyclization mechanism stepwise (formation of a tertiary carbocation that undergoes carbocyclization in a second step), or concerted (single step)?



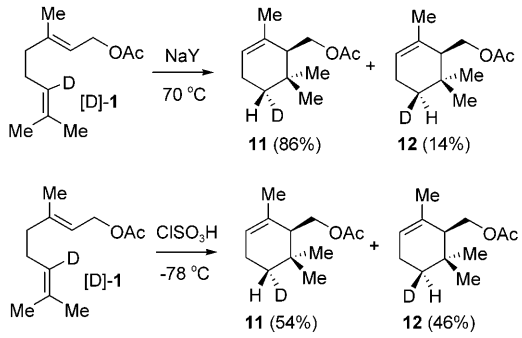
Scheme 3. Stereochemical disposition of the *gem*-dimethyl group in the cyclization of [D_3]-**1**.

Thus, for a deeper mechanistic analysis of the cyclization of **1** we performed further stereoisotopic studies and additionally measured β-secondary isotope effects. As a first target we examined the stereochemistry in the cyclization of 6-[D]-geranyl acetate ([D]-**1**). The synthesis of [D]-**1** was accomplished with >97% deuterium incorporation on C-6 by following the procedure shown in Scheme 4. The known aldehyde **5** produced by the oxidative cleavage of the TBDPS-protected 6,7-epoxygeraniol[24] (TBDPS = *tert*-butyldiphenylsilyl) was oxidized with $NaClO_2$ to the corresponding carboxylic acid **6**. The acid **6** was reduced with $LiAlD_4$ to form the labeled [D_2]-alcohol **7**, which was oxidized with pyridinium chlorochromate (PCC) to yield the deuterated aldehyde **8**. The aldehyde was coupled with isopropylidenetriphenylphosphorane to produce the TBDPS-protected alkene **9**. Finally, alkene **9** was deprotected with tetrabutylammonium fluoride (TBAF) and the resulting alcohol **10** (6-[D]-geraniol) was acetylated with acetic anhydride to form [D]-**1**, in 14% overall isolated yield from geraniol.



Scheme 4. Synthesis of [D]-**1**.

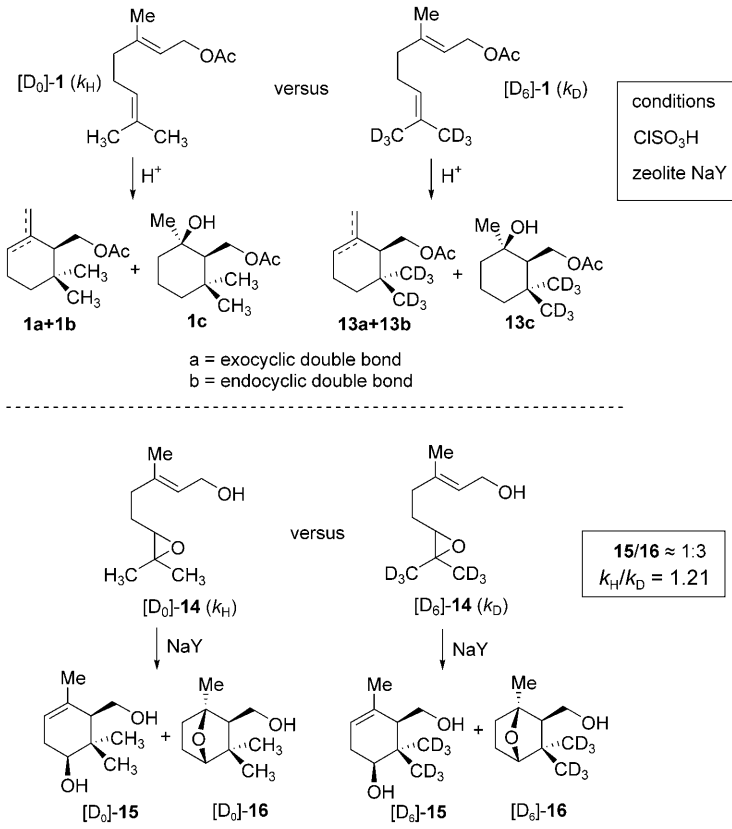
The cyclization of [D]-**1** under zeolite confinement conditions[13] afforded α-cyclogeranyl acetate as a mixture of the two diastereomers **11** and **12** in a relative ratio of 86:14 (Scheme 5). The reaction was almost exclusively driven to α-cyclogeranyl acetate (70 °C, 3 h) to avoid the interfering absorptions in the aliphatic region of the initially formed isomeric γ-cyclogeranyl acetate. The stereochemistry of the major and minor products was assigned based on an NOE spectroscopic analysis of α-cyclogeranyl acetate.[25] In contrast to the zeolite-promoted reaction, the cyclization of [D]-**1** in a homogeneous environment ($ClSO_3H$, 2-nitropropane at −78 or −25 °C) afforded a mixture of the diastereomers **11** and **12** in 82% isolated yield with a very low degree of diastereoselection (diastereomeric ratio (dr) ≈ 6–8%), without thus observing a temperature dependence on the product ratio. Identical results were found by performing the $ClSO_3H$-catalyzed reaction in the less polar CH_2Cl_2 (−78 °C). The results presented in Scheme 5 resemble substantially the stereochemical outcome in the cyclization of [D_3]-**1**[24] (Scheme 3).



Scheme 5. Stereochemistry in the cyclization of [D]-**1**.

A further mechanistic approach regarding the cyclization of geranyl acetate was performed by measuring the intermolecular kinetic β-secondary isotope effects upon competition

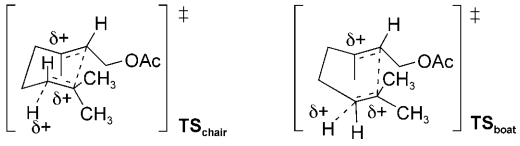
of geranyl acetate ([D_0]-**1**) with the labeled 8,8,8,9,9,9-[D_6]-geranyl acetate ([D_6]-**1**).[26] An isotope effect of $k_H/k_D = 1.30 \pm 0.02$ was measured under homogeneous conditions ($ClSO_3H$, 2-nitropropane, −70 °C, 20–40 s), with α-cyclogeranyl acetate being formed exclusively. Under heterogeneous conditions (zeolite NaY, 20 °C, 3 min) a mixture of α-cyclogeranyl acetate (**1a**), γ-cyclogeranyl acetate (**1b**), and a minor amount of alcohol **1c** were formed with $k_H/k_D = 1.33 \pm 0.03$ (Scheme 6). The isotope effects were measured in a relative ratio of approximately 1:3. The competing cyclization of [D_0]-**14** and [D_6]-**14** (1 min, ≈15–20 % conversion) provided an isotope effect of $k_H/k_D = 1.21 \pm 0.02$ (Scheme 6). Again, the isotope effect was measured by GC. The relatively similar values of β-secondary isotope effects clearly indicate a similarity between the transition states of terpene and epoxy terpene carbocyclization.



Scheme 6. Intramolecular kinetic β-secondary isotope effects for the cyclization of geranyl acetate and 6,7-epoxy geraniol.

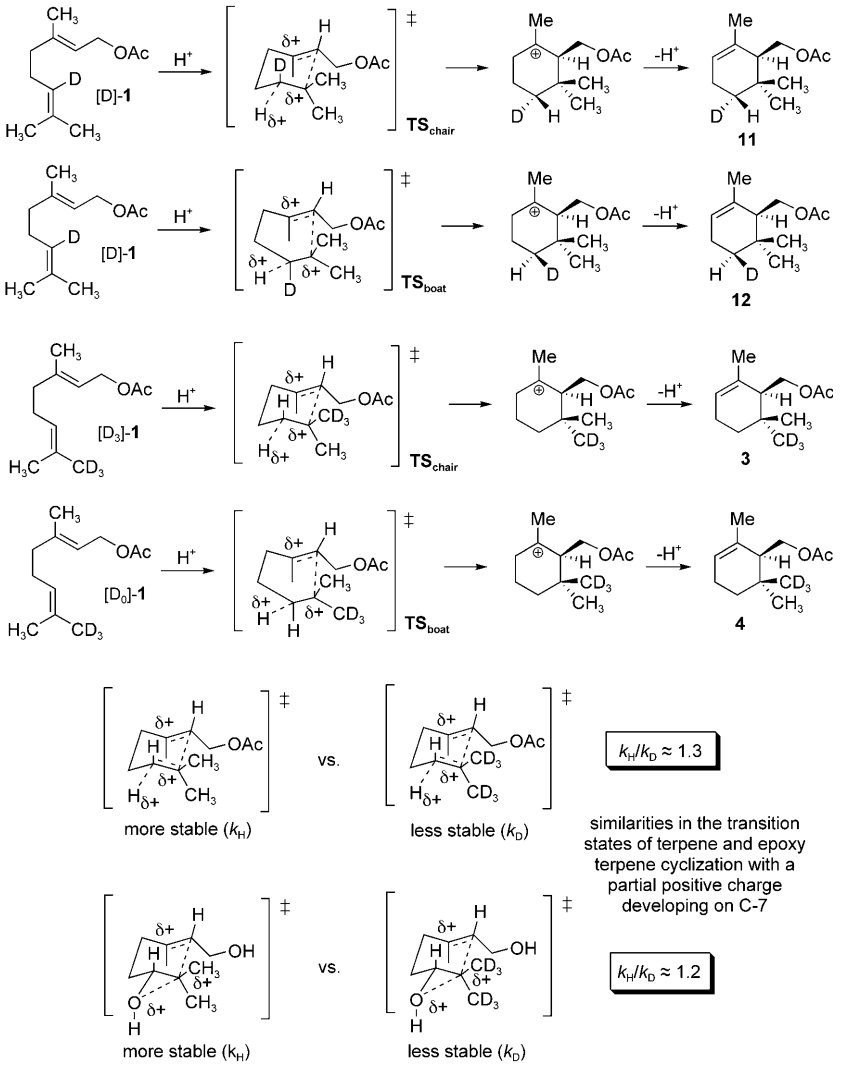
Before analyzing and drawing conclusions from the results of the above stereoisotopic studies, we emphasize that the cyclization of [D_3]-**1** proceeds either under zeolite confinement[24] or under homogeneous conditions without detectable isomerization of the noncyclized starting material. This implies that the low diastereoselection under homogeneous conditions (products **3** and **4**), or the higher diastereoselection under heterogeneous conditions (products **11** and **12**) does not result from any isomerization on the terminal double bond, C6=C7, of [D_3]-**1** prior to cyclization. Based on the current results shown in Schemes 3, 5, and 6, we propose that the acid-catalyzed cyclization of geranyl acetate proceeds through a concerted mechanism, regardless of the reaction medium (homogeneous or heterogeneous in nature), via the two competing chair- ($\mathbf{TS_{chair}}$) and boatlike ($\mathbf{TS_{boat}}$) transition states shown in Scheme 7.

Essentially, for the reaction to occur, the substrate requires a conformational preorganization,[28] so that the proximity of H^+ to the C6=C7 double bond and the suitable chair or boat conformation that brings the two double bonds at a proximal orientation allows the cyclization to take place in a concerted fashion. This is clearly derived from the stereochemical outcome of labeled [D_3]-**1** and [D]-**1**, for which the product distribution is rationalized to arise through concerted chair- and boatlike transition states (Scheme 8). Regarding the reaction in a homogeneous environment, we propose that the energy differ-



Scheme 7.

by GC analysis of the reaction mixture at approximately 10–40 % conversion, as both competing [D_0]-**1** and [D_6]-**1**, as well as their cyclization products are clearly separated on a 60 m capillary column (see the Supporting Information). This magnitude of isotope effect implies a partial positive charge developing on the tertiary carbon atom C-7 in the transition state of the rate-determining step of the cyclization. We decided to compare the value of $k_H/k_D \approx 1.3$ to the kinetic β-secondary isotope effect during the $FeCl_3$-catalyzed[27] cyclization of 6,7-epoxy geraniol ([D_0]-**14**) and its labeled counterpart [D_6]-**14**[26] (Scheme 6) because the acid-catalyzed cyclization of epoxy polyene terpenes is a well-established concerted process. In the presence of $FeCl_3$ (1.0 equiv, CH_2Cl_2, 20 °C), 6,7-epoxygeraniol yields a mixture of the carbocyclization product **15**[14] and the bicyclic ether **16**,[14] through a common carbocationic intermediate,

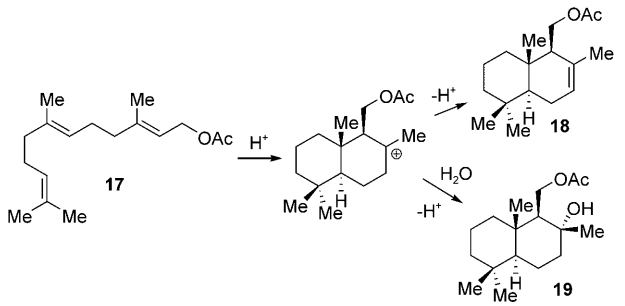


Scheme 8. Proposed transition states for the acid-catalyzed cyclization of geranyl acetate through the stereoisotopic studies of [D_3]-**1**, [D]-**1** and the elucidation of the intramolecular β-secondary isotope effects.

ence between the concerted chair- ($\mathbf{TS_{chair}}$) and boatlike ($\mathbf{TS_{boat}}$) transition states is very small, thus the product diastereoselectivity (**3** versus **4**, or **11** versus **12**), is very low. On the other hand, for the acid-catalyzed intrazeolite cyclization,[29] we postulate that the confined zeolite environment can better accommodate within its cavities the chairlike transition state than the boatlike one, thus **3** predominates over **4**, and **11** over **12**. From the first point of view, a chairlike transition state is expected to be significantly more stable than a boatlike transition state because the chair conformation of cyclohexane is more stable relative to a boat or twist-boat by 6 and 4.5 kcal mol^{-1}, respectively. Yet, a closer examination of the above shown transitions states reveals that the $\mathbf{TS_{chair}}$ is destabilized by the steric strain between the methyl group at C-3 and *gem*-methyl of C-9. In addition, the CH_2OAc substituent develops steric strain with both *gem*-methyl groups at C-8 and C-9, because it is in a *gauche* conformation relative to them. In $\mathbf{TS_{boat}}$, two out of the three destabilizing nonbonding steric interactions appearing in $\mathbf{TS_{chair}}$ are absent, with the only steric strain caused by the interaction of the CH_2OAc group with the *gem*-methyl group at C-8. The torsional strain between the eclipsed C–H bonds within $\mathbf{TS_{boat}}$ is balanced by the significant release of the steric strain present in $\mathbf{TS_{chair}}$. Therefore, we conclude that it is reasonable to assume that the $\mathbf{TS_{chair}}$ and $\mathbf{TS_{boat}}$ transition states are expected to be close in energy. In addition, the magnitude of the β-secondary isotope effect ($k_H/k_D \approx 1.3$, or $k_H/k_D \approx 1.04$ per H/D atom) is consistent with a partial positive charge developing on C-7 in the transition state of the reaction. A full positive charge, considering an intermediate acyclic tertiary carbocation on C-7, would be expected to provide a value of $k_H/k_D \approx 1.8$[31] ($k_H/k_D \approx 1.10$ per H/D atom). Our measured value of $k_H/k_D \approx 1.3$ is close to the β-secondary isotope effect of $k_H/k_D = 1.37$[32] found during the solvolysis of 7-chloro-3,7-dimethyloct-2-ene, in which the π participation of the double bond in a six-membered-ring transition state analogous to the proposed transition states of geranyl acetate cyclization shown in Scheme 8, had been postulated. Apart of the evidence provided by the β-secondary isotope effects, a stepwise mechanism with formation of a tertiary acyclic carbocation as an intermediate can be undoubtedly ruled out: Although the diastereoselective disposition of the *gem*-methyl groups in [D_3]-**1** might be attributed to a slow rotation of the C6–C7 bond in the tertiary carbocation prior to cyclization, for the case of [D]-**1**, no diastereoselection (**11** versus **12**) would be expected to result after protonation on C-6, and subsequent cyclization. Based on these results, we emphasize that in considering terpene cyclization, a fully concerted carbocyclization process has to be taken into account and not a tertiary acyclic intermediate carbocation as the starting point of polycyclization. We consider the temperature independence of the stereochemical results for the cyclization of [D]-**1** and [D_3]-**1** as reasonable, because there is not any obvious difference in the entropy of activation between a chair- and a boatlike transition state.

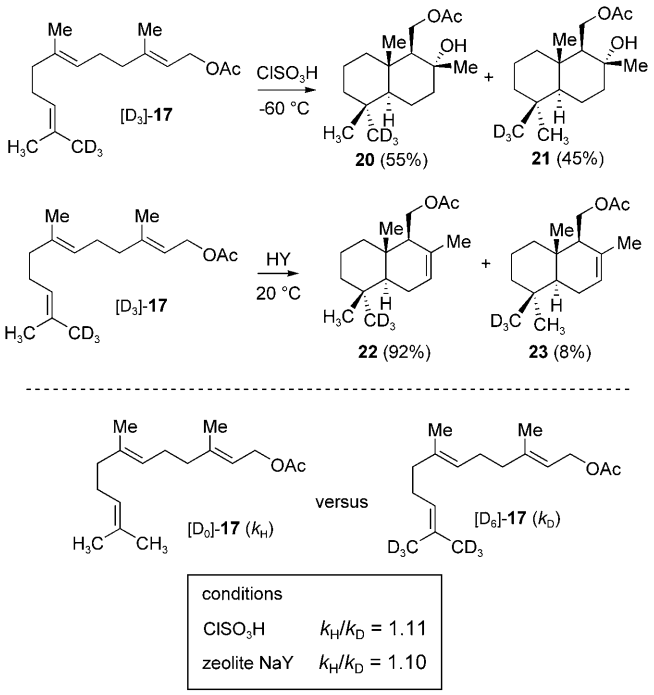
The preference of the $\mathbf{TS_{chair}}$ within the cavities of NaY is attributed to a confinement effect. The absorbing efficiency of porous materials, such as zeolites, is well known to depend significantly on the steric demands of the guest molecules. For example, the relative ratio of the conformers of cyclohexane and its derivatives in solution may significantly change upon absorption in the constrained environment of zeolites.[33] In contrast to silicalite-1, zeolite Y accommodates cyclohexane exclusively in a chair conformation.[34] Therefore, we postulate that $\mathbf{TS_{chair}}$ is energetically more accommodated within the zeolite supercage than $\mathbf{TS_{boat}}$, due a shape selective confinement effect (transition-state shape selectivity[9a]).

Cyclization of farnesyl acetate: Continuing our studies, the mechanism of bicyclization of farnesyl acetate (**17**) was targeted. Under superacidic conditions,[35] farnesyl acetate forms drimenyl acetate (**18**) and/or drimanediol monoacetate **19** depending on the amount of water present in the reaction mixture (Scheme 9). In our hands, by using $ClSO_3H$ as the acidic catalyst (5 equiv), drimanediol monoacetate was mainly formed. The product selectivity depends on the reaction temperature. At −75 °C, **19** is primarily formed, whereas by increasing the reaction temperature to −50 °C, two additional bicyclic diastereomers are formed (GC–MS) in up to 30 % relative yield, in agreement to the temperature-dependent product selectivity observed in the $ClSO_3H$-catalyzed cyclization of geranyl derivatives.[4]



Scheme 9. The acid-catalyzed cyclization of farnesyl acetate.

As indicated earlier, the theoretical calculations on the mechanism of the dicyclization contradict each other. A combined QM/MM approach[21] proposes discrete formation of a monocyclized carbocationic intermediate that subsequently leads to the bicyclic product, whereas DFT calculations support[22] a concerted mechanism for A–B ring formation. Both studies, however, consider a protonated acyclic tertiary carbocation as the reacting species. By analogy to the stereoisotopic studies performed in geranyl acetate, we studied the mechanism of farnesyl acetate cyclization by preparing stereoselectively 12,12,12-[D_3]-farnesyl acetate ([D_3]-**17**),[20] as well as 12,12,12,13,13,13-[D_6]-farnesyl acetate ([D_6]-**17**), following similar synthetic approaches to the synthesis of the corresponding geranyl analogues (see the Supporting Information). The cyclization of [D_3]-**17** was studied under homo- and heterogeneous conditions. Under homogeneous conditions ($ClSO_3H$ (5 equiv), 2-nitropropane, −60 °C, 5 min) mainly the labeled drimanediol monoacetate was formed. The disposition of the *gem*-dimethyl group was not stereoselective, with formation of the diastereomeric **20** and **21** in a relative ratio **20**/**21** of approximately 55:45 (Scheme 10). The stereochemical assignment of the products

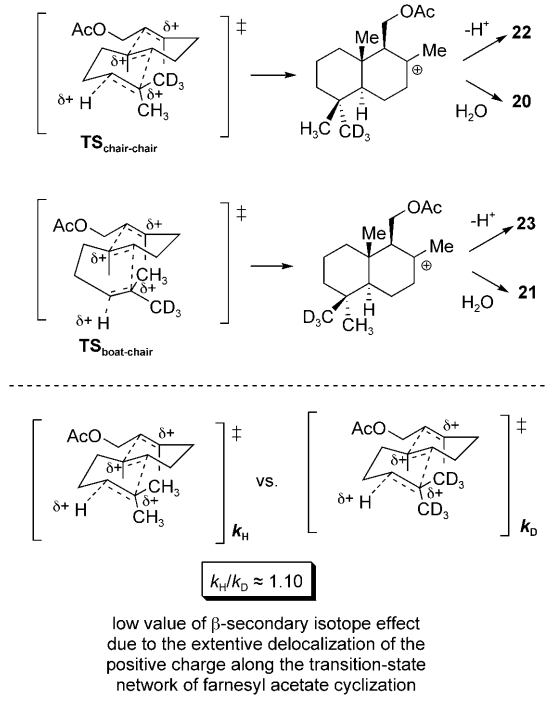


Scheme 10. Stereochemistry in the cyclization of farnesyl acetate [D_3]-**17** and the β-secondary isotope effects for the competition of [D_0]-**17** with [D_6]-**17**.

was achieved by an NOE spectroscopic analysis.[36] This result remarkably resembles the stereochemical outcome in the $ClSO_3H$-promoted cyclization of the geranyl analogue [D_3]-**1**. The cyclization of [D_3]-**17** under zeolite confinement conditions was achieved by using the highly dealuminated zeolite HY (Si/Al = 30:1) as a catalyst at ambient temperature. This relatively mildly acidic zeolite, in contrast to NaY[13] and HY (Si/Al = 2.7:1), promotes the cyclization of farnesyl to drimenyl acetate in good yield, without forming hydrocarbon byproducts (resulting from an acid-catalyzed elimination of the acetate in the starting material).[37] In the presence of dealuminated HY, [D_3]-**17** afforded a mixture of **22**/**23** in 72 % isolated yield and in a relative ratio of approximately 92:8 (Scheme 10). Thus, in contrast to the $ClSO_3H$-catalyzed cyclization, a remarkable stereoselectivity in the disposition of the *gem*-methyl group was observed. Furthermore, the kinetic competition of farnesyl acetate ([D_0]-**17**) with its *gem*-dimethyl deuterated analogue, [D_6]-**17**, was performed. Under homogeneous conditions the relative reaction rate [D_0]-**17**/[D_6]-**17** (k_H/k_D) was 1.11 ± 0.02, compared

with $k_H/k_D = 1.10 \pm 0.02$ under heterogeneous conditions (Scheme 10). Under homogeneous conditions ($ClSO_3H$, $-50\,^{\circ}C$), apart from drimanediol monoacetate ([D_0]-**19** and [D_6]-**19**), two other bicyclic epimers were formed (see the Supporting Information) and the isotope effect was measured after 30 s of reaction when approximately a 30% conversion had been achieved (the reaction was quenched by adding an excess of Et_3N to the reaction mixture). Under HY treatment, approximately 30% conversion was achieved after 30 s (the reaction was stopped by adding moistened methanol into the heterogeneous slurry). Apart from drimenyl acetate (**18**), its exocyclic isomer albicanyl acetate (**24**) was also detected, by comparison with an authentic sample. It is notable that after a few minutes, the reaction had gone to completion and albicanyl acetate had quantitatively isomerized to the thermodynamically more stable drimenyl acetate. Both isotope effects were measured by GC (see the Supporting Information for the details).

To analyze the results of the stereoisotopic experiments, we began with the intrazeolite experiments. The *gem*-dimethyl group disposition in [D_3]-**17** and the intramolecular isotope effect of [D_0]-**17**/[D_6]-**17** ≈ 1.10 support a concerted mechanism for the formation of **22** via a chair–chair preorganized transition state (Scheme 11). The very low magnitude of the β-secondary isotope effect indicates an extensive delocalization of the positive charge along the transition-state framework and is in agreement with the close to unity β-secondary isotope effects obtained in the solvolysis of 2-chloro-2,3-dihydrosqualene[31] and other polyene terpenyl-type chlorides.[32] The minor **23** could derive from a boat–chair preorganized concerted transition state. Regarding the cyclization in solution, the low magnitude of the β-secondary isotope effect supports a concerted bicyclization mechanism, as proposed under heterogeneous conditions, with competition between the boat–chair and chair–chair transition states. A boat–chair transition state is not less thermodynamically stable, for exactly the same reasons as put forward earlier for the transition states of the cyclization of geranyl acetate. The enzymatic cyclization of polyene terpenes through mixed chair- and boatlike transition states is known.[38]

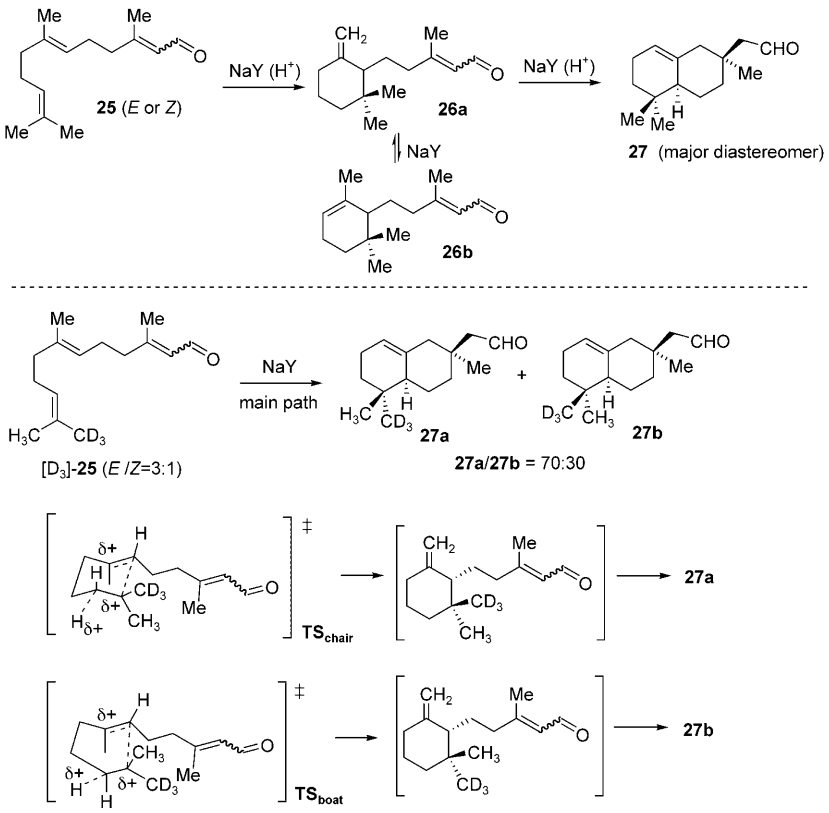


Scheme 11. Mechanistic proposal for the acid-catalyzed cyclization of farnesyl acetate.

Finally, further support for the concerted nature of the bicyclization of farnesyl acetate under zeolite catalysis was obtained by studying the *gem*-dimethyl group disposition in the zeolite NaY-promoted cyclization of 12,12,12-[D_3]-farnesal ([D_3]-**25**). Farnesal (**25**) forms primarily the bicyclic aldehyde **27** (major diastereomer shown in Scheme 12) through a stepwise mechanism involving preferential formation of exomethylenic monocyclic **26a**, which subsequently leads to **27** through a Prins-type cyclization.[17] The stereoselectively labeled farnesal [D_3]-**25** was prepared in two steps from 11,11,11-[D]-(*E*)-6,10-dimethylundeca-5,9-dien-2-one (see the Supporting Information), which is readily available from our previous studies as a mixture of *E* and *Z* isomers at the enal moiety.[15] Treatment with NaY afforded the bicyclic aldehydes **27a** and **27b** in a relative ratio of 70:30 (Scheme 12). Due to the structural similarity of farnesyl acetate and farnesal, we indicate that a hypothetical monocyclization of farnesyl acetate followed by a second distinct dicyclization step should provide a ratio of **22**/**23** analogous to that of **27a**/**27b** ($\approx$70:30), and not the observed **22**/**23** > 90:10. The relative ratio of **27a**/**27b** $\approx$ 70:30 is in close agreement to the ratio of **3**/**4** obtained in the intrazeolite (mono)-cyclization of [D_3]-**1** and is explained in terms of the chair- and boatlike transition states shown in Scheme 12.

Conclusion

We have presented substantial evidence that the acid-catalyzed cyclization of geranyl and farnesyl acetate proceeds through a concerted mechanism. The cyclization occurs through competing chair- and boatlike transition states and a suitable conformation (preorganization) of the terpene is necessary in order for the reaction to take place. The nature of the transition states depends substantially on the reaction medium, with the confinement conditions favoring the chair-like transitions states. We believe that these studies will challenge theoreticians to study the mechanism of terpene cyclization considering a fully concerted process, and not an elusive acyclic tertiary carbocation as the starting point of (poly)cyclization.



Scheme 12. Disposition of the *gem*-dimethyl group in the dicyclization of [D_3]farnesal ([D_3]-**25**) promoted by zeolite NaY.

Experimental Section

General: The reagents and solvents were purchased at the highest available commercial quality and used without purification. The reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates (60F-254) ith UV light as the visualizing method and an acidic mixture of phosphomolybdic acid/cerium(IV) sulfate accompanied by heating of the plate as a developing system. Flash column chromatography was carried out on SiO_2 (silica gel 60, particle size 0.040–0.063 mm) with the eluent specified below. NMR spectra were recorded on a Bruker DPX-300 instrument. Electrospray ionisation mass spectrometry (ES-MS) experiments were performed on a GC-MS QP 5050 Shimadzu single-quadrupole mass spectrometer. GC analyses and kinetics were performed using a Shimadzu GC-17A model equipped with a 60 m HP-5 capillary column.

(*E*)-6-(*tert*-Butyldiphenylsilyloxy)-4-methylhex-4-enoic acid (6): A solution of $NaClO_2$ (13.6 g, 150.3 mmol) and NaH_2PO_4 (17.9 g, 114.6 mmol) in water (90 mL) was added over 20 min to a stirred solution of **5**[24] (6.0 g, 16.4 mmol) and 2-methyl-2-butene (45 mL) in *tert*-butanol (240 mL). The mixture was stirred at ambient temperature for 12 h and then diluted with water (200 mL). The resulting solution was extracted with hexane (2×150 mL) and the organic layer was dried. The crude acid isolated after evaporation of the solvents was used in the next step without chromatographic purification (4.2 g, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.70 (d, J=7.0 Hz, 4H), 7.37–7.43 (m, 6H), 5.42 (br t, J=5.5 Hz, 1H), 4.23 (d, J=5.5 Hz, 2H), 2.44 (t, J=7.0 Hz, 2H), 2.30 (t, J=7.0 Hz, 2H), 1.45 (s, 3H), 1.05 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=179.1, 135.6, 134.8, 134.0, 129.6, 127.6, 124.9, 61.0, 33.9, 32.4, 26.8, 19.2, 16.3 ppm.

2,2-[D_2]-(*E*)-6-(*tert*-Butyldiphenylsilyloxy)-4-methylhex-4-en-1-ol (7): Acid **6** (4.3 g, 11.2 mmol) was added to a slurry of $LiAlD_4$ (0.57 g, 13.5 mmol) in dry ether (20 mL) at 0 °C under an inert atmosphere. After 6 h the reaction mixture was quenched by adding water (0.5 mL) and the resulting slurry was left for an additional 30 min until precipitation of the inorganic salts was complete. The supernatant solution was dried and the solvent was removed to afford the crude alcohol, which was purified by column chromatography (hexane/ethyl acetate 12:1) to produce **7** (3.04 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.70 (d, J=7.0 Hz, 4H), 7.38–7.42 (m, 6H), 5.41 (br t, J=6.0 Hz, 1H), 4.22 (d, J=6.0 Hz), 2.05 (t, J=7.0 Hz, 2H), 1.65 (t, J=7.0 Hz, 2H), 1.46 (s, 3H), 1.05 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=136.8, 135.6, 134.0, 129.5, 127.6, 124.4, 61.8 (quintet, J(C,D)=22.0 Hz), 61.0, 35.7, 30.3, 26.8, 19.2, 16.2 ppm.

1-[D]-(*E*)-6-(*tert*-Butyldiphenylsilyloxy)-4-methylhex-4-enal (8): The deuterated alcohol **7** (1.2 g, 3.18 mmol) was oxidized with PCC (0.8 g, 3.82 mmol) in dry dichloromethane (10 mL). The reaction was complete after 4 h (monitored by TLC). The solvent was concentrated under vacuum, and the residue was purified by column chromatography (hexane/ethyl acetate 20:1) to afford **8** (0.89 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.67 (d, J=6.5 Hz, 4H), 7.38–7.44 (m, 6H), 5.38 (t, J=6.5 Hz, 1H), 4.22 (d, J=6.5 Hz, 2H), 2.50 (t, J=7.0 Hz, 2H), 2.30 (t, J=7.0 Hz, 2H), 1.45 (s, 3H), 1.04 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=135.6, 134.9, 133.9, 129.5, 127.6, 125.0, 124.8, 61.0, 41.7, 31.5, 26.8, 19.2, 16.4 ppm.

6-[D]-(*E*)-*tert*-Butyl(3,7-dimethylocta-2,6-dienyloxy)diphenylsilane (9): *n*BuLi (1.6 M in hexane) was added to a slurry of the triphenylphosphonium salt of 2-iodopropane (1.5 g, 3.47 mmol) in dry THF (10 mL) at 0 °C under an inert atmosphere. After 40 min, aldehyde **8** (0.85 g, 2.3 mmol) was added and the reaction was complete after 10 min. The solvent was removed under vacuum and the resulting solids were washed with hexane (4×10 mL). The combined solvents were concentrated under vacuum and the residue was purified by column chromatography (hexane/ethyl acetate 80:1) to afford **9** (0.65 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.71 (d, J=7.0 Hz, 4H), 7.37–7.42 (m, 6H), 5.39 (br t, J=6.0 Hz, 1H), 5.24 (d, J=6.0 Hz, 2H), 2.07 (t, J=7.5 Hz, 2H), 1.99 (t, J=7.5 Hz, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 1.55 (s, 3H), 1.06 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=137.0, 135.7, 134.2, 131.3, 129.5, 127.6, 124.1, 61.2, 39.5, 26.9, 26.3, 25.7, 19.2, 17.7, 16.3 ppm.

6-[D]-Geraniol (10): A solution of TBAF (1 M in THF, 1.7 mL, 1.7 mmol) was added dropwise to a solution of **9** (0.62 g, 1.57 mmol) in dry THF (15 mL). After 3 h the solution was diluted with diethyl ether, washed with water, and the organic layer was dried. The residue was purified by column chromatography (hexane/ethyl acetate 4:1) to afford **10** (0.24 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.40 (t, J=6.5 Hz, 1H), 4.14 (d, J=7.0 Hz, 2H), 2.09 (t, J=7.0 Hz, 2H), 2.01 (t, J=7.0 Hz, 2H), 1.67 (s, 6H), 1.59 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=139.6, 131.6, 123.5 (t, J(C,D)=23.0 Hz), 123.3, 59.4, 39.5, 26.3, 25.6, 17.6, 16.2 ppm.

6-[D]-Geranyl acetate ([D]-1):K_2CO_3 (0.30 g, 2.22 mmol), acetic anhydride (0.21 mL, 2.22 mmol), and dimethylaminopyridine (0.02 g) were added to a solution of **10** (0.23 g, 1.48 mmol) in ethyl acetate (5 mL). After stirring at 25 °C for 1 h, the reaction mixture was filtered and the filtrate was diluted with diethyl ether. The organic layer was washed with

a saturated aqueous solution of $NaHCO_3$ and dried over $MgSO_4$. Removal of the solvent afforded [D]-**1** (275 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.34$ (t, $J = 7.0$ Hz, 1H), 4.58 (d, $J = 7.0$ Hz, 2H), 2.08 (m, 4H), 2.04 (s, 3H), 1.70 (s, 3H), 1.67 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.1$, 142.3, 131.8, 123.7 (t, J(C,D) = 23.0 Hz), 118.2, 61.4, 39.5, 26.3, 21.1, 17.6, 16.5; MS (EI): m/z (%): 155 $[M-AcOH]^+$ (2), 137 (11), 122 (12), 108 (7), 70 (100).

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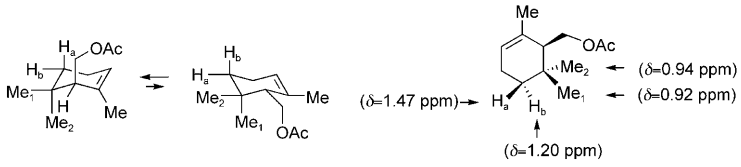

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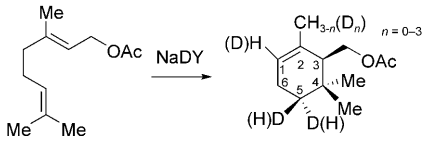
[29] To test whether Brønsted acidity is responsible for the catalytic activity of NaY in terpene cyclization, the zeolite (1 g) was treated for 30 min with D_2O (2×5 mL). Then it was filtered and dried at 120°C under vacuum, in the usual way zeolite NaY is dried/activated to perform cyclization experiments. This isotopically modified zeolite,[30] which we refer to as "NaDY", catalyzed the cyclization of geranyl acetate (**1**) to form after 2 h at 70°C a mixture of α- and γ-cyclogeranyl acetate in a ratio ≈15:1. The loading level of **1**@NaDY was kept low ($n \approx 0.1$–0.2). Examination of the products by ^{1}H NMR spectroscopy revealed an approximately 30–35% incorporation of deuterium atom on the C-5 of the α-cyclogeranyl framework next to the *gem*-dimethyl group. Furthermore, a partial exchange of the hydrogen atoms from the allylic methyl group and the vinylic hydrogen atom on C-3 was obvious. Thus, in addition to the non-deuterium-exchanged vinylic methyl group (CH_3) absorptions due to (CH_2D) and (CHD_2) were seen, and most likely a completely exchanged (CD_3) might be formed to a minor extent. The partial deuterium incorporation on the C-5 of the α-cyclogeranyl carbon skeleton ring is reasonable because during the cyclization, protons are gradually eliminated from the deprotonation of the intermediate cyclogeranyl carbocation, which essentially compete with the intrazeolite D^+ for substrate protonation (versus deuteration). These results indicate that Brønsted acidity (bridging hydroxyl groups, Al-OH-Si), plays a dominant role in the NaY-promoted cyclization of terpenes. In addition, from the ^{1}H NMR spectrum of the cyclized product (see the Supporting Information) it is obvious that D is selectively incorporated *cis* to the CH_2OAc functionality, in agreement to the stereochemistry of the cyclization of [D]-**1** shown in Scheme 5. However, the exact diastereomeric ratio could not be accurately measured due to the overlapping absorptions of the non-deuterium incorporation on C-5 α-cyclogeranyl acetate.



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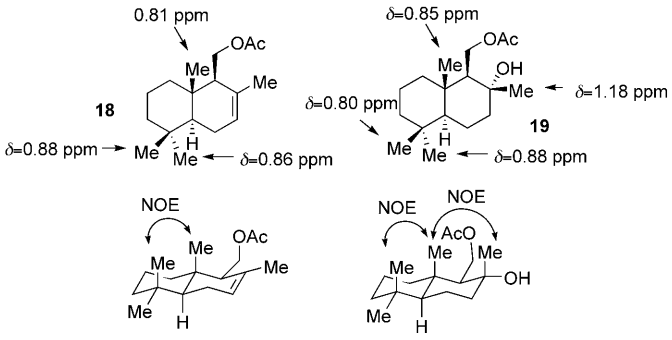
[36] Combined NOE experiments on bicyclic products **18** and **19**, established the following ^{1}H NMR assignments (see the Supporting Information):



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