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Stereoselective Disposition of the Geminal Dimethyl Group in the Cyclization of Geranyl Acetate under Zeolite Confinement Conditions

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The stereochemistry in the acid-catalysed biomimetic cyclization of [8,8,8-D_3]geranyl acetate was examined in solution and under conditions of zeolite Y confinement. In the intrazeolite reaction the *gem*-allylic methyl group adopts a diastereoselective disposition in the cyclization product (64 % *dr*). In contrast, the *gem*-dimethyl disposition in a homogeneous medium ($ClSO_3H$/2-nitropropane) proceeds with negligible diastereoselectivity (*dr* < 5 %). The enhanced diastereoselection within the zeolite is attributed to the proximity of the nucleophilic double bond to the intermediate carbocation, as a result of confinement (entropy effect).

Introduction

The fascinating enzyme-catalysed cyclization of polyene terpenoids has attracted much interest in the bioorganic community over the past 50 years. Product selectivity has been shown to be a delicate synergism between substrate conformation within the enzyme cavities (cyclases) and suitable positioning of the amino acid residues that initiate and terminate the proton-induced chain reactions.[1] Moreover, it has been established through labelling experiments that the stereochemistry of the terminal *gem*-dimethyl group (of the acyclic terpene) is disposed in a highly diastereoselective manner upon cyclization.[2]

Organic chemists have successfully accomplished non-enzymatic cyclizations of terpenoids by using either Brønsted[3] or Lewis acids[4] as catalysts. Ishihara and coworkers prepared a chiral acidic catalyst by combining a typical Lewis acid ($SnCl_4$) with a chiral Brønsted acid and achieved cyclization of terpenoids in an enantioselective manner for the first time.[5] Apart from the cationic cyclization, a catalytic free radical-based methodology for the cascade polycyclization of epoxy polyene terpenoids has recently been established[6] and has been applied as a key step in a significant number of terpenoid syntheses.[7]

Unlike in the enzyme-catalysed reactions, however, the stereochemical disposition of the *gem*-dimethyl groups in the products of Brønsted acid-catalysed cyclizations of polyene terpenoids seems to be completely non-diastereoselective. A Russian group reported over 30 years ago,[8] for example, that the FSO_3H-catalysed cyclization of methyl [8,8,8-D_3]geranate produced methyl [D_3]-α-cyclogeranate, in which two equivalent absorptions for the diastereotopic geminal methyls appeared in the ^1H NMR spectrum.

The use of acidic zeolites in the cyclization of terpenoids in the literature is limited. Sen and co-workers[9] have used the H-forms of the small-pore zeolites A and ZSM-5 as promoters for cyclizations of silyl-substituted epoxide-containing polyenes with moderate to good product selectivities. Presumably cyclization in such porous materials occurs at the openings of the zeolite pores, since the sizes of those epoxy polyenes should not allow them to diffuse into the interiors of the cages. Our group's interests have recently been focused on the application of the slightly acidic[10] zeolite NaY as both microreactor and catalyst to achieve biomimetic cyclizations of terpenoids. Zeolite NaY is a crystalline aluminosilicate, the primary structure of which is made up of edge-sharing SiO_4^{4-} and AlO_4^{5-} tetrahedral,[11] the 3D zeolite framework consisting of supercages of approximately 13 Å in interior diameter. The supercages are interconnected by four "windows", which are tetrahedrally distributed around each cage and have pore entrance diameters of around 7.5 Å.

Results and Discussion

We were pleased to find[12] that small acyclic terpenoids such as geranyl, neryl or farnesyl derivatives undergo biomimetic cyclization in moderate to excellent yield on adsorption within the confined environment of NaY, dried at 120–130 °C under vacuum (10^{-4} Torr) for at least 6 h prior to use. Hexane was the solvent of choice in the heterogeneous reaction slurry, as it has no affinity for the polar intrazeolite environment and allows the reactant terpenes to be adsorbed into the zeolite cavities. The reaction condi-

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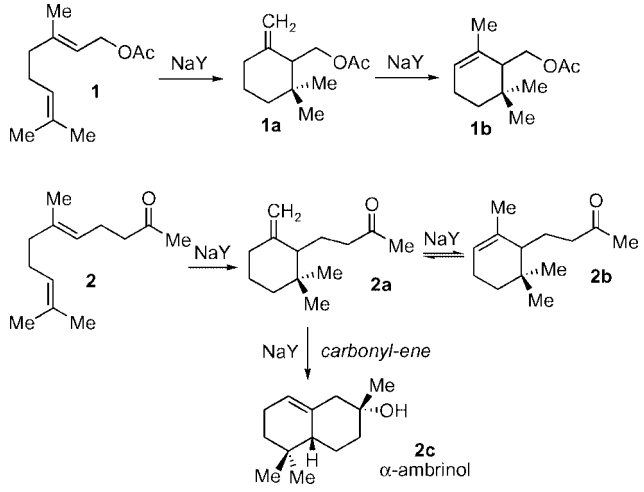
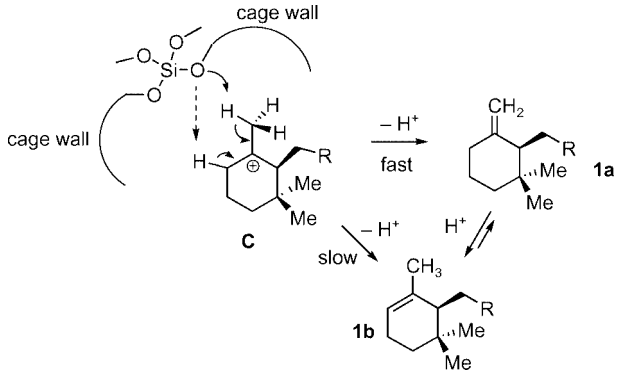
tions resemble those already applied in other types of intrazeolite reactions.[13] Geranyl acetate (**1**) cyclizes to give the corresponding γ- (**1a**) and α-cyclogeranyl (**1b**) isomers in excellent yield (Scheme 1). Initially, **1a** predominates, isomerizing to the thermodynamically more stable **1b** with prolonged reaction time or higher reaction temperature. In addition, geranylacetone (**2**) is selectively transformed into α-ambrinol (**2c**) by a tandem sequence involving a 1,5-diene cyclization followed by a highly diastereoselective intramolecular carbonyl-ene reaction of γ-cyclogeranylacetone (**2a**). Similar cyclization results were reported almost simultaneously by a Chinese group[14] using zeolites NaY and FeY.



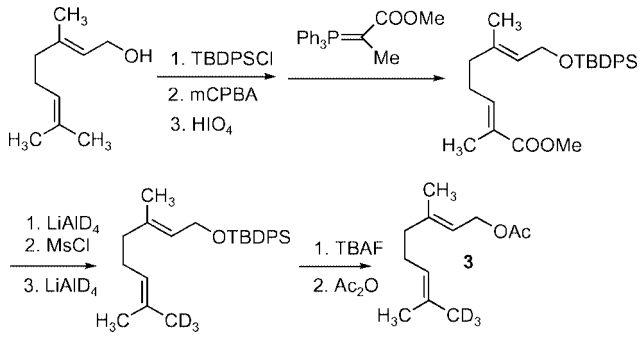
Scheme 1. Zeolite NaY-promoted cyclization of terpenoids.

The predominant formation of γ-cyclogeranyl acetate (**1a**) when the reaction was carried out at ambient temperature could be envisioned as proceeding through kinetically controlled deprotonation of the cyclized carbocation **C** (Scheme 2) by oxygen in the Si–O–Si bonds in the interiors of the zeolite supercages. The methyl group next to the cyclized carbocation is more accessible (than the hydrogen atoms on the cyclohexyl ring) for proton abstraction by the "zeolite wall". The subsequent transformation of **1a** to **1b** could be envisioned as a thermodynamically controlled acid-catalysed process.



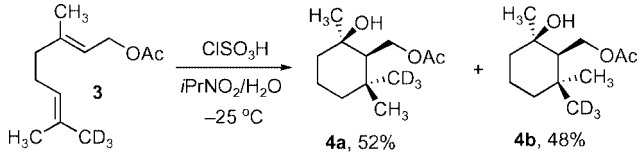
Scheme 2. Possible origin of the intrazeolite product selectivity.

We sought to study the influence of the confined intrazeolite environment on the stereochemical disposition of the geminal dimethyl group in the cyclization of a model terpenoid, namely [8,8,8-D_3]geranyl acetate (**3**). The synthesis of **3** was accomplished in nine steps, in 13% overall yield and with >97% geometrical purity with respect to the C6–C7 double bond (Scheme 3), by a modification of known literature procedures.[2b,15]



Scheme 3. Synthesis of [8,8,8-D_3]geranyl acetate (**3**).

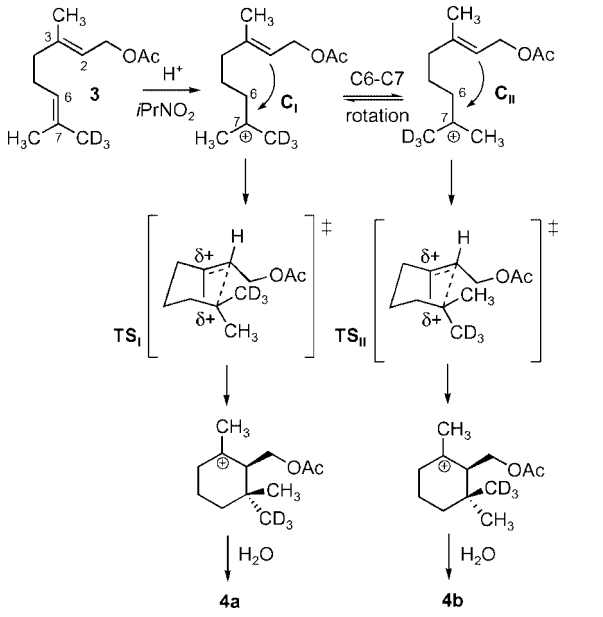
Initially we examined the cyclization of **3** in the presence of $ClSO_3H$[16] as the acid catalyst in solution in 2-nitropropane containing traces of H_2O[17] at –25 °C, in order to probe the signals corresponding to the diastereotopic *gem*-dimethyl groups in the cyclogeranyl products by ^1H NMR. The only products of the crude reaction mixture were the two diastereomeric compounds **4a** and **4b**,[18] in a ratio of 52:48 (Scheme 4). This result concurs with stereochemical studies previously reported for the cyclization of methyl geranate.[8]



Scheme 4. Stereochemistry in the $ClSO_3H$-catalysed cyclization of **3** in *i*$PrNO_2$.

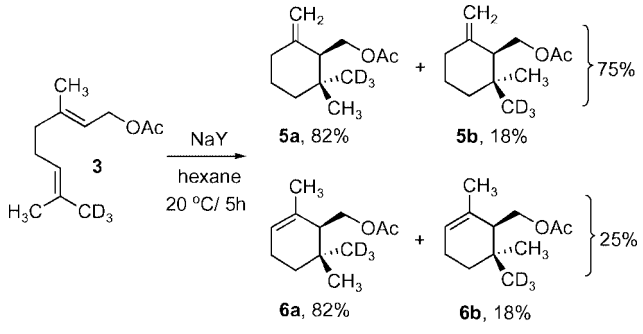
The lack of diastereoselection in the $ClSO_3H$-catalysed transformation of **3** into **4a**+**4b** indicates that extensive rotation around the C6–C7 bond of the initially formed tertiary carbocation $\mathbf{C_I}$ is possible, thus forming rotamer $\mathbf{C_{II}}$ (Scheme 5). Subsequent cyclization of $\mathbf{C_I}$ and $\mathbf{C_{II}}$ via the chair-like transition states $\mathbf{TS_I}$ and $\mathbf{TS_{II}}$, respectively, followed by trapping of the cyclized carbocations with the traces of H_2O from the solvent, would afford almost equimolar formation of **4a** and **4b**.

In contrast, the cyclization of **3** under zeolite confinement conditions (NaY) afforded, after 5 h at ambient temperature, a mixture of the deuterated γ-cyclogeranyl and α-cyclogeranyl acetates in 80% isolated yield and in a relative ratio of ca. 3:1 (Scheme 6, Figure 1). The diastereomeric product ratios of **5a**/**5b** for γ-cyclogeranyl acetate, and **6a**/**6b** for the α-cyclogeranyl acetate were identical (82:18). When the reaction was performed at 70 °C for 1 h, α-cyclogeranyl acetate (**6**) was mainly formed, yet the diastereomeric ratio (**6a**/**6b** ≈ 80:20) remained almost un-



Scheme 5. Mechanism for the $ClSO_3H$-catalysed cyclization of **3**.

changed (see Supporting Information). Moreover, a ratio of **6a/6b** ca. 80:20 was again observed when **3** was confined within the highly acidic zeolite HY (25 °C, 1 h).



Scheme 6. Intrazeolite cyclization of **3** at 20 °C.

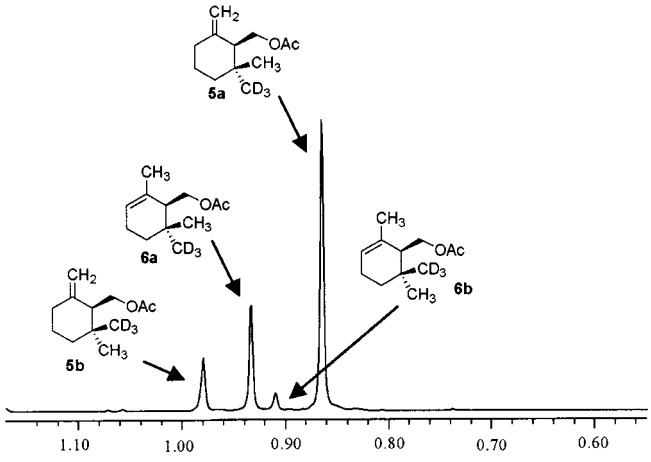


Figure 1. Part of the ^1H NMR spectrum of a mixture of products **5a**, **5b**, **6a** and **6b** in the 0.8–1.1 ppm region.

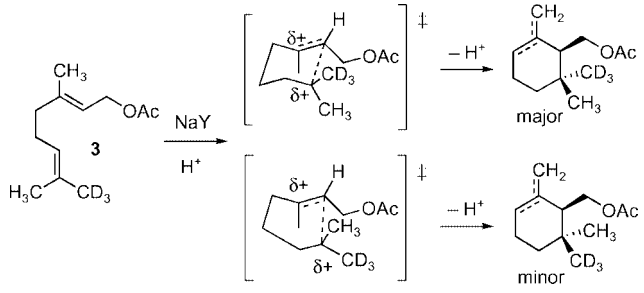
To ensure that all the reacting substrate had been adsorbed into the zeolite cavities, low loading levels were used (n = 0.1–0.2). This loading essentially corresponds to 1 molecule of geranyl acetate per 5–10 zeolite supercages. The intrazeolite results were identical when zeolite NaY from three different commercial sources (Aldrich, Degussa, Zeolyst) was used, while the reaction mass balance was >82% in all experiments apart from in the reaction with HY, where it was moderate (65%). In one experiment, the reaction was stopped before completion, and the unreacted **3** was examined, but no isomerization of the C6–C7 double bond was detectable by ^1H NMR spectroscopy. The stereochemistry of all the products was assigned by nOe experiments. Upon irradiation of the more shielded *gem*-methyl group of γ-cyclogeranyl acetate (δ = 0.87 ppm) and of the more deshielded one in the case of α-cyclogeranyl acetate (δ = 0.94 ppm), significant signal enhancement of the signals of the diastereotopic methylene hydrogen atoms of the $-CH_2OAc$ functionality was observed (see Supporting Information), indicative of a *cis* arrangement between them.[19]

In addition, for the reaction in solution ($ClSO_3H$, 2-nitropropane), we wanted to exclude the possibility that the *gem*-dimethyl group might initially dispose stereoselectively (but not stereospecifically), but that the cyclogeranyl carbocation might revert to a mixture of $\mathbf{C_I}$ and $\mathbf{C_{II}}$ through a possible reversibility in the cyclization step (Scheme 5), with gradual loss of diastereoselectivity thus taking place. For this purpose we treated a mixture containing mainly **5a** and **5b** (dr = 64%) produced from the intrazeolite reaction of **3** at ambient temperature (Scheme 6) with $ClSO_3H$ in dry iPrNO$_2$ under experimental conditions strictly identical to those applied in the cyclization of **3** in solution. A mixture of **6a/6b** was isolated in a ratio of ca. 80:20, which implies the lack of such a mechanistic scenario.

We propose that this interesting enhanced diastereoselectivity seen in the cyclization of **3** in NaY and HY might be attributable to a change in the energy reaction profile on going from the homogeneous solution to the zeolite environment. In solution, the initially formed tertiary carbocation $\mathbf{C_I}$ (Scheme 5) presumably has a barrier to rotation around the C6–C7 bond approximately 2 kcal mol^{-1} lower than the activation energy of its accompanying cyclization step, so almost 95% of the $\mathbf{C_I}$ population undergoes reversible rotation around the C6–C7 bond prior to cyclization, and essentially a product ratio of **4a/4b** = 52:48 results. In the NaY or HY, however, the stereochemical outcome would require that around 40% of the $\mathbf{C_I}$ population should undergo such a rotation prior to the nucleophilic attack by the C2–C3 double bond. In other words, the barrier to rotation around the C6–C7 bond of $\mathbf{C_I}$ in the intrazeolite reaction is slightly higher than the activation energy for the cyclization. These energy profile changes can be interpreted in terms of an entropy effect. In the confined zeolite cavity, the C2–C3 double bond is on average closer to the initially formed carbocation than is the case in the reaction in solution. This proximity contributes to a significant decrease in the activation energy of the cyclization step. We postulate

that the remarkable stereochemical dispositions[2] of the terminal *gem*-dimethyl groups in enzyme-catalysed cyclizations of terpenoids imply barriers to rotation around the C–$C_{carbocation}$ bonds in the transient dimethyl-substituted carbocations at least 3 kcal mol^{-1} higher than the activation energies of the accompanying C–C bond-formation steps. The confined environment of an enzyme cavity should favour such an energy profile, due to the close proximity of the reacting double bond and the carbocation, so the cyclization step would be almost barrierless.[1e–1f]

An alternative explanation for the observed diastereoselection in the intrazeolite cyclization reaction might be the major diastereomers (**5a** or **6a**) arising from chair-like transition states, while the minor diastereomers (**5b** and **6b**) arise from boat-like transition states (Scheme 7). This scenario would require that rotation around the C6–C7 bond of $\mathbf{C_I}$ be negligible (Scheme 5). Although it is difficult to distinguish between the two proposed mechanisms, the second explanation is less likely since the energy difference between a boat- and a chair-like transition state would be expected to be much higher than 0.8 kcal mol^{-1}.[20] Nevertheless, the current results clearly establish that, within zeolite Y, rotation around the C6–C7 bond of the initially formed carbocation is slower than its cyclization rate, as a result of the proximity of the nucleophilic C2–C3 double bond.



Scheme 7.

Conclusions

In conclusion, we have shown that the confined environment of the zeolite Y significantly alters the reaction energy profile for the cyclization of a model terpenoid (geranyl acetate) relative to the reaction in solution.

Experimental Section

General: Nuclear magnetic resonance spectra were obtained on a 500 MHz instrument. Isomeric purities were determined by ^{1}H NMR, ^{13}C NMR and by GC or GC-MS on an HP-5 capillary column. All spectra reported here were taken in $CDCl_3$.

Intrazeolite Cyclization of [8,8,8-D_3]Geranyl Acetate (3): [8,8,8-D_3]-Geranyl acetate (**3**, 20 mg) was added to a slurry containing NaY (0.5 g), previously dried[12] at 120 °C for at least 6 h under vacuum (10^{-4} Torr), in hexane (5 mL), and the heterogeneous mixture was either stirred at room temperature for 5–6 h or heated to 70 °C for 1 h. After that period, the reaction mixture was filtered, and the filtrate was kept. The solid material was further washed with methanol (2 × 5 mL for 30 min each time) and then filtered again. The combined solvent extracts were evaporated to afford the cyclized products α- and γ-cyclogeranyl acetate (16 mg, 80%). The ^{1}H NMR spectroscopic data for the labelled γ-cyclogeranyl and α-cyclogeranyl acetate (**5a/5b** and **6a/6b**, respectively) matched the spectroscopic data for **1a** and **1b** reported earlier by us,[12] with the only differences appearing in the region of 0.8–1.1 ppm, where the *gem*-methyl group absorptions reflect the ratios of **5a/5b** and **6a/6b**.

Cyclization of [8,8,8-D_3]Geranyl Acetate (3) Promoted by $ClSO_3H$ in 2-Nitropropane: [8,8,8-D_3]Geranyl acetate (20 mg, 0.1 mmol) was added at –25 °C to a solution of $ClSO_3H$ (0.18 μL, 0.26 mmol) in 2-nitropropane (as obtained from commercial sources, 0.3 mL). After 30 min, triethylamine (0.1 mL) dissolved in diethyl ether (2 mL) was added and the solution was washed with brine. The organic layer was dried with $MgSO_4$, the solvent was removed under vacuum, and the oily residue was chromatographed (hexane/ethyl acetate, 4:1) to afford the diastereomeric (2-hydroxy-2,6,6-trimethylcyclohexyl)methyl [D_3]acetate (**4a/4b**, 12 mg, 53% isolated yield) as a colourless oil. The ^{1}H NMR spectroscopic data for the mixture of the labelled **4a/4b** matched the spectroscopic data of the unlabelled cyclic alcohol reported by us earlier.[12]

Supporting Information (see also the footnote on the first page of this article): Experimental details for the synthesis of [8,8,8-D_3]geranyl acetate (**3**). Copies of ^{1}H and ^{13}C NMR spectra for the intermediate compounds in the synthesis of **3**, cyclization reactions, and nOe experiments.

Acknowledgments

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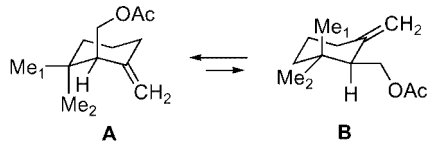
[17] The 2-nitropropane was used as received from commercial sources and contains traces of H_2O.
[18] The perprotio analogue of the diastereomeric deuterated alcohols **4a** and **4b** is a known compound,[12] and is formed stereoselectively in the halosulfonic acid-catalysed cyclization of geranyl acetate (see ref.[3]).
[19] The γ- and α-cyclogeranyl derivatives preferentially adopt conformations in which the $–CH_2OAc$ groups adopt pseudoaxial orientations (difference of approximately 0.5 kcal mol^{-1} relative to the pseudoequatorial). See: a) R. L. Snowden, J.-C. Eichenberger, S. M. Linder, P. Sonnay, C. Vial, K. H. Schulte-Elte, *J. Org. Chem.* **1992**, *57*, 955–960; b) C. Fehr, *Angew. Chem.* **1998**, *110*, 2509–2512; *Angew. Chem. Int. Ed.* **1998**, *37*, 2407–2409. Irradiation of the more shielded *gem*-methyl group in γ-cyclogeranyl acetate (**1a**), resonating at δ = 0.87 ppm, results in a moderate signal enhancement for the tertiary allylic hydrogen atom and a significant one for the methylene hydrogen atoms of the $–CH_2OAc$ functionality. The opposite enhancement trends were found upon irradiation of the more deshielded methyl group, resonating at δ = 0.99 ppm. The nOe enhancement trends presented above indicate that the methyl group resonating at δ = 0.87 ppm is *trans* to the tertiary allylic hydrogen atom, and the methyl group absorbing at δ = 0.99 ppm is *cis*. This argument can be explained by considering an equilibrium of conformers **A** and **B** for **1a**, with **A** being predominant.



conformers of **1a**

The pseudoequatorial *gem*-methyl group (Me_1) of conformer **A**, which after ring inversion is converted to pseudoaxial in conformer **B**, would be expected upon irradiation to enhance the signal of the $–CH_2OAc$ hydrogens significantly and the signal of the tertiary allylic hydrogen moderately. On the other hand, the pseudoaxial methyl group (Me_2) of conformer **A** (pseudoequatorial in conformer **B**) would be expected upon irradiation to give a significant signal enhancement of the tertiary allylic hydrogen atom and a moderate one for the $–CH_2OAc$. Similar nOe analysis holds for **1b**, which establishes that the *gem*-methyl *cis* to the $–CH_2OAc$ resonates at δ = 0.94 ppm, and the *trans* one at δ = 0.92 ppm. Moreover, from a combination of DEPT and 2D-NMR techniques it was found that the tertiary allylic hydrogen atom of **1a** resonates at δ = 2.16 ppm and that of **1b** at δ = 1.72 ppm.

[20] An energy difference of 0.8 kcal mol^{-1} between two transition states reflects a product ratio of around 80:20.

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