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Zeolite NaY-Promoted Monocyclization of Epoxy Polyene Terpenes: A Unique Route for the Direct Synthesis of Incompletely Cyclized Naturally Occurring Terpenols

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Abstract: A variety of epoxy polyene terpenes cyclize readily by confinement within zeolite NaY to form primarily products of monocyclization. The monocyclization pathway is highly predominant, irrespectively of the side chain of the epoxy terpene, while the monocyclic products possess regioselectively an exomethylenic double bond. The selective monocyclization in the case of epoxyfarnesyl acetate, epoxyfarnesylacetone or 2,3-epoxysqualene, provides a direct route to the synthesis of a variety of natural products, such as elengasidiol, farnesiferols B–D, achilleol A, camelliol C and to four farnesylacetone-derived metabolites isolated from the brown algae *Cystophora monoliformis*. The optical rotation of achilleol A derived from the cyclization of (*S*)-2,3-epoxysqualene matches with that of the natural product, thus the absolute configuration of achilleol A was established as 1*S*,3*R*. From the mechanistic point of view, the NaY-promoted cyclization of 9,10-epoxygeranylacetone, selectively deuterium labelled at the C-10 methyl group, is >97% stereoselective with respect to the topicity of the *gem*-dimethyl group. This result is in agreement with a concerted mechanism. Finally, we have proved through labelling experiments, for the first time, that the biomimetic transformation of epoxy polyene terpenes to 2,3,4-trimethylcyclohexanones upon acid catalysis is a highly stereoselective process. Thus, the less hindered *gem*-methyl group on the epoxide functionality becomes α- to the carbonyl in the final isomerized product.

Keywords: green chemistry; heterogeneous catalysis; natural products; reaction mechanisms; terpenoids; zeolites

Introduction

The acid-catalyzed cyclization of epoxy polyenes has attracted the interest of the organic chemists for the past 50 years,[1] especially due to the early discovery that this reaction is involved in the biosynthesis of a vast number of terpenols. The most known among them is the oxidosqualene cyclase-catalyzed cyclization of 2,3-epoxysqualene to lanosterol, the biogenetic precursor of cholesterol and other triterpenoids.[2] The cyclase cavity provides an ideal compartment, for the acyclic epoxy polyene to adopt a suitable conformation, so that upon protonation of the epoxide functionality by an aspartic acid residue,[3] iterative intermolecular nucleophilic attacks of the proximal double bonds to the protonated epoxide or to the intermediate carbocations, provide fused polycyclic products in a highly stereoselective manner. On many occasions organic chemists have attempted to reproduce this fascinating enzymatic reaction using acids as catalysts with varying degrees of success. Brønsted acids have very rarely been used as promoters,[4] while super acids (such as FSO_3H)[5] which are superior catalysts in terpene cyclization fail to provide cyclization of epoxy terpenes, leading to solvolysis products of the epoxide, instead. On the other hand, Lewis acids such as BF_3,[6] $SnCl_4$,[6] $ZrCl_4$,[7] $FeCl_3$,[8] $Sc(OTf)_3$,[9] $Bi(OTf)_3$,[10] $InBr_3$,[11] and, especially, $MeAlCl_2$[12] have been widely used, often providing efficient polycyclization with good diastereoselectivity. In addition to the cationic cyclization provided by acidic catalysts, a Ti(III)-promoted free-radical methodology has been developed[13] for the cascade polycyclization of epoxy

terpenes, and found significant applications in the synthesis of natural products.[14]

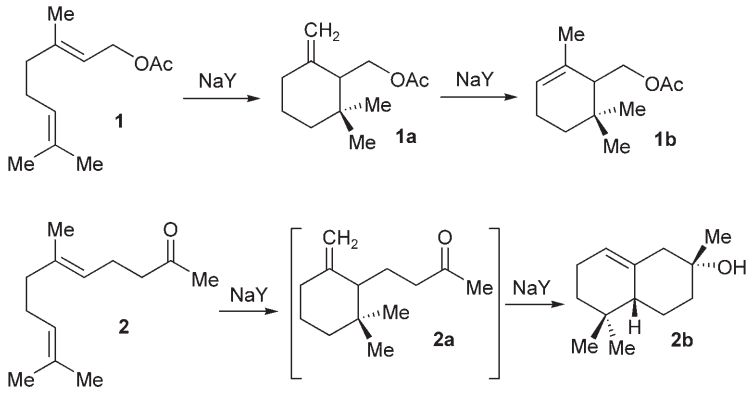
Recently, we examined the efficiency of acidic porous materials such as zeolites, as hosts and catalysts as well, for the cyclization of polyene terpenoids. Our concept was that the zeolite cavity would provide the necessary acidic sites for initiating the cationic cyclization, whereas substrate confinement in a restricted space[15] would decrease its conformational mobility and thus provide product(s) stereocontrol. The remarkable stereocontrol in the enzyme-catalyzed cyclization of terpenes is primarily attributed to the suitable substrate conformation by confinement within the restricted environment of the enzyme cavity. Zeolites are mixed aluminosilicates that catalyze reactions[16] by confining the substrates within "active site" cavities, and have found significant applications in heterogeneous photocatalysis.[17] We have chosen faujasites (zeolites MY, M = cation) as catalysts. They possess a 3D framework which consists of supercages, whose interior diameter is approximately 13 Å. The supercages are interconnected by four "windows" which are tetrahedrally distributed around each cage and have a pore entrance diameter of around 7.5 Å. Such cage dimensions are ideal to host relatively large organic molecules, such as higher terpenes. Zeolite NaY was our first choice, as it is a very mild acidic catalyst due to a limited amount of intrazeolite Brønsted sites.[18] We were pleased to find[19] that small acyclic terpenes undergo a clean cyclization reaction under essentially extremely mild conditions. For example, geranyl acetate (**1**) forms at the initial reaction stages primarily γ-cyclogeranyl acetate (**1a**) which on prolonged reaction time isomerizes to α-cyclogeranyl acetate (**1b**, Scheme 1). The most remarkable finding of those initial studies was that geranylacetone (**2**) and its geometrical isomer (nerylacetone) provide a direct one-pot highly diastereoselective cascade to α-ambrinol (**2c**), a valuable compound in the fragrance industry, through the intermediate formation, but not isolable, γ-cyclogeranylacetone (**2a**).

Results and Discussion

Cyclization of Small Epoxy Terpenoids

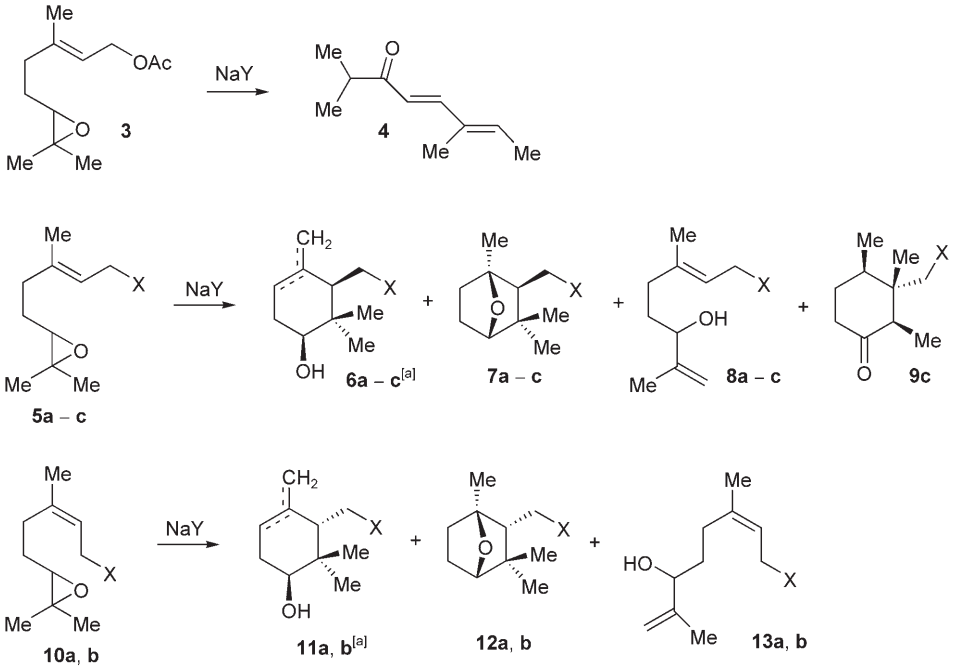
As a continuation of our studies, we explored the efficiency of NaY as a catalyst for the cyclization of epoxy polyene terpenes. The use of acidic zeolites or other porous materials for the cyclization of epoxy terpenoids is very limited in the literature. Sen and co-workers[20] have used the H-form of the small-pore zeolites A and ZSM-5 for the cyclization of suitable silyl-substituted epoxy polyenes. A moderate to good product selectivity was achieved. It was postulated that cyclization initiates at the opening of the zeolite pores, as the size of the substrates does not allow them to diffuse into the interior of the cages. By contrast to the small pore zeolites A and ZSM-5, we anticipated complete adsorption (confinement) of epoxy polyene terpenes possessing up to 30 carbon atoms (triterpenes) within NaY supercages, as it well known that the faujasite cavities can host even steroids.[21] Initially, the cyclization of the small acyclic terpenoids **3**, **5a–d** and **10a**, **b** shown in Table 1 was examined.[22] The reactions were carried out by adding a hexane solution containing a suitable amount of the epoxy terpenoid (see discussion below) to the dry NaY, and the resulting slurry was left reacting for a certain period of time (Table 1).

Hexane was the proper reaction solvent as due to its non-polar nature it allows the facile diffusion of the epoxides into the polar zeolite cages. That was clearly evident by GC examination of the supernatant hexane which revealed the absence of any reacting epoxide or product(s) during the course of the reaction or at the end. This implies a complete substrate confinement within the zeolite pores, under the low substrate loading levels used in our experiments. Subsequently, the zeolite was filtered and treated with methanol to extract the adsorbed products (see Experimental Section).



Scheme 1. Zeolite NaY-promoted cyclization of small terpenoids.

Table 1. Cyclization of small acyclic epoxy terpenoids promoted by zeolite NaY.

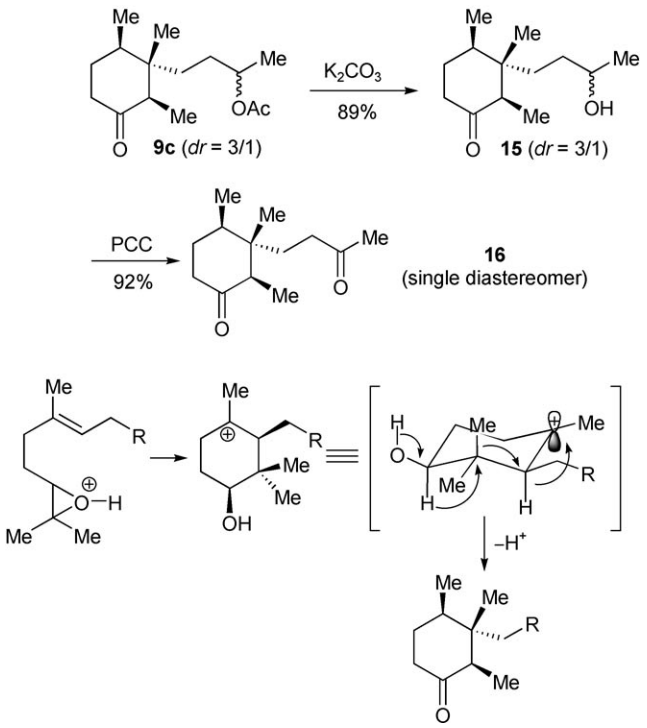


Substrate	X	Reaction time [min]	Yield	Products (relative ratio)	*exo/endo*[a]
3		10	78%	**4**	-
5a	OH	10	76%	**6a/7a/8a** = 70/20/10	8/1
5b	CH_2COMe	10	92%	**6b/7b/8b** = 70/25/5	12/1
5c	$CH_2CH(OAc)Me$[b]	15	83%	**6c**[b]/**7c**[b]/**8c**[b]/**9c**[c] = 55/22/8/15	4/1
10a	OAc	35	78%	**11a/12a/13a/4** = 40/20/10/30	8/1
10b	CH_2COMe	45	85%	**11b/12b/7b/13b** = 70/6/2/22	9/1

[a] We define as *exo* the regioisomer for which the double bond is exocyclic (disubstituted), and *endo* that in which the double bond is endocyclic (trisubstituted).
[b] Mixture of two diastereomers in ratio 1/1.
[c] Mixture of two diastereomers in a ratio ~3/1.

We were gratified to find that, with the exception of 6,7-epoxygeranyl acetate (**3**), NaY promotes the fast cyclization of the epoxy terpenoids to form stereoselectively and regioselectively mainly the exomethylenic cyclohexanols **6a–c** or **11a**, **b** (Scheme 2). The stereochemistry of the products depends on the configuration of the adjacent nucleophilic double bond. Thus, alkenes with the (*E*)-configuration afford *cis* cyclization products (**6**), while those with (*Z*), afford *trans* (**11**). The bicyclic ethers (**7** or **12**) and the allylic alcohols (**8** or **13**) are formed as side-products. The stereochemistry of these products depends again on the configuration of the nucleophilic double bond. To ensure complete reactant adsorption within the zeolite cavities, low loading levels (~0.1 mmol of substrate per 1 g of dry NaY) were used. While the geranyl derivatives (**3**, **5a–c**) react smoothly at ambient temperature, going to completion within 10–15 min, the neryl derivatives (**10a**, **b**) require up to 45 min reaction time. At higher loading levels (1 mmol of the geranyl-derivatives **5a**, **b** per 1 g of dry NaY), the reactions went to completion on heating at 70 °C for 1 hour. The combined product yields vary from 76–92%. The isomerization of the predominantly formed, in the cases of regioisomeric products **6** or **11**, *exo*- to the *endo*-double bond occurs slowly under the reaction conditions. Thus, prolonged intrazeolite treatment of the epoxides (1–2 h) results in a drop of the ratio *exo*/*endo* double bond isomers from a typical 8–12/1 value to approximately 3–6/1.

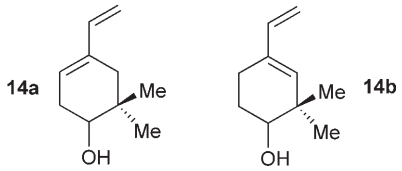
From the practical point of view, the cyclization procedure describe herein is extremely simple, absolutely mild, and environmentally friendly, as toxic and difficult to handle Lewis acids are avoided, no aqueous work-up is necessary, while the yields are quite acceptable. Furthermore, this methodology provides a powerful and direct route to a series of synthetically useful exomethylenic cyclohexanols and bicyclic ethers. For instance, cyclized products **6a**,[23] **7a**,[23] and **6b**[13] have been used as valuable blocks in terpenoid



Scheme 2. Structural characterization of by-product **9c**, and a plausible mechanism for its formation.

synthesis. It is important to note that the regioselective formation of exomethylenic cyclized products, such as **6a–c** or **11a**, **b**, under acidic conditions, can be achieved only by using silicon as a controlling element, in the cyclization of terpenes bearing a trialkylsilyl group on the allylic methyl group where termination of the cyclization is pursued.[24] This methodology, however, requires additional synthetic steps for the introduction of the trialkylsilyl group on the terpene backbone.

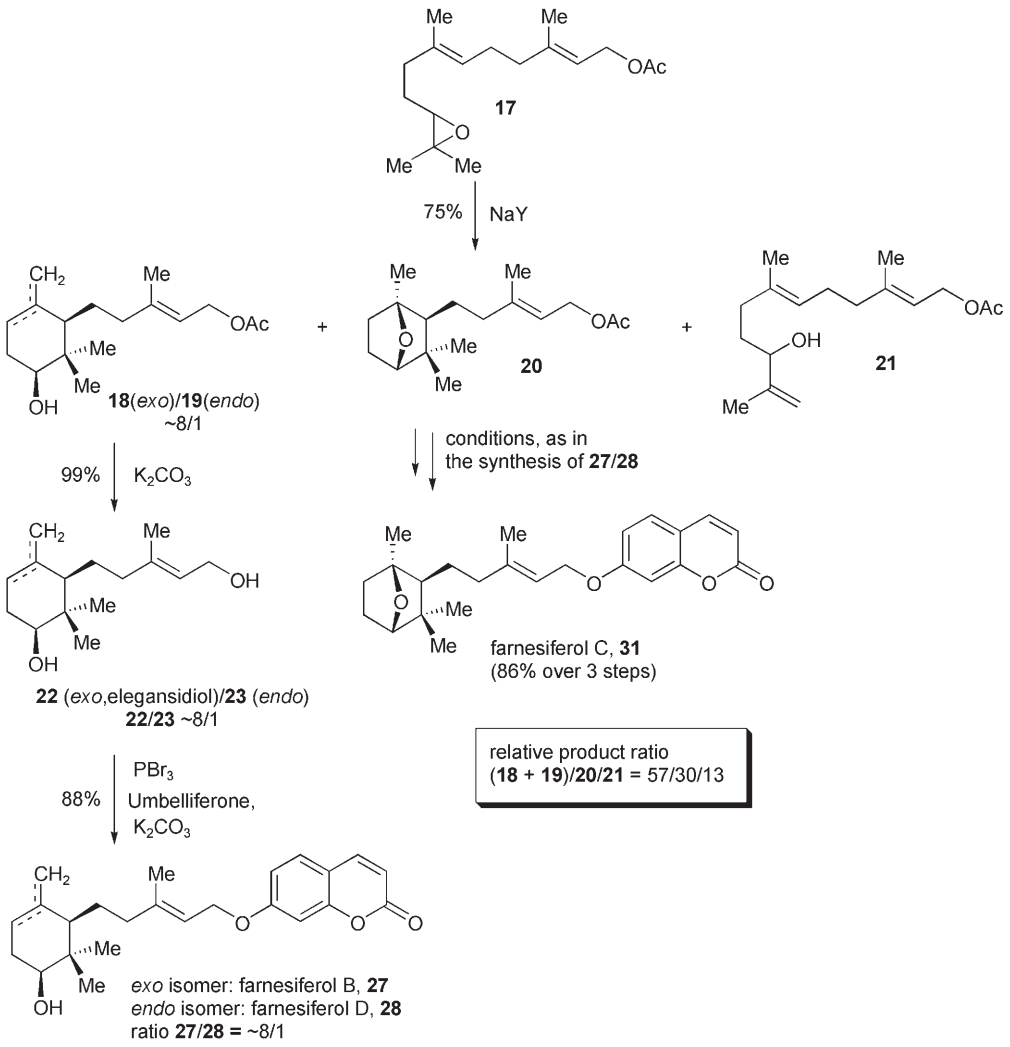
It was somewhat surprising that while 6,7-epoxygeraniol (**5a**) cyclizes to form mainly **6a**, the corresponding acetate **3** does not afford any cyclization products. Instead, (4*E*,6*E*)-2,6-dimethylocta-4,6-dien-3-one (**4**) was produced in 78% isolated yield. Dienone **4** along with its (4*E*,6*Z*)-geometrical isomer are known[25] to arise upon treatment of linalool oxide with 25% H_2SO_4, or through the acid-catalyzed isomerization of 6,7-epoxy myrcene (**14**). In our case, formation of **4** from **3** can be envisioned to have occurred through an epoxide to ketone isomerization in combination with an elimination of the acetate functionality and subsequent diene isomerization. At this stage, however, we do not want to speculate as to why we see this switch in mode of reaction upon going from **5a** to its acetoxy analogue **3**, especially in the light of our observation that **14** does not form any **2** upon NaY treatment, but primarily the isomeric cyclization products **14a** and **14b**[26] in a ~3/1 relative ratio, and in 46% isolated yield after column chromatography.



Another interesting feature of the results presented in Table 1, is the formation of the 2,3,4-trimethylcyclohexanone derivative **9c** in 15% relative yield, observed only in the specific case of epoxide **5c**. Compound **9c** appears as a mixture of 2 diastereomers in a relative ratio ~3/1, and was characterized by transforming it to the known diketone **16**,[27] through PCC oxidation of its hydrolysis product, alcohol **15** (Scheme 2). The relative stereochemistry on the stereogenic center of the side chain for the diastereomers **9c** could not be assigned. Compounds possessing the 2,3,4-trimethylcyclohexanone moiety are well known to arise as by-products in the Lewis acid-catalyzed cyclization of epoxy polyene terpenes,[28] through the widely postulated mechanism shown in Scheme 2. It is also notable that several natural products such as cordiaquinone B,[29] striatenone,[30] and ascochlorin[31] bear the characteristic 2,3,4-trimethylcyclohexanone moiety, indicative that their biosynthesis occurs through such a delicate pathway (1,2-succesive shifts of two hydrides and one methyl group).

Cyclization of Higher Epoxy Polyene Terpenes

In order to prove the worth of our new cyclization protocol in organic synthesis, we extended our studies[22] to the examination of the cyclization of higher epoxy polyene terpenes, with 10,11-epoxyfarnesyl acetate (**17**) being the first target. The intrazeolite reaction of **17** went to completion after 15 min to afford selectively the monocyclization products **18** and **19**, the bicyclic ether **20**, and the allylic alcohol **21** (analogous to the by-products **8** or **13** of Table 1), in a relative ratio **18**/**19**/**20**/**21** = 51/6/30/13, and in 75% combined isolated yield (Scheme 3). The very important result of this reaction was that only monocyclized products were formed, despite the presence of additional double bond that could provide access to products of dicyclization, as occurs upon treatment of **17** with Lewis acids.[32] The non-separable mixture of the regioisomeric alcohols **18** and **19** was easily isolated from the crude reaction mixture by column chromatography, and hydrolyzed almost quantitatively, using K_2CO_3 in methanol, to afford the racemic sesquiterpenol elegansidiol (**22**),[33] along with its minor endocyclic isomer **23** (ratio **22**/**23** ~ 8/1). There are three known syntheses of elegansidiol so far,[34] however, applying multiple steps compared to our approach and by using less or non-bioinspired approaches. Ele-

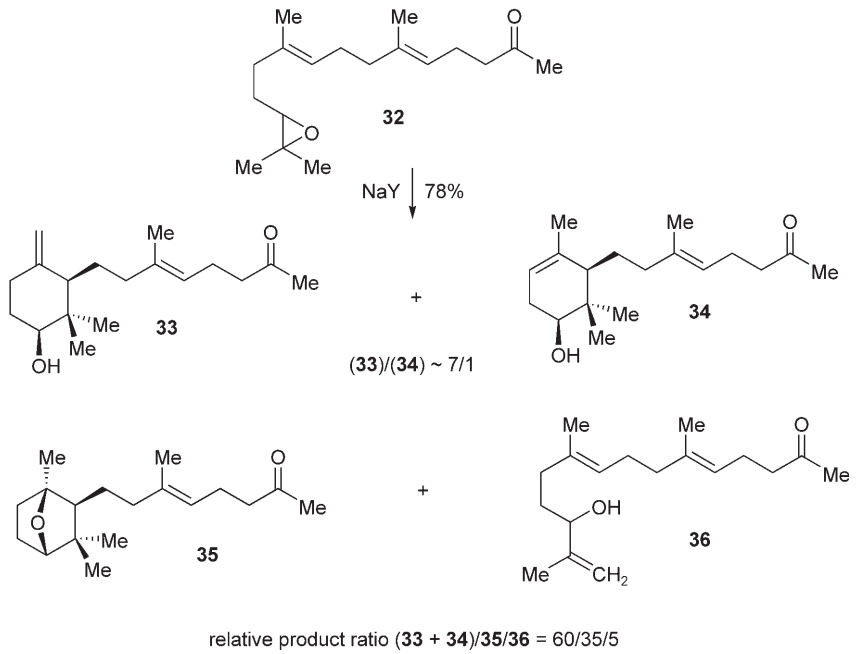


Scheme 3. Monocyclization of 10,11-epoxyfarnesyl acetate (**17**) promoted by NaY: synthesis of elegansidiol and farnesiferols B–D.

gansidiol might be directly expected from the cyclization of 10,11-epoxyfarnesol (**24**). Epoxide **24** (prepared by hydrolysis of **17**) was treated with NaY under identical conditions to **17**. Due to the relative lability of the allylic alcohol under the acidic zeolite conditions, substantial dehydration occurred either on the reacting epoxy alcohol or on the products. The dehydration products rather undergo several skeletal rearrangements/isomerizations, thus generating a complex reaction mixture. Nevertheless, an approximately 15–20% of elegansidiol was seen in the crude reaction mixture after 10 min reaction time (**22**/**23** ~7/1), thus, this direct approach to elegansidiol suffers from poor yield.

The closely related structure of the products **18** and **19** with farnesiferols B–D[27,35] prompted us to achieve their synthesis (Scheme 3). Thus, reaction of the regioisomeric mixture **22** and **23** with PBr_3 (1.1 equiv.) afforded selectively the corresponding allylic bromides **25** and **26**. Finally, alkylation of the potassium salt of 7-hydroxycoumarin (umbelliferone) with the allylic bromides **25** and **26** yielded an inseparable mixture of farnesiferol B (**27**) and farnesiferol D (**28**) in a relative ratio of ~8/1, and in 87% isolated yield from **18/19** (over 3 steps). In addition, the analogous 3-step transformation to the minor bicyclic ether **20** furnished farnesiferol C (**31**) in 86% overall yield.

The clean and primary formation of monocyclized products in the case epoxy farnesyl acetate was encouraging, since a variety of naturally occurring, incompletely cyclized terpenols, among them nassauvirevolutin A,[36] achilleol A,[37] or its double bond isomer camelliol C,[38] could derive from the incomplete cyclization of suitable epoxy polyene precursors under NaY treatment conditions. Thus, for a further exploration, we turned our attention to a mixture of farnesylacetone-derived metabolites co-isolated[39] from the brown algae *Cystophora monoliformis*, as

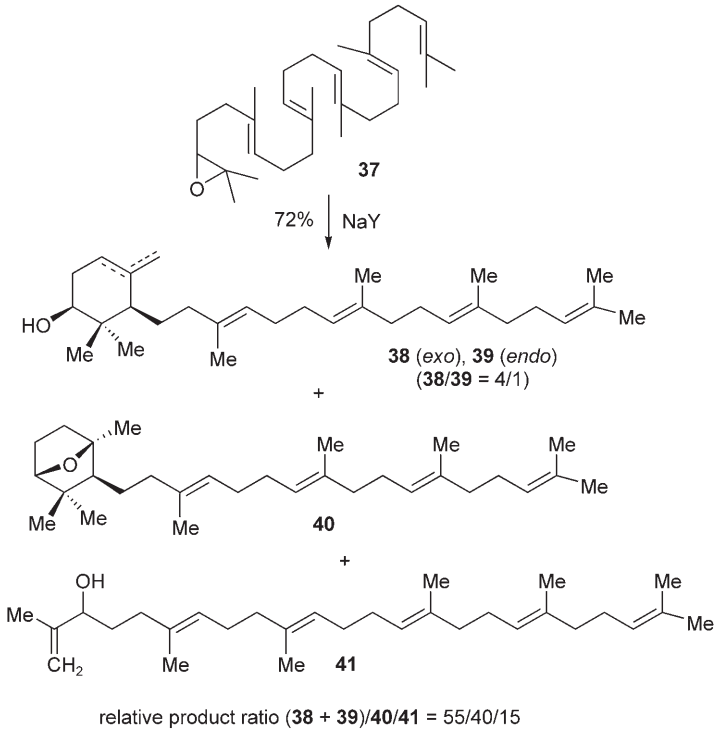


Scheme 4. NaY-promoted cyclization of epoxy *trans*,*trans*-farnesylacetone (**32**).

they could readily derive from the intrazeolite cyclization of 13,14-epoxy-*trans*,*trans*-farnesylacetone (**32**).[40] Treatment of **32** with NaY, afforded a mixture of **33**, **34**, **35** and **36** in 78% isolated yield, and in a relative ratio of 53/7/35/5, respectively (Scheme 4). We were pleased to realize that all intrazeolite products **33**–**36**, along with *trans*,*trans*-farnesylacetone and epoxide **32**, belong to the family of those metabolites. The major **33** and **34** species (γ- and α-cystophorol, respectively)[41] were co-isolated after column chromatography as an inseparable mixture, while the minor **35** and **36** species were also isolated, and their NMR spectroscopic data matched with those of the natural products. This result provides another example for the unique ability of NaY as a powerful and highly selective cyclization catalyst towards the synthesis of naturally occurring compounds, employing a simple and biomimetic strategy.

Finally, we extended the scope and limitation of the zeolite-promoted cyclization, by studying the reaction of the triterpene 2,3-epoxysqualene (**37**). Reaction of **37** (0.1 mmol) with 1 g activated NaY yielded after 10 min a mixture of achilleol A/camelliol C (**38** and **39**, respectively), the bicyclic ether **40**[42] and the naturally occurring allylic alcohol **41**.[43] The relative ratio (**38**+**39**)/**40**/**41** was 55/40/15 and the combined isolated yield 72% (Scheme 5). Achilleol A[37] and camelliol C[38] arose as an inseparable mixture in a relative ratio of ~4/1. They were easily separated from the rest of the crude reaction mixture by flash chromatography. Prolonged treatment of 2,3-epoxysqualene within NaY (1 hour, 20 °C) result to the decrease of the overall yield to 58%, and to the additional formation of new unidentified triterpene alcohols (most probably dicyclization or polycyclization products) in ~10–15% relative yield, with accompanying decrease of the relative yield of the achilleol A/camelliol C fraction. Under those conditions, the relative yield of achilleol A/camelliol C was *ca.* 30%, while their ratio **38**/**39** became almost 1/1. Recently, Matsuda and co-workers reported[44] that 2,3-epoxysqualene affords very slowly products of cyclization on treatment with the slightly acidic silica gel (0.02% of 2,3-epoxysqualene undergoes cyclization during column chromatography purification). This SiO_2-derived product mixture consists primarily of polycyclized structures, with achilleol A and camelliol C, not detected among them. In our opinion, the change in product selectivity for the cyclization of 2,3-epoxysqualene reflects the different environment where cyclization takes place (within cavities for NaY, and on the surface for SiO_2).

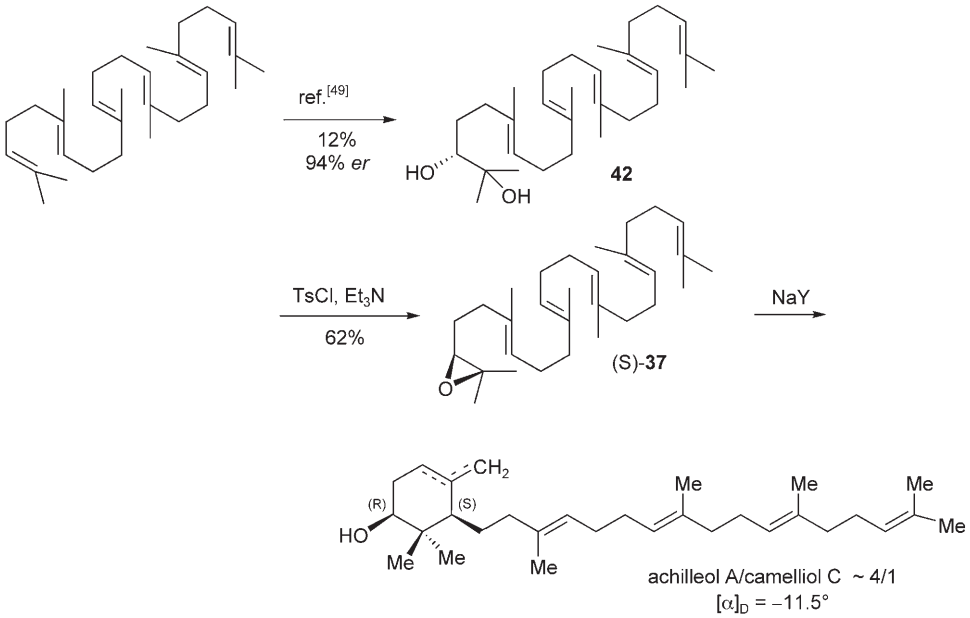
The methodology presented herein is a fast route to the synthesis of achilleol A and camelliol C, essentially within a two-step process from squalene. These triterpene alcohols (as a mixture) have been prepared by Barrero and co-workers[45] applying a multi-step sequence using geranylacetone as the starting material. On treatment of 2,3-epoxysqualene with Lewis acids mainly tricyclic products are formed,[46] as well as, in the presence of Ti(III) species[13a] (radical-initiated cyclization). Additionally, by means of biochemical engineering, through specific mutation of the amino acid sequence of the cyclases, it was possible to alter the typical 2,3-oxidosqualene to lanosterol route with formation of partially cyclized terpenes such as achilleol A and camelliol C.[47] The current results in-



Scheme 5. Cyclization of 2,3-epoxysqualene (**37**) promoted by NaY.

dicate that NaY may be applied as a general monocyclization catalyst for epoxy polyene terpenoids regardless of if the side chain is tethered to the epoxy geranyl moiety. To the best of our knowledge, *zeolite NaY is the only acidic catalyst that provides selectively products of monocyclization with epoxy polyene terpenes,* as any Lewis acid gives rise to products of polycyclization.

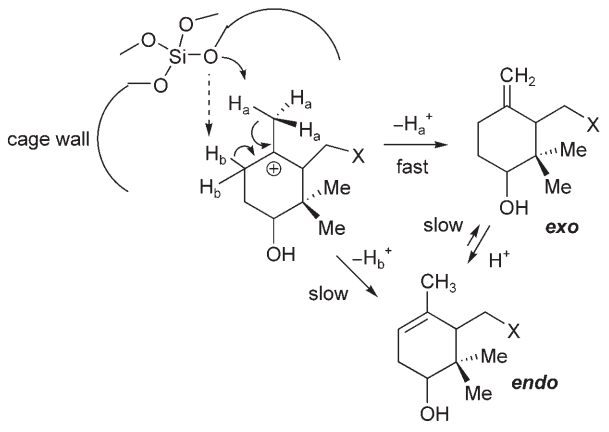
To establish the unknown absolute configurations of achilleol A and camelliol C, we prepared the optically active (*S*)-2,3-oxidosqualene (*S*-**37**)[48] in 94% *er*, by asymmetric dihydroxylation of squalene,[49] to form the (*R*)-2,3-diol **42** in 12% isolated yield, followed by treatment of the diol with tosyl chloride under basic conditions (Scheme 6). The NaY-promoted cyclization of (*S*)-**37** afforded the expected reaction products



Scheme 6. Absolute configurations of (−)-achilleol A and (−)-camelliol C.

shown in Scheme 5. The achilleol A/camelliol C fraction was isolated (ratio achilleol A/camelliol C = 4/1), and showed a specific rotation of $[\alpha]_D$: −11.5° (*c* 0.4 in $CHCl_3$). This establishes the absolute configuration of the natural products as (1*S*,3*R*) for achilleol A[50] and (1*S*,5*R*) for camelliol C. The specific rotation of the naturally occurring achilleol A is $[\alpha]_D$: −10.9° (*c* 0.9 $CHCl_3$),[37] while for camelliol C, $[\alpha]_D$: −12.9° (*c* 0.2 in $CHCl_3$).[38a] The similarity in the absolute configuration of the naturally occurring achilleol A and camelliol C with that on the A ring of lanosterol, clearly indicates that both are incompletely cyclization products of (*S*)-2,3-epoxysqualene, the biogenetic precursor of lanosterol and related polycyclized triterpene alcohols.

The selective formation of monocyclized exomethylenic regioisomers in all epoxy terpenoids studied throughout this manuscript could be envisioned to occur through a kinetically-driven deprotonation of the monocyclized carbocation (Scheme 7), by the oxygen atom of the Si–O–Si or Si–O–Al moieties in the interior walls of the zeolite cages. The hydrogen atoms on the methyl group (H_a) are more accessible for abstraction by the "zeolite wall' relative to the H_b hydrogen atoms on the cyclohexyl ring, primarily due to steric reasons. Thus, the zeolite cavity can be considered as a *bi-functional catalyst* (acidic initiation and basic deprotonation). The isomerization of the *exo* to the *endo* regio-isomer is a slow process within the timescale of our experiments (*ca.* 10 min), and becomes significant only on prolonged reaction time (more than an hour). Finally, we point out that, the fast deprotonation of the monocyclized carbocation prevents further nucleophilic attack by any adjacent double bonds to form product(s) of polycyclization.



Scheme 7. Mechanistic arguments on the selective and regioselective monocyclization of epoxy polyene terpenoids promoted by NaY.

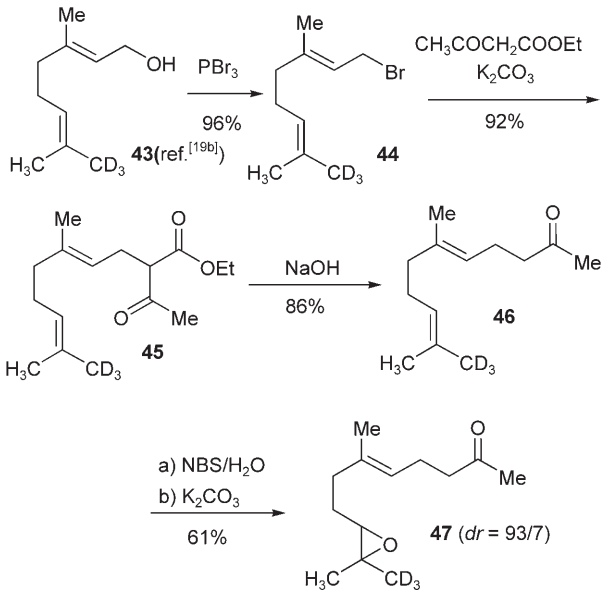
Mechanistic Studies

a) *gem*-Dimethyl Group Topicity during the Cyclization

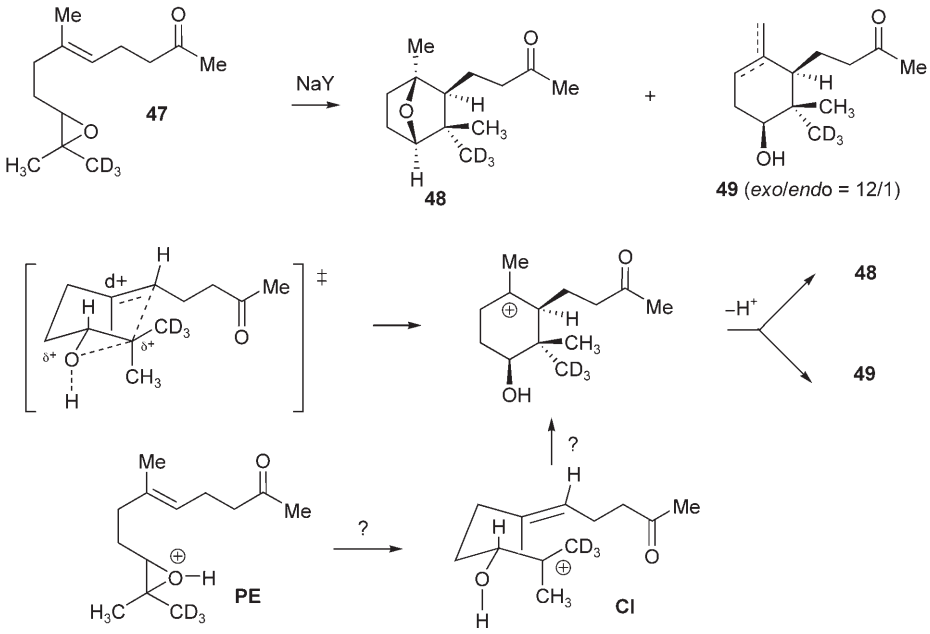
The enzyme-catalyzed cyclization of epoxy polyene terpenes is widely accepted to occur through a concerted mechanism. For example, Hoshino and coworkers[51] studied the squalene-hopene cyclase-catalyzed cyclization of a specifically deuterium-labelled 2,3-epoxysqualene, and found >97% topicity in terms of the *gem*-methyl group on the product, 3β-hydroxyhopene. This stereochemical outcome provides strong evidence for a concerted reaction. Regarding the reaction under Lewis acid conditions, van Tamelen[52] came to similar conclusions, by studying the cyclization of a specifically deuterium-labelled epoxy farnesyl acetate. Finally, Corey and Staas[53] proposed a concerted mechanism on the basis of kinetic data, using a protic acid (dichloroacetic acid) as a catalyst, to mimic the Brønsted nature of the acidic initiator in cyclases (aspartic acid).

To shed light on the intrazeolite reaction mechanism we prepared the deuterium labelled epoxy geranylacetone **47** in 93% diastereomeric purity. The synthesis was accomplished in four trivial steps as shown in Scheme 8, from geraniol-8,8,8-d_3 (**43**) that was readily available from our previous studies.[19b] Thus, **43** was transformed to the labelled bromide **44**, which alkylated ethyl acetoacetate, and the produced **45** was saponified/decarboxylated to form the geranylacetone-d_3 (**46**).

Treatment of **47** with NaY gave the expected cyclized products **48** and **49** (Scheme 9) in a relative

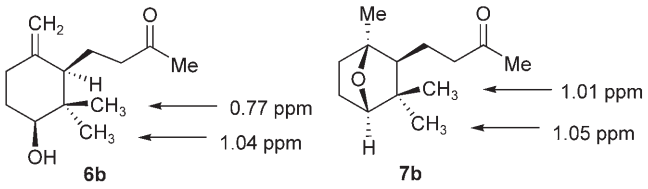


Scheme 8. Synthesis of the deuterium-labelled epoxy geranylacetone **47**.



Scheme 9. Stereochemistry for the cyclization of **47**@NaY, and the proposed mechanism.

ratio of ~1/3, for which the presence of one diastereomer was clearly evident by ^{1}H NMR in terms of the *gem*-dimethyl group topicity. More specifically, for both **48** and **49**, it was established through nOe experiments (see below the resonances of the *gem*-methyls for the perprotio **6b** and **7b**) that the CD_3 group is *cis*-arranged to the tertiary hydrogen atom on the stereogenic center bearing the side chain ($-CH_2CH_2COCH_3$).

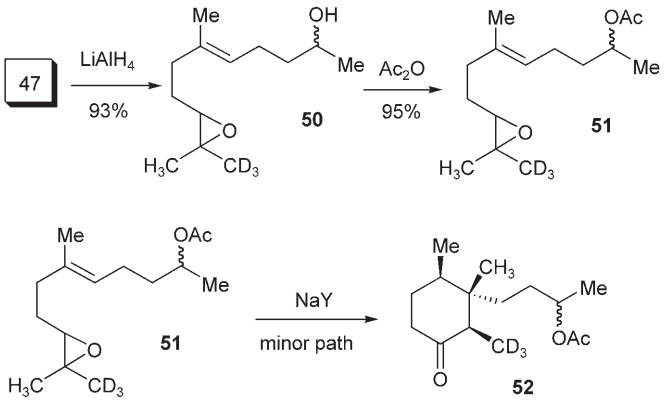


This stereochemical outcome is more likely in agreement with a concerted cyclization mechanism through the transition state shown in Scheme 9. The possibility that the open carbocation **CI** (Scheme 9) is formed upon protonation of the epoxide (**PE**, Scheme 9), which cyclizes in an accompanying step, cannot be excluded. Yet, it requires that the activation energy of the second cyclization step, be at least 3 kcal mol^{-1} lower compared to the barrier to rotation around the C(OH)–$C_{carbocation}$ bond.

b) Stereochemistry in the Transformation of Epoxy Polyene Trpenes to 2,3,4-Timethylcyclohexanones

Having in our hands the deuterium-labeled epoxide **47**, we undertook an examination of the stereochemistry regarding the formation of the 2,3,4-trimethylcyclohexanone derivative **9c** (minor pathway) upon treatment of the epoxide **5c** with NaY (Scheme 2). Thus, **47** was reduced to the alcohol **50** as an equimolar mixture of two diastereomers (with respect to the epoxide and hydroxy functionalities). Subsequently, **50** was acetylated to form **51**. The epoxy acetate **51** was isolated as a mixture of two equimolar diastereomers with respect to the epoxide and hydroxy functionalities, and had 93% stereochemical purity in terms of the *gem*-dimethyl moiety. Upon zeolite treatment, we isolated the minor trimethylcyclohexanone derivative **52** shown in Scheme 10.

From the ^{1}H NMR it was obvious that the α-methyl group with respect to the carbonyl functionality was the deuterated one, while the methyl group on the tertiary carbon atom was the protonated one (see Supporting Information). This result clearly establishes the so far proposed,[27,28,54,55] *but never proven*, stereochemical rearrangements during the isomerization of an epoxide to 2,3,4-trimethylcyclohexanone under acid catalysis. Among the two stereoselectively disposed *gem*-methyl groups of the intermediate cyclized carbocation (see also Scheme 9), the protonated methyl group which is axially oriented in a pseudo-chair conformation shifts, giving rise to the stereoselective formation of **52** (Scheme 11). Similar stereochemical results (selective shift of the CH_3 group relative to the CD_3) were obtained upon Lewis



Scheme 10. Synthesis of the labeled epoxide **51**, and the stereochemistry of the by-product **52** isolated after treatment with NaY.

acid treatment of **51** ($SnCl_4$, CH_2Cl_2, 0 °C), with formation of **52** in *ca.* 10% relative yield (*dr* ~ 3/1). This result indicates an identical mechanism for the formation of trimethylcyclohexanones either under homogeneous or heterogeneous conditions (zeolite confinement).

Conclusions

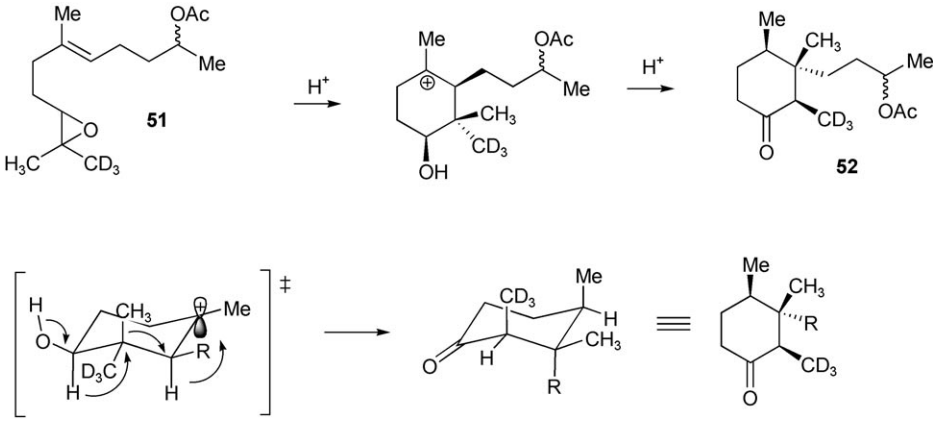
In conclusion, we presented herein a novel methodology for the direct synthesis of incompletely cyclized terpenols upon treatment of epoxy polyene terpenoids with the slightly acidic zeolite NaY. All epoxides studied yielded primarily monocyclic products possessing selectively an exomethylenic double bond. This methodology is unique, as Lewis acids provide products of polycyclization, and allows the fast and efficient synthesis of the naturally occurring elegansidiol, farnesiferols B–D, γ-cystophorol, achilleol A and camelliol C. Additionally, the absolute configuration of (−)-achilleol A was established. The methodology presented herein is extremely mild, environmentally friendly, does not require an extractive aqueous work-up, and gives yields that are quite acceptable. Finally, through deuterium-labelling experiments we propose a concerted mechanism for the zeolite-promoted cyclization reaction, while for the first time, we unravelled the mechanistic aspects of the proposed, but never proven, mechanism for the transformation of epoxy polyene terpenes to 2,3,4-trimethylcyclohexanones under acid catalysis. We believe that solid acids will provide in the future a more practical and environmentally benign methodology for several organic transformations. The environmentally benign nature of the zeolites and other porous solid acids[56] justify further exploration towards new frontiers in organic chemistry.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a 500 MHz instrument. Isomeric purities were determined by ^{1}H NMR and by GC analysis on a 60 m HP-5 capillary column. All spectra reported herein were taken in $CDCl_3$. The synthesis of compounds **3**, **4**, **5a**, **b**, **6a**, **b**, **7a**, **b**, **10a**, **b**, **11a**, **b**, **12a**, **b**, **17**, **18**, **19**, **20**, **22**, **23**, **27**, **28**, **29**, **30** and **31** have been described in the Supporting Information of ref.[22] The general method for the synthesis of epoxy terpenoids, as well as, the spectroscopic data for substrates **5c**, **14**, **32** and **37**, are presented in the Supporting Information Section.

Intrazeolite Cyclization of the Epoxy Terpenes

To a slurry containing 1 g of NaY (dried at 120 °C at least for 6 h under vacuum of 10^{-4} torr) in 5 mL hexane, were added approximately 50 mg of the epoxy polyene and the heterogeneous mixture was stirred at room temperature for 10–15 min for the geranyl, farnesyl and squalene derivatives, or for 30–45 min for the neryl derivatives (**10a**, **b**). After that period, the reaction mixture was filtered, and the filtrate was retained. The solid material was further washed



Scheme 11. Specific shift of the CH_3 relative to the CD_3 group during the formation of **52**.

with 2×10 mL of methanol for 30 min each time, and then filtered again. The combined solvent extracts were evaporated to afford the cyclized products in 70–90% yield. For larger scale experiments, 1 mmol of geranyl derivatives was used per 1 g of dry NaY, and the reaction was complete after 1 hour by heating to 70 °C.

Spectroscopic Data of the Intrazeolite Products

From Epoxide 5c

4-(3-Hydroxy-2,2-dimethyl-6-methylenecyclohexyl)butan-2-yl acetate (**6c**-*exo*, mixture of 2 diastereomers ~1/1): ^{1}H NMR: δ = 4.88 (m, 1H), 4.87 (s, 1H), 4.59 (s, 1H), 3.41 (dd, J_1 = 4.0 Hz, J_2 = 10.0 Hz, 1H), 2.33 (m, 1H), 2.03 (s, 3H), 1.99 (m, 1H), 1.84 (m, 1H), 1.72–1.47 (m, 6H), 1.21 (d, J = 4.0 Hz, 3H), 1.03 (s, 3H), 1.02 (s, 3H of the second diastereomer), 0.73 (s, 3H), 0.72 (s, 3H of the second diastereomer).

4-(5-Hydroxy-2,6,6-trimethylcyclohex-2-enyl)butan-2-yl acetate (**6c**-***endo***, mixture of 2 diastereomers ~1/1): ^{1}H NMR (characteristic absorptions): δ = 5.25 (br. s, 1H), 4.90 (m, 1H), 3.46 (dd, J_1 = 6.0 Hz, J_2 = 8.0 Hz, 1H), 2.03 (s, 3H), 1.22 (d, J = 6.5 Hz, 3H), 0.97 (s, 3H), 0.98 (s, 3H of the second diastereomer), 0.83 (s, 3H), 0.82 (s, 3H of the second diastereomer).

4-(1,3,3-Trimethyl-7-oxa-bicyclo[2.2.1]heptan-2-yl)butan-2-yl acetate (**7c**-***endo***, mixture of 2 diastereomers ~1/1): ^{1}H NMR: δ = 4.86 (m, 1H), 3.72 (d, J = 5.5 Hz, 1H), 2.03 (s, 3H), 1.71–1.43 (m, 7H), 1.37 (m, 1H), 1.31 (s, 3H), 1.30 (s, 3H of the second diastereomer), 1.22 (d, J = 6.5 Hz, 3H), 1.17 (m, 1H), 1.04 (s, 3H), 1.03 (s, 3H of the second diastereomer), 1.00 (s, 3H), 0.99 (s, 3H (s, 3H of the second diastereomer).

4-(1,2,6-Trimethyl-3-oxocyclohexyl)butan-2-yl acetate (**9c**, mixture of 2 diastereomers ~4/1): ^{1}H NMR (major diastereomer): δ = 4.87 (m, 1H), 2.43 (m, 1H), 2.34 (m, 2H), 2.04 (s, 3H), 1.95 (m, 1H), 1.85 (m, 1H), 1.63 (m, 1H), 1.51–1.31 (m, 4H), 1.25 (d, J = 6.0 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H), 0.59 (s, 3H); ^{13}C NMR (major diastereomer): δ = 213.7, 170.7, 71.1, 50.4, 43.2, 41.6, 36.2, 32.3, 30.9, 28.8, 21.4, 20.0, 15.0, 14.3, 7.4; ^{1}H NMR (minor diastereomer, characteristic absorptions): δ = 0.91 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H); ^{13}C NMR (minor diastereomer, characteristic absorptions): δ = 71.2, 36.1, 19.9, 15.4, 14.9, 7.5.

From Epoxide 14 (Myrcene Oxide)

6,6-Dimethyl-4-vinylcyclohex-3-enol (**14a**):[26] ^{1}H NMR: δ = 6.38 (dd, J_1 = 16.0 Hz, J_2 = 10.0 Hz, 1H), 5.59 (br. s, 1H), 5.09 (d, J = 16.0 Hz, 1H), 4.93 (d, J = 10.0 Hz, 1H), 3.56 (m, 1H), 2.44 (br. d, J = 11.0 Hz, 1H), 2.18 (br. d, J = 11.0 Hz, 1H), 2.15 (d, J = 13.0 Hz, 1H), 1.97 (d, J = 13.0 Hz, 1H), 0.99 (s, 3H), 0.95 (s, 3H).

2,2-Dimethyl-4-vinylcyclohex-3-enol (**14b**):[26] ^{1}H NMR: δ = 6.35 (dd, J_1 = 16.0 Hz, J_2 = 10.0 Hz, 1H), 5.41 (s, 1H), 5.09 (d, J = 16.0 Hz, 1H), 4.91 (d, J = 10.0 Hz, 1H), 3.59 (m, 1H), 2.29 (td, J_1 = 13.0 Hz, J_2 = 5.0 Hz, 1H), 2.19 (td, J_1 = 13.0 Hz, J_2 = 5.0 Hz, 1H), 1.86 (m, 1H), 1.77 (m, 1H), 1.09 (s, 3H), 1.01 (s, 3H).

From Epoxide 32

(*E*)-8-[(1,3-*cis*)-3-Hydroxy-2,2-dimethyl-6-methylenecyclohexyl]-6-methyloct-5-en-2-one (**33**):[39a] ^{1}H NMR: δ = 5.04 (t, J = 6.5 Hz, 1H), 4.86 (s, 1H), 4.57 (s, 1H), 3.40 (dd, J_1 = 9.5 Hz, J_2 = 4.0 Hz, 1H), 2.44 (t, J = 7.0 Hz, 2H), 1.80–2.35 (m, 7H), 2.13 (s, 3H), 1.60 (s, 3H), 1.45–1.70 (m, 4H), 1.02 (s, 3H), 0.71 (s, 3H); ^{13}C NMR: 209.0, 147.2, 136.8, 122.5, 108.4, 77.2, 50.9, 43.8, 40.5, 38.5, 32.9, 32.2, 29.8, 25.9, 23.7, 22.4, 16.0, 15.2.

(*E*)-8-[(1,5-*cis*)-5-Hydroxy-2,6,6-trimethylcyclohex-2-enyl]-6-methyloct-5-en-2-one (**34**):[39a] ^{1}H NMR (characteristic absorptions): δ = 5.22 (br. s, 1H), 5.07 (t, J = 7.0 Hz, 1H), 3.44 (dd, J_1 = 9.5 Hz, J_2 = 6.0 Hz, 1H), 0.95 (s, 3H), 0.82 (s, 3H).

(*E*)-6-Methyl-8-{(1*R**,2*S**,4*S**)-1,3,3-trimethyl-7-oxa-bicyclo[2.2.1]heptan-2-yl}oct-5-en-2-one (**35**):[39a] ^{1}H NMR: δ = 5.06 (t, J = 6.5 Hz, 1H), 3.71 (d, J = 5.5 Hz, 1H), 2.46 (t, J = 7.0 Hz, 2H), 2.26 (m, 2H), 2.13 (s, 3H), 1.90 (m, 3H), 1.65 (m, 1H), 1.61 (s, 3H), 1.33–1.49 (m, 2H), 1.29 (s, 3H), 1.14 (m, 1H), 1.04 (s, 3H), 1.00 (s, 3H); ^{13}C NMR: δ = 208.8, 136.7, 122.6, 86.7, 86.1, 55.2, 45.2, 43.8, 39.8, 39.0, 29.9, 26.1, 26.1, 25.8, 23.4, 22.4, 18.9, 15.9.

(5*E*,9*E*)-13-Hydroxy-6,10,14-trimethylpentadeca-5,9,14-trien-2-one (**36**):[39a] ^{1}H NMR: δ = 5.13 (t, J = 6.5 Hz, 1H), 5.07 (t, J = 6.5 Hz, 1H), 4.94 (t, J = 1.0 Hz, 1H), 4.84 (t, J = 1.0 Hz, 1H), 4.04 (m, 1H), 2.46 (t, J = 6.5 Hz, 1H), 2.27 (m, 2H), 2.12 (s, 3H), 1.94–2.09 (m, 6H), 1.73 (s, 3H), 1.60–1.67 (m, 2H), 1.61 (br. s, 6H); ^{13}C NMR: δ = 208.9, 147.6, 136.2, 134.7, 124.6, 122.7, 110.9, 75.5, 43.7, 39.6, 35.7, 33.3, 29.9, 26.4, 22.5, 17.7, 16.0.

From 2,3-Epoxysqualene (37)

(1,3-*cis*)-2,2-Dimethyl-4-methylene-3-[(3*E*,7*E*,11*E*)-3,8,12,16-tetramethylheptadeca-3,7,11,15-tetraenyl]cyclohexanol (**38**,[37] achilleol A): ^{1}H NMR: δ = 5.10 (m, 4H), 4.86 (br. s, 1H), 4.59 (br. s, 1H), 3.41 (dd, J_1 = 9.5 Hz, J_2 = 4.0 Hz, 1H), 2.32 (td, J_1 = 13.0 Hz, J_2 = 5.0 Hz, 1H), 1.95–2.10 (m, 16H), 1.55–1.75 (m, 4H), 1.67 (s, 3H), 1.58 (s, 12H), 1.01 (s, 3H), 0.70 (s, 3H); ^{13}C NMR: δ = 147.4, 135.6, 135.3, 135.1, 131.4, 124.6, 124.5, 124.5, 124.4, 108.5, 77.4, 51.0, 40.7, 39.9, 39.9, 38.8, 33.3, 32.4, 28.5, 28.4, 26.9, 26.8, 26.0, 25.8, 23.9, 17.8, 16.3, 16.2, 16.2, 15.6.

(1,5-*cis*)-4,6,6-Trimethyl-5-[(3*E*,7*E*,11*E*)-3,8,12,16-tetramethylheptadeca-3,7,11,15-tetraenyl]cyclohex-3-enol (**39**,[28] camelliol C): ^{1}H NMR (selected absorptions): δ = 5.22 (br. s, 1H), 5.10–5.15 (m, 4H), 3.45 (t, J = 7.0 Hz, 1H), 0.96 (s, 3H), 0.82 (s, 3H).

(1*R**,2*S**,4*S**)-1,3,3-Trimethyl-2-[(3*E*,7*E*,11*E*)-3,8,12,16-tetramethylheptadeca-3,7,11,15-tetraenyl]-7-oxa-bicyclo-[2.2.1]heptane (**40**): ^{1}H NMR: δ = 5.11 (m, 4H), 3.71 (d, J = 5.0 Hz, 1H), 1.85–2.12 (m, 14H), 1.67 (s, 3H), 1.59 (br. s, 12H), 1.35–1.50 (m, 6H), 1.32 (s, 3H), 1.17 (m, 1H), 1.04 (s, 3H), 1.01 (s, 3H); ^{13}C NMR: δ = 135.4, 135.2, 134.9, 131.2, 124.5, 124.3, 86.7, 86.1, 55.3, 45.3, 41.3, 39.8, 39.7, 39.0, 28.2, 26.8, 26.7, 26.7, 26.2, 26.1, 25.8, 25.7, 23.4, 18.8, 17.7, 16.0.

(6*E*,10*E*,14*E*,18*E*)-2,6,10,15,19,23-Hexamethyltetracosa-1,6,10,14,18,22-hexaen-3-ol (**41**):[43] ^{1}H NMR: δ = 5.08 (m, 6H), 4.93 (br. s, 1H), 4.82 (br. s, 1H), 4.02 (br. t, *J* = 6.5 Hz), 1.92–2.12 (m, 18H), 1.70 (br. s, 6H), 1.66 (br. s, 3H), 1.61 (m, 2H), 1.59 (br. s, 15H).

3-(3-Hydroxybutyl)-2,3,4-trimethylcyclohexanone (15, mixture of 2 diastereomers ~3/1)

The keto acetate **9c** (11 mg) was hydrolyzed with K_2CO_3 (2 equiv.) in methanol to form **15** (89% yield) as a mixture of two diastereomers in a ratio of ~3/1. ^{1}H NMR (major diastereomer): δ = 3.77 (m, 1H), 2.45 (m, 1H), 2.35 (m, 2H), 1.98 (m, 1H), 1.85 (m, 1H), 1.62 (m, 1H), 1.45 (m, 2H), 1.37–1.20 (m, 3H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.60 (s, 3H); ^{13}C NMR (major diastereomer): δ = 213.9, 68.5, 50.5, 43.3, 41.6, 36.2, 32.9, 32.0, 31.0, 23.7, 15.4, 15.0, 7.5; ^{1}H NMR (minor diastereomer, characteristic absorptions): δ = 0.92 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (minor diastereomer, characteristic absorptions): δ = 68.6, 33.0, 15.4, 15.0, 7.6.

(2*R**,3*S**,4*R**)-2,3,4-Trimethyl-3-(3-oxobutyl)cyclohexanone (16, single diastereomer)

The keto alcohol **15** (9 mg) was oxidized with 1.5 equiv. of PCC in CH_2Cl_2 at room temperature to afford after 3 h the known diketone **16**[27] as a single diastereomer. Purification was performed by passing the concentrated reaction residue through a short pad of celite using diethyl ether as eluant (92% yield). ^{1}H NMR: δ = 2.46 (m, 1H), 2.35 (m, 4H), 2.19 (s, 3H), 1.88 (m, 2H), 1.61 (m, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.62 (s, 3H); ^{13}C NMR: δ = 213.0, 208.4, 50.5, 43.0, 41.5, 37.1, 36.4, 30.8, 30.6, 30.1, 15.2, 15.1, 7.6.

(*S*)-2,3-Epoxysqualene [(*S*)-37]

In one-necked flask were placed 1.0 g (2.43 mmol) of squalene, 0.1 g (5%) of $(DHQD)_2$-PHAL, 2.4 g (7.3 mmol) of $K_3Fe(CN)_6$, 1.0 g (7.3 mmol) of K_2CO_3, 0.23 g (2.43 mmol) of $CH_3SO_2NH_2$, 0.25 mL of OsO_4 solution (2.5 wt% in *t*-BuOH), and 20 mL of *t*-BuOH. The mixture was stirred at 0 °C for 48 h. HPLC analysis revealed 60% conversion of squalene. Then it was diluted with 10 mL of CH_2Cl_2 and washed with a solution of 2 N NaOH. The organic residue was carefully chromatographed with hexane/ethyl acetate = 10/1 to separate the more polar 2,3-diol from the less polar mixture of the internal 6,7- and 10,11-diols.[57] The desired (*R*)-2,3-dihydroxysqualene (**42**)[49] was isolated in 12% yield and in 94% *er*. The enantiomeric purity was determined by converting **42** to the mono-MTPA ester and subsequent ^{1}H NMR analysis.[58] ^{1}H NMR of **42**: δ = 5.19 (t, *J* = 6.5 Hz, 1H), 5.08–5.15 (m, 4H), 3.35 (dd, J_1 = 10.5 Hz, J_2 = 2.0 Hz, 1H), 2.24 (m, 1H), 1.96–2.11 (m, 18H), 1.68 (s, 3H), 1.62 (s, 3H), 1.60 (br. s, 12H), 1.20 (s, 3H), 1.15 (s, 3H); ^{13}C NMR of **42**: δ = 135.2, 135.0, 134.9, 134.8, 131.3, 125.2, 124.5, 124.4, 124.3, 78.3, 73.0, 39.8, 39.7, 39.7, 36.8, 29.7, 28.3, 26.8, 26.7, 26.6, 26.4, 25.7, 23.3, 17.7, 16.1, 16.0, 15.9. The (*R*)-**42** diol (120 mg, 0.27 mmol) was treated with TsCl (73 mg, 0.4 mmol), Et_3N (80 μL, 0.55 mmol) and DMAP (67 mg, 0.55 mmol) in dichloromethane at room temperature. After 4 days, the compete transformation of diol to the (*S*)-2,3-epoxysqualene was realized. Purification was accomplished by column chromatography (hexane/ethyl acetate = 10/1) to isolate 72 mg of epoxide (62% yield).

Synthesis of the Deuterium-Labelled Epoxy Geranylacetone 47

To a solution of geraniol-8,8,8-d_3, **43** (0.4 g, 2.55 mmol) in 5 mL dry diethyl ether were added at 0 °C, 0.1 mL (1.0 mmol) of PBr_3. After 30 min a saturated solution of $NaHCO_3$ was added and the resulting solution was extracted with Et_2O. The ether layer was dried and the solvent was removed under vacuum to afford geranyl bromide-8,8,8-d_3 (**44**) in 96% yield. ^{1}H NMR of **44**: δ = 5.53 (t, *J* = 7.5 Hz, 1H), 5.07 (t, *J* = 6.5 Hz, 1H), 4.03 (d, *J* = 7.5 Hz, 2H), 2.08 (m, 4H), 1.73 (s, 3H), 1.60 (s, 3H). Subsequently, the labelled bromide **44** (0.51 g, 2.3 mmol), alkylated the anion of ethyl acetoacetate formed upon treatment of ethyl acetoacetate (0.35 mL, 2.78 mmol) with 0.38 g K_2CO_3 (2.78 mmol) in 10 mL dry acetone. The reaction was complete after 12 h at 65 °C. The ethyl α-geranyl-d_3 acetoacetate **45** was isolated in 92% yield. ^{1}H NMR of **45**: δ = 5.04 (m, 2H), 4.19 (q, *J* = 7.0 Hz, 2H), 3.43 (t, *J* = 6.5 Hz, 1H), 2.55 (t, *J* = 7.0 Hz, 2H), 2.22 (s, 3H), 2.04 (m, 2H), 1.97 (t, *J* = 7.0 Hz, 2H), 1.63 (s, 3H), 1.59 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR of **45**: δ = 203.1, 169.6, 138.3, 131.5, 124.0, 119.7, 61.3, 59.8, 39.6, 29.1, 26.9, 25.6, 17.7, 16.1, 14.1. By heating an alkaline (1.6 M NaOH) ethanolic solution containing 0.72 g of the keto ester **45** for 3 h at 70 °C, the saponification/decarboxylation was complete. The reaction mixture was extracted with Et_2O and the organic residue was chromatographed using hexane/ethyl acxetate = 10/1 as eluant to afford geranylacetone-d_3 (**46**) in 88% yield. From the examination of the NMR spectrum we concluded that **46** was 93% geometrically pure in terms of the labelling topicity on the terminal double bond. ^{1}H NMR of **46**: δ = 5.07 (t, *J* = 7.0 Hz, 2H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.27 (m, 2H), 2.13 (s, 3H), 2.06 (m, 2H), 1.97 (t, *J* = 7.0 Hz, 2H), 1.61 (s, 3H), 1.59 (s, 3H); ^{13}C NMR of **46**: δ = 208.9, 136.4, 131.3, 124.2, 122.5, 43.8, 39.7, 30.0, 29.6, 22.5, 17.6, 16.0. Finally, geranylacetone-d_3 (**46**) was epoxidized in 61% isolated yield according to the general procedure for the synthesis of epoxy terpenoids (NBS/H_2O, K_2CO_3) presented earlier, to form the labelled epoxide **47**. ^{1}H NMR of **47**: δ = 5.12 (t, *J* = 7.0 Hz, 1H), 2.68 (t, *J* = 7.0 Hz, 1H), 2.46 (t, *J* = 7.0 Hz, 2H), 2.27 (m, 2H), 2.16 (m, 1H), 2.13 (s, 3H), 2.07 (m, 1H), 1.63 (s, 3H), 1.61 (m, 2H), 1.25 (s, 3H); ^{13}C NMR of **47**: δ = 208.6, 135.4, 123.2, 64.0, 58.3, 43.5, 36.2, 29.9, 27.3, 22.3, 18.7, 15.9.

Synthesis of the Deuterium-Labelled Epoxide 51

To a solution of epoxide **47** (0.26 g, 1.22 mmol) in dry THF were slowly added at 0 °C 0.32 mL (0.32 mmol) $LiAlH_4$ (1 M in THF). After 30 min the reaction mixture was quenched with H_2O. Following an extractive work-up, the labeled epoxy alcohol **50** was isolated in 93% yield, as an equimolar mixture of two diastereomers, with respect to the epoxide and hydroxy functionalities. ^{1}H NMR of **50**: δ = 5.17 (t, *J* = 7.0 Hz, 1H), 3.76 (m, 1H), 2.67 (t, *J* = 6.5 Hz, 1H), 2.08 (m, 4H), 1.68 (br. s, 1H), 1.63–1.57 (m, 2H), 1.61 (s, 3H), 1.48 (m, 2H), 1.23 (s, 3H), 1.17 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR of **50**: δ = 134.7, 124.6, 67.8, 64.1, 58.2, 39.1, 36.4, 27.4, 24.4,

23.6, 18.7, 16.0. Subsequently, **50** was acetylated in 95% yield by reaction with 0.17 mL acetic anhydride (1.81 mmol), in the presence of 0.25 g K_2CO_3 (1.81 mmol) and DMAP (0.02 g) and using ethyl acetate, as solvent. ^{1}H NMR of **51**: $\delta = 5.15$ (t, $J = 7.0$ Hz, 1H), 4.88 (m, 1H), 2.69 (t, $J = 6.0$ Hz, 1H), 2.14 (m, 1H), 2.09 (m, 1H), 2.03 (s, 3H), 2.02 (m, 2H), 1.65 (m, 3H), 1.50 (m, 1H), 1.26 (s, 3H), 1.21 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR of **51**: $\delta = 170.7$, 134.8, 123.9, 70.6, 64.0, 58.2, 36.3, 35.9, 27.4, 23.9, 21.4, 19.9, 18.7, 15.9.

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