Tricyclization of an Epoxypolyene Utilizing Zeolites as Next-Generation Biomimetic Cyclization Promoters: Evidence of Surface and Pore Selectivity in the Cyclization Process[†]

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A new approach for the biomimetic polyene cyclization of epoxyolefins is demonstrated by the zeolite-promoted tricyclization of **1**. Reaction of **1** with a variety of zeolitic materials, including Zeolite A, Mordenite, Faujasite, and ZSM-5, yielded variable amounts of cyclic and acyclic epoxide-rearranged materials. Small-pore Zeolite A, in either the Na or Li form, caused the exclusive formation of ketone **3**, while both H−Mordenite and H−ZSM-5 were sufficiently reactive to provide tricyclic products in modest yields. Low recovery of polyene **1** was observed when larger-pore zeolites of type Beta and H−Faujasite were utilized as cyclization promoters, suggesting that decomposition products had been included within the zeolite cavity. Dramatic improvement in reaction selectivity was achieved after surface dealumination of H−ZSM-5, which gave 52% (isolated yield) of tricycle **2**. Compared to the Lewis acid cyclization of **1** by Ti(O*i*Pr)Cl₃ or MeAlCl₂, the reaction is highly stereoselective, producing the all-trans tricycle as the predominant product. These results, in conjunction with surface and pore deactivation studies using pyridine bases, suggest that the cyclization is initiated at the opening of the zeolite pores, with concurrent adsorption of the polyene onto the aluminosilicate surface.

Introduction

The enzyme catalyzed cyclization of squalene and its epoxide derivative by a group of structurally related polyene cyclases represents one of the more challenging reactions known to synthetic chemists.[1] While a number of elegant methods are available for the construction of polycyclic materials through a nonenzymic (biomimetic) approach,[2] few attempts have been made to develop cyclization promoters that mimic the characteristics of the naturally occurring cyclization biocatalysts.[3] The seminal work of van Tamelen and co-workers and the recent efforts of both the Johnson and Corey groups, utilizing Lewis acids for the tri-, tetra-, and pentacyclization of epoxyolefins, demonstrate the practical utility of mastering biomimetic cyclization chemistry for the preparation of both natural and unnatural steroid and polycyclic materials.[4−7]

Zeolites (i.e., aluminosilicates) are important industrial materials that are used in ion exchange, hydrocarbon cracking, and small molecule syntheses.[8] They possess two important properties, namely acidity and porosity, which make them useful as heterogeneous acids and selective absorbents. This latter characteristic has been utilized to control the regioselectivity in several organic reactions, elevating the status of zeolites in the minds of synthetic organic chemists from water scavengers to shape-selective catalysts.[9]

As an extension of current biomimetic polyene cyclization methods, we were interested in expanding biomime-cry to include the development of promoters that possess common features of the known oxidosqualene cyclases. In this paper we present the first application of zeolites as promoters of a epoxypolyene tricyclization. Results from these studies indicate that both zeolite acidity and

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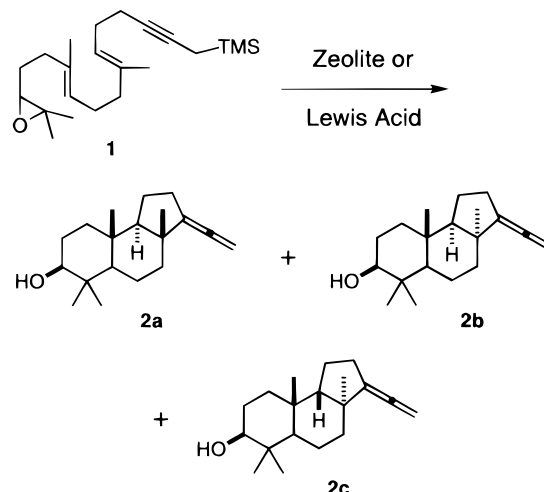[†] This paper is dedicated to the memory of William S. Johnson.
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adsorption of the epoxide moiety and polyene tail to the zeolite pores and surface, respectively, are essential for the chemistry to proceed, demonstrating the potential of these materials as cyclase surrogates.

Results and Discussion

To examine the reactivity of zeolites in polyene cyclization chemistry, epoxypolyene **1** was prepared. This material, which possesses a propargylic silane functionality to allow for five-membered ring termination of the cyclization cascade, was previously studied by Johnson and co-workers and is known to produce a mixture of isomeric tricyclic products (Scheme 1).[5d] Thus, in addition to comparing differences in promoter reactivity, we were also interested in using polyene **1** as a model compound for studying the regioselectivity of cyclization caused by zeolite versus Lewis acid promoters. Construction of **1** followed previously published methods,[5a,10] relying on two sequential Claisen rearrangements to provide the all-trans stereochemistry of the polyene backbone and epoxidation of the resulting trisnoraldehyde with the sulfur ylide of isopropyldiphenylsulfonium tetrafluoroborate.

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Initial cyclization studies utilized previously developed methodology from our laboratory, involving partially hydrated 4 Å molecular sieves.[10] To our surprise, reaction of **1** with either the Na or the more acidic Li form of Zeolite A in refluxing CHCl$_3$ provided ketone **3** in *quantitative* yield. Although the acid-catalyzed rearrangement of trisubstituted epoxides is a facile process,[11] this chemistry was unanticipated for the zeolite-promoted reaction since analogous conditions resulted exclusively in the bicyclization of the corresponding truncated polyene. Differences in reactivity for the above bi- versus tricyclizations demonstrates the difficulty in performing more elaborate polycyclizations and supports the theory that a through-space electronic interaction exists between the cyclization initiator (i.e., the epoxide functionality) and the $\Delta^{6,7}$ π system.[1a,4b,12]

Although a wide variety of molecular sieves can serve as acid catalysts, Zeolite A is rarely used in fine chemical synthesis. This is due, in part, to the fact that its external pore size is too small (i.e., 4 Å outer diameter for NaA) to allow for wide-range compound absorption into the inner spherical cavity, and that its structural integrity in compromised upon formation of the more acidic H-form.[13] Instead, common aluminosilicates that are utilized industrially include Faujasite (or Zeolite X/Y), Mordenite, Zeolite Beta, and ZSM-5. These materials have either spherical or tubular pores with diameters that exceed that of Zeolite A (Table 1).[14]

Results for the zeolite-promoted cyclization of polyene **1** using Faujasite, Mordenite, Zeolite Beta, and ZSM-5 are presented in Table 2. In all cases, loss of starting material occurred; however, significant differences in reactivity were observed for each of the zeolites tested. In the case of Na−Faujasite (Na−Fau), H−Mordenite (H−Mor), and H−ZSM-5, cyclization proceeded to provide

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Table 1. Commercially Available Zeolite Types and Their Structures

zeolite type	shape	pore size (Å)
Zeolite A	spherical	4.1
ZSM-5	tubular	5.3 × 5.6 and 5.1 × 5.5
Mordenite	tubular	6.5 × 7.0
Faujasite	spherical	7.4
Zeolite Beta	tubular	7.6 × 6.4 and 5.5 × 5.5
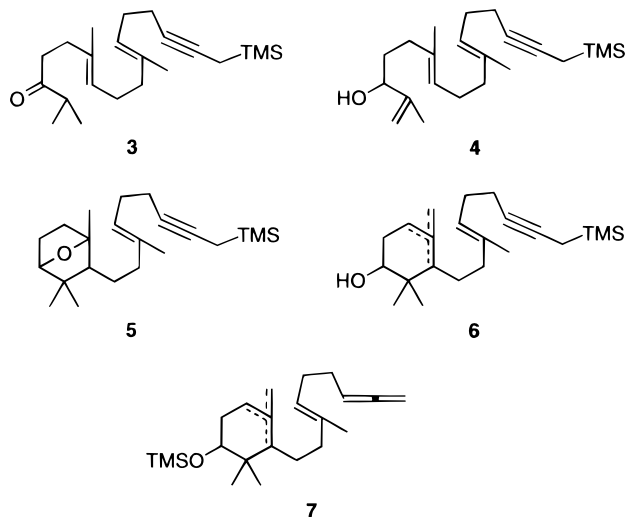
Figure 1. Byproducts obtained in the zeolite-promoted cyclization of **1**.

a mixture of products, including the desired tricycle (**2**), as well as epoxide-rearranged materials (ketone **3** and allylic alcohol **4**), bicyclic ether **5**, and several other partially cyclized materials (Figure 1). The bicyclic ether is commonly formed in epoxyene cyclizations and results from monocyclization followed by oxygen addition to the corresponding tertiary carbocation intermediate.[5,6,11] The other partially cyclized materials, which accounted for as much as one-third of the products formed, were identified after partial separation of a preparative scale cyclization as monocycles **6** and **7**.[15] Interestingly, reaction of epoxide **1** with the larger pore zeolites H−Faujasite and Zeolite Beta (H-Bea) resulted in extremely low mass recovery, as determined by GLC and ^{1}H NMR analysis of the reaction filtrate.[16] No additional soluble materials were recovered after refluxing the zeolites in water/methanol or by citric acid treatment. These results, in conjunction with the observation that both Faujasite and Beta type zeolites darkened to either a tan or orange-brown color during their reaction with epoxypolyene **1**, support the hypothesis that extensive decomposition to coke-type products has occurred.[17]

Changes in the reaction profile occurred as a result of modification to several reaction parameters, the results of which are summarized in Tables 2−6. While halogenated and aromatic solvents could be used in the zeolite-promoted reaction, aliphatic solvents were significantly worse at effecting the cyclization of **1**, affording as the predominant reaction products ketone **3** and bicyclic

ether **5** (Table 3). Similarly we found that temperature had an profound effect on the outcome of the reaction. Although higher temperatures were beneficial in increasing reaction rate, the addition of polyene **1** *to an already refluxing suspension* of H−ZSM-5 resulted in a significant increase in ketone formation, at the expense of tricycle **2** (Table 4).

An examination of the effect of zeolite aluminum content (as indicated by the corresponding Si/Al ratio) and equivalents indicated that proper interaction of the polyene with the zeolite lattice was important for tricyclization. We found that increased silica content, as seen in the cyclization of ZSM-5 with Si/Al ratios of 30, 80, 150, and 280, respectively, gave rise to higher quantities of ketone **3** and less bicyclic ether **5** (Table 2) and that decreased quantities of zeolite in the reaction medium (i.e., 20 versus 0.1 equiv, Table 5) not only slowed the reaction but gave lower selectivity toward tricyclization. Interestingly, little change in reactivity was observed for the H−Mordenite promoted cyclization of **1** using zeolites with Si/Al ratios of 16 and 100, respectively (Table 2); however, these materials have lower external surface volume than ZSM-5 and may therefore be reasonably insensitive to changes in silica content.[18]

Because extramatrix alumina is commonly found at the pore entrances of commercially available zeolites (causing potentially undesirable chemistry), we first treated ZSM-5 and Mordenite with nitric acid (0.8, 8, and 12 M) for different times.[19] A dramatic improvement was noted when ZSM-5 (Si/Al = 30 and 150) and Mordenite (Si/Al = 100) were treated for 15 min with 8 M nitric acid (Table 6).[20] Thus, reaction with polyene **1** with 5 equiv (by weight) of acid-treated ZSM-5 (Si/Al = 30) in refluxing dichloroethane resulted in clean conversion to bicyclic ether **5** and tricycle **2**, with decreased monocycle formation and partial suppression of ketone formation. Using these conditions, semipreparative scale cyclization of **1** with acid-treated H−ZSM-5 (Si/Al = 30) provided 52% isolated yield of **2**. Treatment of Mordenite with nitric acid is known to create mesoporous structures;[8b] as with H−ZSM-5, we found that this zeolitic material showed marked improvement upon acid treatment. Heavily dealuminated H−ZSM-5 (8 and 12 M nitric acid, 1 h), which retains little of its original zeolite structure, was found to be a poor cyclization promoter of **1**, resulting in the formation of large quantities of epoxide rearrangement products (data not shown).

To compare the effectiveness of the zeolite-promoted cyclizations with traditional cyclization promoters we examined the reaction of **1** with Ti(*i*OPr)Cl₃ and MeAlCl₂, two highly effective Lewis acid promoters for the cyclization of epoxypolyenes.[5,6] Johnson and co-workers previously studied the cyclization of **1** and found that the use of 10 equiv of the mixed titanium reagent resulted in the formation of three tricyclic products (**2a**, **2b**, and **2c**) in a 4:1:1 ratio.[5d] Using similar reaction conditions, we

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(15) Compounds **6** and **7** were partially purified by MPLC and identified by ^{1}H NMR/GLC correlation analysis.

(16) Additional ^{1}H NMR studies were performed by reacting polyene **1** with Zeolite Beta in D₄-dichloroethane. Direct ^{1}H NMR analysis of the filtrate before and after zeolite washing indicated that a trace amount of unidentified aliphatic hydrocarbon material was present in solution.

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(20) *Note*: The presence of extramatrix alumina varies between zeolite lot numbers, as well as between zeolite manufacturers. In some instances, we found that acid treatment was not necessary and in fact, could be detrimental to zeolite performance.

Table 2.   Reaction Profile of 1 Using Several Different Zeolites

		recovered materials (%)[a]					
zeolite[b]	equiv[c]	starting material (**1**)	tricyclic products (**2**)	ketone (**3**)	allylic alcohol (**4**)	bicyclic ether (**5**)	partially cyclized products (**6** and **7**)
none[d]		100					
NaA[e]	30			100			
LiA[e]	30			100			
H-Faujasite (5)[f]	5	−[g]	−	−	−	−	−
Na-Faujasite (5)[f]	5	29.3	16.5	22.7		12.0	19.4
H-Beta (25)[f]	5	−[g]	−	−	−	−	−
H-Mordenite (16)[f]	5		21.4	14.8	2.4	26.2	29.8[h]
H-Mordenite (100)[f]	5		20.7	10.4		31.0	31.9[i]
H-ZSM-5 (30)[f]	10		29.1	9.1	2.2	29.1	32.2
H-ZSM-5 (80)[f]	10		28.2	8.8		27.9	35.2
H-ZSM-5 (150)[f]	10		26.3	13.2	2.5	19.9	37.9
H-ZSM-5 (280)[f]	10		25.8	21.1	5.4	17.5	30.2

[a] GLC yield. [b] Reaction conditions: 2.9 mM polyene **1** in dichloroethane, reflux, 15 min. [c] By weight. [d] Reaction time, 1 h. [e] Using CHCl$_3$ as solvent. [f] Si/Al ratio. [g] Decomposition and/or inclusion occurred. [h] 2.4% unidentified. [i] 6.0% unidentified.

Table 3.   Effect of Solvent on the Zeolite-Promoted Cyclization of Polyene 1

	recovered materials (%)[a]					
solvent[b]	starting material (**1**)	tricyclic products (**2**)	ketone (**3**)	allylic alcohol (**4**)	bicyclic ether (**5**)	partially cyclized products (**6** and **7**)
hexane		9.5	40.7		25.0	12.6[c]
toluene	4.4	27.2	14.1		25.1	29.3
CHCl$_3$		15.3	26.0	4.5	21.4	32.8
CH$_2$Cl$_2$		24.4	10.1		29.3	36.2
dichloroethane		29.1	9.1	2.2	29.1	32.2

[a] GLC yield. [b] Reaction conditions: 10 equiv (by weight) of H-ZSM-5, Si/Al ratio = 30, 2.9 mM polyene **1**, reflux, 30 min. [c] 12.3% unidentified.

Table 4.   Effect of Temperature on the Zeolite-Promoted Cyclization of Polyene 1

	recovered materials (%)[a]					
addition temp[b]	starting material (**1**)	tricyclic products (**2**)	ketone (**3**)	allylic alcohol (**4**)	bicyclic ether (**5**)	partially cyclized products (**6** and **7**)
0 °C[c]	76.8	6.4	2.6	1.9	4.7	7.7
rt[d]		25.3	11.3		26.5	36.9
rt to reflux[d]		29.1	9.1	2.2	29.1	32.2
reflux[e]		12.0	30.6	10.3	17.3	19.1[f]

[a] GLC yield. [b] Reaction conditions: 10 equiv (by weight) H-ZSM-5, Si/Al ratio = 30, 2.9 mM polyene **1** in dichloroethane, 30 min. [c] Reaction time, 1 h. [d] Polyene was added at rt. [e] Polyene was added to an already refluxing suspension of zeolite in dichloroethane. [f] 10.7% unidentified.

Table 5.   Effect of Zeolite Equivalents on the Cyclization of Polyene 1

	recovered materials (%)[a]					
equiv[b,c]	starting material (**1**)	tricyclic products (**2**)	ketone (**3**)	allylic alcohol (**4**)	bicyclic ether (**5**)	partially cyclized products (**6** and **7**)
20		28.9	6.8		30.3	34.1
5		28.3	14.5		25.5	31.7
1		21.3	24.2		17.9	36.6
0.1	15.7	7.4	33.3	8.1	8.6	11.2[d]

[a] GLC yield. [b] By weight, using H-ZSM-5, Si/Al ratio = 30. [c] Reaction conditions: 2.9 mM polyene **1** in dichloroethane, reflux, 30 min. [d] 15.7% unidentified.

obtained identical results (Table 7). Reaction of **1** with 0.5 equiv of MeAlCl$_2$ also yielded a mixture of tricyclic materials but interestingly, did not generate significant quantities of bicyclic ether **5**.

While the reaction of **1** with H−ZSM-5 yielded significant quantities of ketone **3**, bicyclic ether **5**, and several partially cyclized and tricyclic products, the all-trans tricycle (**2a**) was formed in much higher quantities than

the corresponding aluminum- and titanium-mediated reactions. Thus, reaction of polyene **1** with H−ZSM-5 (Si/Al = 30, 80, or 150) showed a dramatically different reaction profile than that observed in the Lewis acid-mediated cyclizations, *yielding three tricyclic isomers in a 10:0.5:0.6 ratio*. X-ray crystal structure analysis of the major tricycle formed (after MPLC purification of the corresponding *p*-bromobenzoate) confirmed this material

**Table 6. Effect of Acid and Base Treatments on ZSM-5 and Mordenite Reactivity**

		recovered materials (%)[a]					
promoter[b]	zeolite pretreatment[c]	starting material (**1**)	tricyclic products (**2**)	ketone (**3**)	allylic alcohol (**4**)	bicyclic ether (**5**)	partially cyclized products (**6** and **7**)
ZSM-5 (30)[d]	8 M HNO₃		42.0	6.2		28.2	17.7[e]
ZSM-5 (150)[d]	8 M HNO₃		32.1	13.4	15.6	20.1	17.8
Mordenite (16)[d]	0.8 M HNO₃		35.5	17.9		24.8	21.7
Mordenite (100)[d]	0.8 M HNO₃		50.4			30.0	19.7
ZSM-5 (30)[d,f]	8 M HNO₃, then 10% 2,6-di-*tert*-butylpyridine	54.5	15.0	7.9	2.1	4.7	15.8
ZSM-5 (30)[d,f]	8 M HNO₃, then 10% pyridine	96.0	2.1	0.1		1.7	0.1

[a] GLC yield. [b] Reaction conditions: 5 equiv by weight of zeolite, 4.5 mM polyene **1** in dichloroethane, reflux, 15 min. [c] Zeolites were stirred with acid at room temperature for 15 min, washed with deionized water, and then dried at 115 °C overnight. For base treatments, acid-washed zeolites were treated with a 10% solution of pyridine in hexane at room temperature for 2 h, washed with hexane, and then dried at 115 °C overnight. [d] Si/Al ratio. [e] 5.9% unidentified. [f] Reaction performed at room temperature for 30 min.

Table 7. Comparison of Reactivity between Zeolite and Lewis Acid-Promoted Cyclization of 1

	recovered materials (%)[a]			
promoter	bicyclic ether (**5**)	partially cyclized products (**6** and **7**)	tricyclic products (**2**)	isomeric ratio of **2**[b] **2a:2b:2c**
Ti(O*i*Pr)Cl₃[c]	15.8	12.3	68.6[d]	4:1.1:1.1
MeAlCl₂[e]	3.6	1.7	84.9[f]	4.5:1:1.2
H-ZSM-5[g]	28.2	17.7	42.0[h]	10:0.5:0.6

[a] GLC yield. [b] Unambiguous assignment of **2b** and **2c** was not performed for these studies. [c] Reaction conditions: 3 equiv of Lewis acid, CH₂Cl₂, −78 °C. [d] Remainder: 2.3% ketone **3**. [e] Reaction conditions: 0.5 equiv of Lewis acid, CH₂Cl₂, −78 °C. [f] 9.5% unidentified. [g] Reaction conditions: 10 equiv by weight of acid-treated H-ZSM-5 (Si/Al = 30), 3.8 mM polyene **1** in dichloroethane, reflux, 15 min. [h] Remainder: 6.2% ketone **3**.
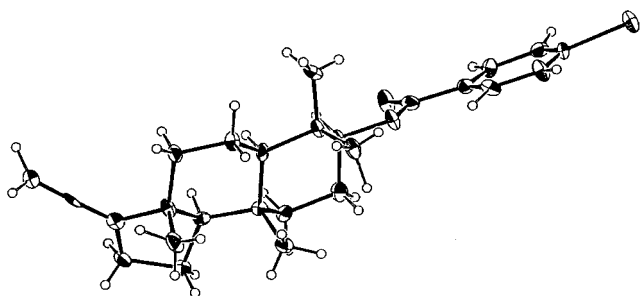
Figure 2. ORTEP drawing of the *p*-bromobenzoate derivative of tricycle **2a**.

to be isomer **2a** (Figure 2). Although we have yet to obtain sufficient quantities of the minor components for crystal structure determination, previous studies by Johnson and co-workers establish their assignment as tricycle **2b** and B-boat isomer **2c**. The formation of a B-boat tricycle in related Lewis acid-promoted epoxide tricyclizations has been observed[4c,6d,21] and indicates that the cyclization of squalene epoxide to protolanosterol (which requires the formation of a B-boat transition state) may be thermodynamically accessible in a nonenzymatic environment.

On the basis of the above results, it appears that there are mechanistic differences between the Lewis acid and ZSM-5 mediated cyclization of **1**. The fact that the zeolite reaction selectively provides tricycle **2a** concurrent with

the production of significant quantities of partially cyclized materials suggests that two competing factors may be in play, namely (i) interaction of the polyene backbone with the external zeolitic surface and (ii) epoxide activation at the entrance of the zeolite pores. Although the structures of both ZSM-5 and Mordenite prohibit the inclusion of polyene **1** in a reactive (i.e., tricyclic) conformation, calculated volumes of energy-minimized structures **5** and **6** indicate that initial epoxide ring opening may occur within a zeolite cavity.[22] Subsequent cyclization of the partially included polyene would account for the preponderance of bicyclic ether **5** and other partially cyclized products, due to sequestration of the prerequisite monocyclization intermediate. Related pore-restricted chemistry has been seen in the ZSM-5 catalyzed isomerization of heptadecane.[9d]

To determine whether the zeolite-promoted reaction is perturbed by inactivation of either the zeolite surface or cavity, H−ZSM-5 was treated with 2,6-di-*tert*-butylpyridine (DTBP) and pyridine, respectively.[9b,c] The former base is too large to enter the zeolitic pores and therefore selectively coats the surface of ZSM-5, neutralizing all external acidic sites. Because pyridinium salts such as PPTS are weak acids that can cause epoxide ring opening chemistry at higher temperatures,[23,24] all cyclization studies involving the use of base-modified zeolites were conducted at room temperature. DTBP-treated zeolites were slightly less reactive than their untreated counterparts but showed similar reactivity with respect to product profile (Table 6). In contrast, pyridine treatment, which inactivates both the surface and inner pores of ZSM-5, caused almost complete suppression of reactivity. These results, taken together with the effect of acid treatment, temperature, and equivalents on the cyclization of **1**, as well as the observed regioselectivity of cyclization, indicate that ketone formation occurs preferentially at the external zeolite surface, that cyclization is initiated at the zeolite pores, and that both the external and internal surfaces are required for tricyclization to

(21) Smith, A. B.; Kinsho, T.; Sunazuka, T.; Ōmura, S. *Tetrahedron Lett.* **1996**, *37*, 6461−6464.

(22) Using Spartan SGI version 4.1.1, Wavefunction, Inc., 18401 Von Karman, Suite 370, Irvine, CA 92715.

(23) Polyene **1** was treated with 1 equiv of PPTS in dichloroethane at 0 °C, rt, 40 °C, and reflux temperature for 30 min. While no reaction was observed at 0 °C, a small amount of ketone **3** and allylic alcohol **4** were formed at room temperature. Essentially complete conversion of polyene **1** to a mixture of **3** and **4** occurred at reflux temperature.

(24) Zeolite-promoted addition of amines to epoxides has been demonstrated; see: (a) Takeuchi, H.; Kitajima, K.; Yamamoto, Y.; Mizuno, K. *J. Chem. Soc., Perkin Trans. 2* **1993**, 199−203. (b) Onaka, M.; Kawai, M.; Izumi, Y. *Chem. Lett.* **1985**, 779−782.
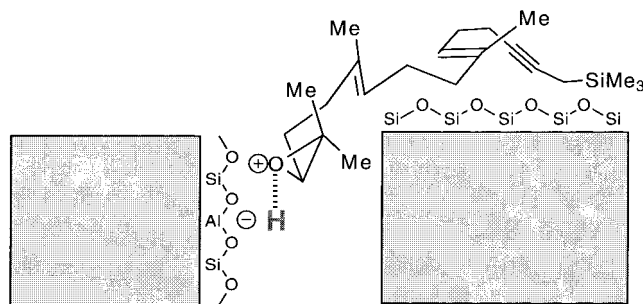
Figure 3. Proposed surface and pore interaction of zeolite ZSM-5 with epoxypolyene **1**.

proceed. The differential reactivity of polyene **1** with either external or pore-localized acidic sites is supported by the characterization of five different acid types within the H−ZSM-5 lattice, as determined by calorimetric/adsorption (Cal-Ad) measurements.[25]

In describing the favorable effect of carbocationic stabilizing groups in biomimetic polyene cyclizations, Johnson had proposed that appropriately positioned "negative point charges" are required in the active site of oxidosqualene cyclases.[26] Thus, in the formation of the all-trans tetracycle dammaradienol, transition state stabilization by several axial stabilizing groups could account for the high stereospecificity of cyclization. We believe that in the zeolite-promoted cyclization of **1** a similar effect is in play, which provides the high selectivity obtained in the formation of tricycle **2a**. In the zeolite case, it is the interaction of the polyene backbone with the zeolitic surface in conjunction with pore-mediated epoxide activation which results in the formation of the all-trans tricycle (Figure 3).

Conclusion

The first demonstration of a biomimetic tricyclization of an epoxypolyene, utilizing zeolites as next-generation cyclization promoters, has been presented. The reaction is selective for the all-trans-olefin and is affected by both dealumination and base treatments. We believe that these results are consistent with a model that involves simultaneous epoxide activation at the zeolitic pore and polyene absorption onto the external zeolite surface, suggesting that zeolites may function as surrogates to normal oxidosqualene cyclase action.

Experimental Section

General Methods. Unless otherwise stated, all fine chemicals and solvents were obtained from commercial sources and were used without further purification. 4 Å Molecular sieves (both powder and pellet forms) were purchased from Aldrich Chemical Co. The following zeolites were a gift from PQ (Zeolyst International) Corp: Na−Fau, Si/Al = 5 (CBV 100); H−Fau, Si/Al = 5 (CBV 600); H−Bea, Si/Al = 25 (CP 811BL-25); H−ZSM-5, Si/Al = 30 (CBV 3020); H−ZSM-5, Si/Al = 80 (CBV 8020); H−ZSM-5, Si/Al = 150 (CBV 1502); H−ZSM-5, Si/Al = 280 (CBV 2802). Mordenite samples (H−Mor, Si/Al = 16 and 100) were obtained from Tosoh Corp. THF was distilled from benzophenone sodium ketyl, dichloroethane and CHCl₃ were distilled from K₂CO₃, and CH₂Cl₂ and toluene were

(25) (a) Drago, R. S.; Dias, S. C.; Torrealba, M.; de Lima, L. *J. Am. Chem. Soc.* **1997**, *119*, 4444−4452. (b) Parrillo, D. J.; Gorte, R. J.; Farneth, W. E. *J. Am. Chem. Soc.* **1993**, *115*, 12441−12445.

(26) Johnson, W. S.; Lindell, S. D.; Steele, J. *J. Am. Chem. Soc.* **1987**, *109*, 5852−5853.

distilled from CaH₂. ¹H and ¹³C NMR spectra were recorded at 300 and 75 MHz, respectively, on a GE QE−300 spectrometer, using CDCl₃ as solvent. Gas−liquid chromatography was performed on a DB-5 30 m capillary column, using the following temperature gradient: 200 °C for 1 min, 10 °C/min to 325 °C for 5 min. Crystal structure determination was performed at the Indiana University Molecular Structure Center, Bloomington, IN.

Zeolite Treatments. (1) Oven-dried zeolites were heated at 115 °C overnight. (2) Acid-treated zeolites (150 mg) were stirred in 10 mL of 0.8, 8, or 12 M HNO₃ for 15 min or 1 h and then separated from the liquid phase by centrifugation. The zeolites were washed with deionized water (5 × 25 mL) by sequential resuspension and centrifugation and then dried at 115 °C overnight. (3) Base-treated zeolites (30 mg) were soaked in 2 mL of 10% 2,6-di-*tert*-butylpyridine (w/v) or pyridine (v/v) in hexane for 2 h at room temperature. The zeolites were then filtered, rinsed with hexanes (4 × 5 mL), and dried at 115 °C overnight.

(6*E*)-2,6-Dimethyl-12-trimethylsilyl-1,6-dodecadien-10-yn-3-ol. To a rapidly stirring mixture of magnesium turnings (387 mg, 15.9 mmol) in dry THF (10 mL) at room temperature was added 1,2-dibromoethane (5 μL), followed by the dropwise addition of 2-bromopropene (1.6 mL, 18 mmol) in THF (20 mL). After the reaction mixture was stirred for 1 h at room temperature and cooled to 0 °C, (4*E*)-4-methyl-10-trimethylsilyl-4-decen-8-yn-1-al (1.9 g, 8 mmol) in THF (5 mL) was added. The reaction mixture was stirred for 2 h at 0 °C, quenched with saturated aqueous NH₄Cl (5 mL), concentrated to approximately half its original volume, diluted with 5% HCl (10 mL), and extracted with ether (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ and brine, dried (MgSO₄), and concentrated. Flash chromatography (10% ether in hexanes) of the resulting residue provided the product as an oil (1.5 g, 66%): ¹H NMR δ 5.21 (m, 1H), 4.92 (br s, 1H), 4.81 (br s, 1H), 4.02 (m, 1H), 2.14 (br s, 5H), 2.02 (m, 3H), 1.71 (s, 3H), 1.61 (s, 3H), 1.39 (s, 2H), 0.06 (s, 9H); ¹³C NMR δ 147.5, 135.6, 123.7, 110.9, 78.6, 75.6, 76.6, 35.6, 33.1, 28.1, 19.3, 17.5, 16.1, 6.9, −2.2; IR (neat) cm⁻¹ 3378, 2955, 2918, 2215, 1660, 1450, 1250, 1172, 1062, 899, 852.

Ethyl (4*E*,8*E*)-4,8-Dimethyl-14-trimethylsilyl-4,8-tetradecadien-12-yn-1-oate. The above allylic alcohol (2.7 g, 9.6 mmol), triethyl orthoacetate (8.8 mL), and a trace amount of propanoic acid (10 μL) were heated at 130 °C for 2 h with removal of the ethanol formed during the reaction by slow distillation. The reaction mixture was then cooled to room temperature, poured into brine containing 1 M H₂SO₄ (5 mL), and stirred at 0 °C for 30 min. After extraction of the aqueous layer with ether (3 × 100 mL), the combined organic phases were washed with saturated aqueous NaHCO₃ and brine, dried (MgSO₄), and concentrated. The residue was purified by flash chromatography (2% ether in hexanes) to give pure ester as an oil (2.91 g, 86%): ¹H NMR δ 5.13−5.06 (m, 2H), 4.05 (q, 2H, *J* = 7.35 Hz), 2.36−2.29 (m, 2H), 2.33−2.20 (m, 2H), 2.09 (br s, 4H), 2.06−1.98 (m, 2H), 1.94−1.87 (m, 2H), 1.55 (br s, 6H), 1.35 (s, 2H), 1.18 (t, 3H, *J* = 7.35 Hz), 0.03 (s, 9H); ¹³C NMR δ 173.1, 135.5, 133.1, 124.9, 123.3, 78.6, 77.2, 60.0, 39.4, 34.5, 33.1, 28.0, 26.4, 19.3, 16.0, 15.7, 14.1, 6.8, −2.3; IR (neat) cm⁻¹ 2955, 2907, 2217, 1736, 1443, 1373, 1251, 1159, 1041, 849.

(4*E*,8*E*)-4,8-Dimethyl-14-trimethylsilyl-4,8-tetradecadien-12-yn-1-al. To a stirred solution of the above ester (1.05 g, 3.0 mmol) in dry ether (25 mL) at −94 °C was added DIBALH (3.6 mL, 1.0 M in hexane) dropwise over 20 min. The reaction was stirred for another 1 h at −94 °C, then methanol (1 mL) was slowly added along the flask wall. The solution was allowed to warm to 0 °C and diluted with 5% HCl (20 mL), and after vigorous stirring for 15 min, the reaction mixture separated into two layers. After extraction of the aqueous layer with ether (3 × 60 mL), the combined organic phases were washed with saturated aqueous NaHCO₃ and brine, dried (MgSO₄), and concentrated to give a clear oil. Purification by flash chromatography (2 to 5% ether in hexanes) gave pure aldehyde (0.77 g, 83%): ¹H NMR δ 9.71, (br s, 1H), 5.14−5.08 (m, 2H), 2.47 (t, 2H, *J* = 7.35 Hz), 2.27

(t, 2H, J = 7.35 Hz), 2.12 (br s, 4H), 2.06−2.01 (m, 2H), 1.99−1.95 (m, 2H), 1.57 (s, 3H), 1.56 (s, 3H), 1.37 (s, 2H), 0.05 (s, 9H); ^{13}C NMR 202.3, 135.5, 125.2, 123.5, 78.6, 77.3, 42.1, 39.4, 31.8, 28.0, 26.4, 19.3, 16.0, 6.9, −2.2; IR (neat) cm^{-1} 2956, 2909, 2845, 2716, 2219, 1727, 1435, 1388, 1251, 1169, 857.

(6*E*,10*E*)-2,3-Epoxy-2,6,10-trimethyl-16-trimethylsilyl-6,10-hexadecadien-14-yne (1). To a suspension of isopropyldiphenylsulfonium tetrafluoroborate (492 mg, 1.6 mmol) in THF (10 mL) at −78 °C was added *tert*-butyllithium dropwise (0.6 mL, 1.7 M solution in hexanes). After the resulting yellow ylide was stirred for 45 min, the above aldehyde (117 mg, 0.38 mmol) in THF (2 mL) was added. The reaction mixture was stirred between −78 and −60 °C for 1 h and then quenched by the addition of saturated aqueous NH$_4$Cl (2 mL). After warming to room temperature, the two layers were separated, and the aqueous layer was extracted with ether (3 × 5 mL). The combined organic layers were washed (brine), dried (MgSO$_4$), and concentrated to give a light yellow oil. Flash chromatography (hexane to 5% EtOAc in hexane) provided epoxide **1** as a colorless oil (121 mg, 91%): GC t_R = 9.11 min; ^{1}H NMR δ 5.18−5.14 (m, 2H), 2.70 (t, 1H, J = 5.9 Hz), 2.16−1.97 (m, 10H), 1.70−1.55 (m, 2H), 1.61 (s, 6H), 1.41 (s, 2H), 1.30 (s, 3H), 1.27 (s, 3H), 0.09 (s, 9H); ^{13}C NMR δ 135.7, 134.0, 124.8, 123.3, 78.7, 77.3, 64.1, 58.2, 39.6, 36.3, 28.1, 27.4, 26.5, 24.8, 19.4, 18.7, 16.1, 15.9, 6.9, −2.2; IR (neat) cm^{-1} 2955, 2918, 2850, 2215, 1450, 1376, 1245, 1172, 1125, 852.

Tricyclization Procedures. Analytical cyclizations were performed using 1.5−5 mg of polyene **1**. Semipreparative and preparative cyclizations were performed using 25−50 and 100−150 mg of polyene **1**, respectively.

Preparative Cyclization of 1 Using ZSM-5. To a suspension of acid-treated zeolite ZSM-5 (Si/Al = 30, 600 mg, 5-fold excess by weight) in dichloroethane (DCE, 100 mL) at room temperature was added a solution of **1** (120 mg, 0.35 mmol) in 1 mL of DCE. The mixture was stirred for 1 min at room temperature and then rapidly heated to reflux. After 15 min, the reaction flask was cooled to room temperature, the suspension was filtered through a fritted glass funnel, and the recovered zeolite was rinsed consecutively with ether and methanol (3 × 3 mL each). The combined filtrate was dried over MgSO$_4$, filtered, and concentrated. The resulting oil was purified by flash chromatography (5% EtOAc in hexane) to provide tricycle **2a** (51 mg, 53%), bicyclic ether **5** (10 mg), ketone **3** (1.3 mg), and a mixture of tricyclic and partially cyclized materials (9.8 mg, mixture of **6**, **7**, **2b** and **2c**).

2a: GLC t_R = 8.78 min; ^{1}H NMR δ 4.69−4.62 (m, 2H), 3.2 (dd, 1H, J = 6.1, 2.2 Hz), 2.61−2.50 (m, 1H), 2.41−2.29 (m, 1H), 1.80−1.39 (m, 10H), 1.34−1.02 (m, 2H), 0.99 (s, 3H), 0.98 (s, 3H), 0.87 (s, 3H), 0.80 (s, 3H); ^{13}C NMR δ 199.9, 113.3, 79.2, 62.0, 56.0, 44.5, 38.8, 38.3, 38.0, 37.1, 28.1, 27.1, 26.8, 21.6, 20.5, 19.1, 15.9, 15.2; IR (neat) cm^{-1} 3383, 2938, 2860, 1961, 1462, 1450, 1041, 1023, 843.

3: GLC t_R = 9.40 min; ^{1}H NMR δ 5.18 (br m, 1H), 5.16−5.09 (m, 1H), 2.65 (sextet, 1H, J = 6.6 Hz), 2.53 (t, 2H, J = 7.4 Hz), 2.25−2.16 (m, 6H), 2.11−1.87 (m, 4H), 1.60 (s, 6H), 1.41 (br s, 2H), 1.09 (d, 6H, J = 6.6 Hz), 0.08 (s, 9H); ^{13}C NMR δ 214.6, 135.8, 133.9, 124.7, 123.4, 78.8, 77.5, 40.9, 39.6, 39.1, 33.5, 28.1, 26.5, 19.4, 18.2, 16.1, 6.9, −2.1; IR (neat) cm^{-1} 2969, 2917, 2226, 1712, 1472, 1444, 1387, 1248, 850.

4: GLC t_R =9.69 min; ^{1}H NMR δ 5.18−5.12 (m, 2H), 4.92 (br s, 1H), 4.83 (br s, 1H), 4.03 (t, 1H, J = 6.6 Hz), 2.18−1.97 (m, 10H), 1.72 (s, 3H), 1.67 (m, 2H), 1.60 (s, 6H), 1.41 (br s, 2H), 0.08 (s, 9H); ^{13}C NMR δ 147.5, 135.8, 134.7, 124.7, 123.4, 110.9, 78.8, 77.0, 75.6, 39.6, 35.7, 33.2, 28.1, 26.5, 19.4, 17.6, 16.1, 15.9, 6.9, −2.1; IR (neat) cm^{-1} 3370, 2957, 2915, 2856, 2221, 1448, 1251, 1174, 851.

5: GLC t_R = 8.97 min; ^{1}H NMR δ 5.18 (br m, 1H), 3.71 (d, 1H, J = 5.9 Hz), 2.16 (br s, 6H), 1.99−1.76 (m, 4H), 1.72−1.36 (m, 3H), 1.60 (br s, 3H), 1.41 (br s, 2H), 1.32 (s, 3H), 1.06 (s, 3H), 1.01 (s, 3H), 0.08 (s, 9H); ^{13}C NMR δ 136.2, 123.4, 86.69, 86.04, 78.70, 55.22, 45.21, 39.81, 38.97, 29.67, 28.06, 26.07, 25.73, 23.37, 19.42, 18.89, 16.04, 6.92, −2.12; IR (neat) cm^{-1} 2954, 1250, 1004, 850.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of polyene **1** and cyclization products, as well as X-ray structure data for tricycle **2a** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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