Biomimetic Cyclization of Small Terpenoids Promoted by Zeolite NaY: Tandem Formation of α-Ambrinol from Geranyl Acetone

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Dedicated to Professor Anastasios Varvoglis on the occasion of his retirement.

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Abstract: Zeolite NaY promotes efficiently the biomimetic cyclization of small acyclic terpenes. Geranyl and neryl acetone undergo a novel tandem 1,5-diene cyclization/carbonyl-ene reaction to form the natural product α-ambrinol isolated in >65% yield.

Keywords: α-ambrinol; green chemistry; heterogeneous catalysis; terpenes; zeolites

Introduction

The acid-promoted cyclization of polyene terpenoids is one of Nature's most significant pathways for the formation of a wide variety of cyclic or polycyclic biomolecules. The high degree of diastereoselectivity in these biogenetic pathways is controlled by confinement of the acyclic polyene molecules within the cavities of the enzymes called cyclases.[1] The conformational immobility of the reacting substrates in the confined environment allows the cascade attack of the proximal double bonds to an intermediate carbocation,[2] proceeding in a highly stereoselective manner. Non-enzymatic cyclization of the acyclic terpenoids has been achieved by various means, such as catalysis by protic acids,[3] super acids[4] or Lewis acids,[5] *via* radical-initiated pathways,[6] and by photoinduced electron-transfer.[7] The acid-catalyzed cyclization of polyenes (e.g., by FSO_3H) requires very low reaction temperatures (approximately −80 °C), multimolar excess of the acid relative to the substrate, while toxic nitro compounds are preferentially used as solvents.[8] In addition, increasing the reaction temperature results in a significant decrease of product selectivity.[8b]

We sought to examine the efficiency of the confined environment of zeolite NaY to carry out the biomimetic cyclization of polyene terpenoids. Zeolite NaY, whose pore size is around 7.5 Å,[9] is slightly acidic and contains both Brønsted[10] and Lewis[11] acid sites. The use of acidic zeolites in the cyclization of terpenoids is very limited in the literature. Sen and co-workers[12] have used the H-form of the small-pore zeolites A and ZSM-5, as promoters for the cyclization of epoxide-containing polyenes, with moderate to good product selectivity. It was postulated that cyclization is initiated at the opening of the zeolite pores, since the size of the substrates does not allow them to diffuse into the interior of the cages.

Results and Discussion

Geranyl acetate was chosen as a model terpenoid substrate and the reaction occurred by substrate adsorption into NaY in a hexane slurry. At low loading levels of n = 0.1–0.2, which practically means around 15–25 mg of geranyl acetate per 1 g of NaY, facile cyclization occurred at 25 °C after 15–20 minutes, to form a mixture of γ-cyclogeranyl acetate (**1a**), α-cyclogeranyl acetate (**1b**) and the minor terpenic alcohol **1c** as a single diastereomer[13] (Scheme 1). The products were extracted from the porous material by adding moistened THF or methanol (see Experimental Section). The ratio of **1a**/**1b** varies with the reaction time. At the initial stages, **1a** is formed predominately, whereas for prolonged intrazeolite treatment (1–2 hours), **1a** isomerizes to **1b** which finally becomes the major or only product. Alcohol **1c** was formed in 1–10% relative yield depending on the amount of H_2O present in the interior of the zeolite cages, despite its extensive drying at 120–130 °C under vacuum. At higher loading levels of approximately 2–3 mmol of geranyl acetate per 1 g of NaY, the cyclization proceeds in >75% isolated yield, however, it requires heating to 70 °C for 12–24 hours, with formation of

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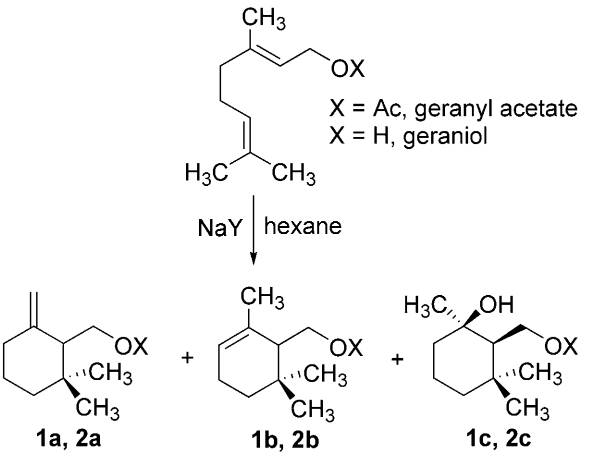
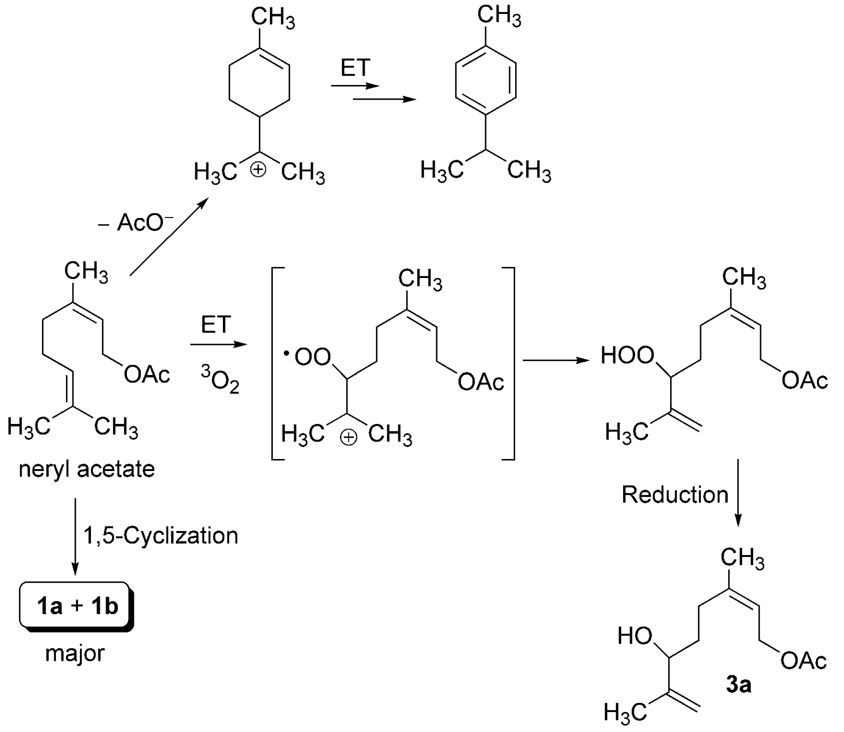


Scheme 1. Cyclization of geranyl acetate and geraniol by confinement within zeolite NaY.

1b in >92% selectivity. Under these higher loading level conditions, **1c** was formed in traces (<0.5%). The mass balance of all intrazeolite reactions was always >75%.

Under the same reaction conditions (reaction time, loading levels) applied to geranyl acetate, geraniol undergoes analogous cyclization reaction (Scheme 1) without suffering from significant dehydration, to form a mixture of γ- and α-cyclogeraniol[14] (**2a** and **2b**, respectively) in 65% isolated yield. The ratio of **2a**/**2b** again depends on the reaction conditions. In addition to **2a** and **2b**, the minor terpenic diol **2c** (1–15%) was isolated and fully characterized,[13] while the aromatic *p*-cymene was formed in 2–4% relative yield. Under superacidic conditions,[15] or in the presence of $Tl(ClO_4)_3$,[16] geraniol is known to undergo cyclization to form mainly iridoid-type bicyclic furans.

Neryl acetate reacted more slowly compared to geranyl acetate, and gave in addition to the cyclogeranyl acetates **1a** and **1b** (~60% relative yield), the aromatic component *p*-cymene (~30%) and various amounts (~10–15%) of the allylic alcohol **3a**.[17] Formation of *p*-cymene can be envisioned through intramolecular nucleophilic attack of the terminal double bond at the allylic carbon atom to eliminate the acetate functionality and form a mixture of *p*-menthadienes. Such compounds (limonene, terpinolene, etc.) are known to dehydrogenate readily to *p*-cymene within NaY.[18] The surprising formation of **3a** can be tentatively rationalized by invoking an electron-transfer (ET) mechanism. Ionization of organic compounds *via* an ET pathway within faujasites under non-irradiative conditions is well known.[19] The postulated radical cation of neryl acetate most probably reacts with molecular oxygen to form an allylic hydroperoxide, which in turn is reduced to the allylic alcohol **3a** (Scheme 2). We have noticed in our laboratory that generally hydroperoxides are partially reduced to the corresponding alcohols by confinement within NaY, or even by silica gel under chromatographic conditions. Under an inert atmosphere (nitrogen gas), allylic alcohol **3a** was formed in <3% relative yield, which most

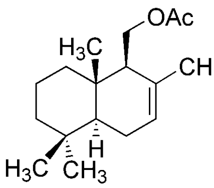


Scheme 2. Postulated pathway for the formation of by-product **3a**, and the transformations of neryl acetate within NaY.

likely indicates that the oxygen atom of the hydroxyl functionality arises from the participation of molecular oxygen, in accordance with the above-postulated mechanism. Nevertheless, this ene-type allylic hydroxylation reaction seems to be general with other trisubstituted alkenes, and is currently under investigation from the mechanistic and synthetic points of view.

On the other hand, neryl alcohol dehydrates substantially under the reaction conditions (NaY) and gives cyclogeraniols **2a** and **2b** in only 15–20% relative yield, accompanied by a complicated non-polar product mixture.

The higher terpene analogue farnesyl acetate, afforded at loading levels of 50 mg per 1 g of NaY (12 hours at 70 °C), drimenyl acetate[20] (**4a**), in low yield (up to 20%). The majority of the reaction mixture consisted of a non polar fraction containing at least 8 sesquiterpenes possessing the molecular formula $C_{15}H_{24}$ (GC-MS). It is likely that they arise from elimination of the acetate group whereby the resulting carbocation undergoes several skeletal rearrangements to form the sesquiterpene mixture. In addition, farnesol suffers within NaY from substantial dehydration, as judged by the formation of a complicated reaction mixture (mostly non polar sesquiterpenes).

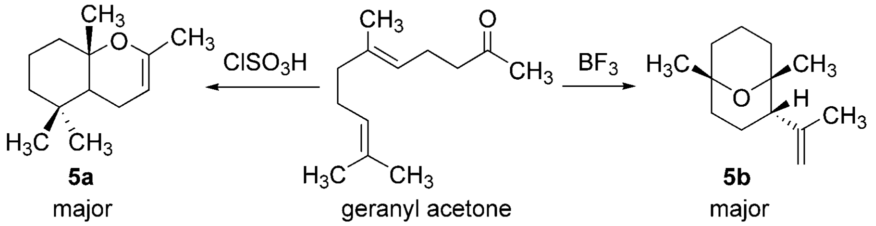


4a

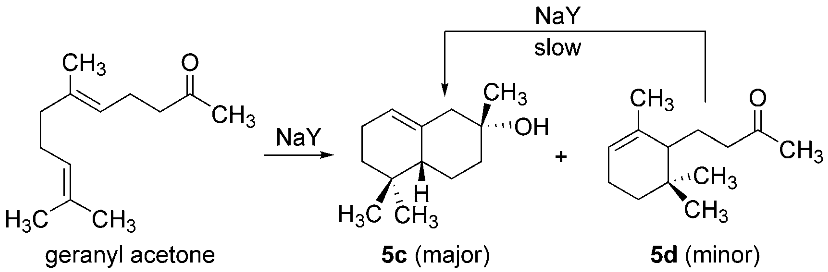
We next studied the NaY-promoted transformation of geranyl acetone. Its acid-catalyzed cyclization in solution has been studied in the past (Scheme 3) and found to give mainly the chromene **5a** when treated with strong Brønsted acids,[8b] such as FSO_3H or $ClSO_3H$, and the bicyclic ether **5b** in low diastereomeric excess as the major product under Lewis acid conditions[21] (BF_3 or $SnCl_4$).

Upon treatment with NaY, however, no **5a** or **5b** was produced. Instead, the natural product (±)-α-ambrinol (**5c**) was mainly formed in a highly diastereoselective manner (>97% de), accompanied by dihydro-α-ionone (**5d**) as a by-product (Scheme 4). The relative yield of α-ambrinol compared to dihydro-α-ionone depends on the reaction time. By adsorbing 0.5 mmol of geranyl acetone in 1 g of NaY, and refluxing at 70 °C for 6 hours the ratio of **5c**/**5d** was 60/40, however, for prolonged reaction times (up to 48 hours) a ~95/5 relative ratio of **5c**/**5d** can be achieved. Dihydro-α-ionone itself was also found to give slowly α-ambrinol (35% relative yield after 3 days at 70 °C). Moreover, the geometrical isomer of geranyl acetone, neryl acetone, cyclizes within NaY more slowly compared to geranyl acetone giving, however, mainly **5c** relative to **5d**, just as geranyl acetone did.

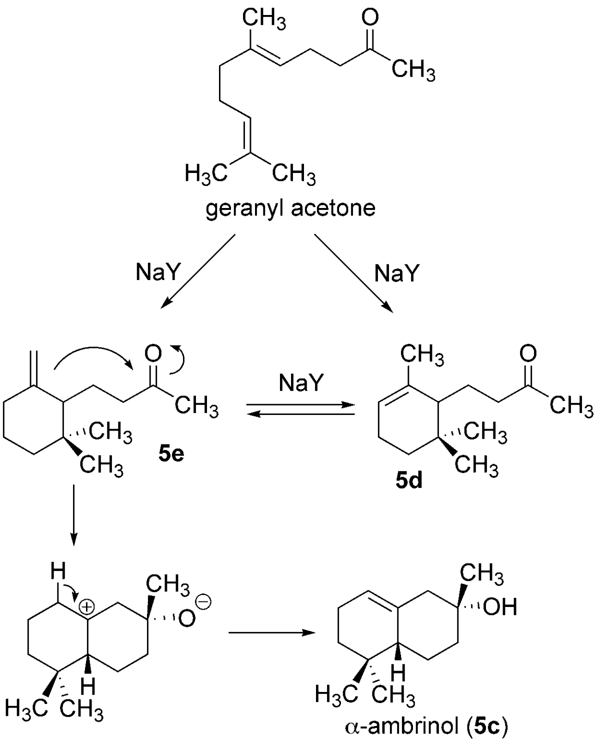
The formation of α-ambrinol (**5c**) from geranyl acetone can be explained by considering an initial cyclization of the 1,5-diene moiety to form an intermediate mixture of γ- and α-cyclogeranyl derivatives **5e** and **5d**, respectively (Scheme 5). The isomeric **5e** undergoes a tandem intermolecular carbonyl-ene reaction to form α-ambrinol. In addition, **5d** slowly isomerizes to the less thermodynamically favourable **5e**, which in turn gives **5c**. It is likely that the carbonyl group of **5e** is activated by coordination to a Na^+ within the zeolite supercages, to undergo the intermolecular ene attack. Okachi and Onaka[22] have shown that formaldehyde encapsulated within NaY is highly activated by Na^+ coordina-



Scheme 3. Cyclization of geranyl acetone under Brønsted or Lewis acid conditions.



Scheme 4. Cyclization of geranyl acetone promoted by NaY.



Scheme 5. Proposed mechanism for the formation of α-ambrinol (**5c**) from geranyl acetone within NaY.

tion, and affords readily carbonyl-ene reactions with a variety of alkenes. To the best of our knowledge, this is the first example of a tandem 1,5-diene cyclization/carbonyl-ene reaction, and needs further attention from the synthetic point of view. Kraus and Kim reported recently[23] the first example of a tandem Diels–Alder/carbonyl-ene reaction, which leads stereoselectively to the formation of *cis*-decalins.

α-Ambrinol (**5c**) is a constituent of many essential oils,[24] and a valuable fine chemical in the perfume industry. Apart from a limited number of literature synthetic procedures,[25] many patented syntheses can be also found. However, the shortest reported synthetic methodology requires four consecutive steps, which reveals the superiority of our novel methodology not only because of its simplicity, but from the environmental point of view. Hence, the environmentally benign nature of the zeolite medium and its application in the "one-pot" synthesis of α-ambrinol (**5c**) from the relatively cheap mixture of geranyl and neryl acetone, justifies further exploration and optimization (such as to carry out the reaction in the presence of microwave irradiation).

Conclusion

In conclusion, we have shown that zeolite NaY promotes the efficient biomimetic cyclization of small acyclic terpenoids. For the case of geranyl and neryl acetones the valuable natural product (±)-α-ambrinol (**5c**) was formed in one step, *via* a tandem cyclization/ene reaction, in relatively good yield and by using an environmentally friendly procedure. We are currently exploring new applications of NaY and other acidic zeolites[26] in the cyclization of terpenes and epoxyterpenes.

Experimental Section

General Remarks

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 herein were taken in $CDCl_3$. The terpenes used in this study are commercially available. Zeolite NaY (obtained from Aldrich or Degussa) was dried at 120–130 °C under vacuum (10^{-4} torr) for at least 6 hours prior to use.

General Procedure for the Intrazeolite Reactions

To a slurry containing 1 g of dry NaY in 10 mL of hexane, were added 0.3 g of geranyl acetate and the heterogeneous mixture was refluxed at 70 °C for 12 hours. The reaction mixture was cooled to room temperature and then filtered. The filtrate was kept and the solid material was further repeatedly treated with 2 × 10 mL of methanol for 30 minutes each time, and then filtered again. The combined solvent extracts were evaporated to afford 0.25 g of the cyclized products (mainly 1b). An alternative extraction procedure can be applied by adding 10 mL of moistened tetrahydrofuran to the hexane slurry, stirring for 2 hours and then filtration. The later protocol generates often some impurities in the crude reaction mixture by the air oxidation of THF. If necessary, the crude products were chromatographed to remove solvent impurities. The yields of the isolated products after chromatography vary from 60 to 70%. For the case of geranyl acetone, the reaction was performed by refluxing for 24 hours a slurry containing 0.5 g of the terpene and 2 g of NaY in 20 mL of hexane, to afford 0.44 g of 5c and 5d in a ratio 4/1. α-Ambrinol (5c) can be easily separated from dihydro-α-ionone by flash column chromatography using hexane/ethyl acetate = 5/1 as eluent (0.30 g, 60% yield). The isolated yield can rise up to 75% by extending the reaction time to 48 hours.

NMR Spectral Data

1a: ^{1}H NMR: $\delta = 4.83$ (br s, 1H), 4.60 (br s, 1H), 4.26 (dd, 1H, $J_1 = 11.0$ Hz, $J_2 = 5.0$ Hz), 4.22 (dd, 1H, $J_1 = 11.0$ Hz, $J_2 = 11.0$ Hz), 2.17 (m, 2H), 2.05 (m, 2H), 2.02 (s, 3H), 1.55 (m, 1H), 1.43 (m, 1H), 1.33 (m, 1H), 0.99 (s, 3H), 0.87 (s, 3H); ^{13}C NMR: $\delta = 171.22$, 147.09, 109.73, 62.81, 52.12, 37.85, 34.31, 33.40, 28.73, 25.04, 23.37, 21.07.

1b: ^{1}H NMR: $\delta = 5.46$ (br s, 1H), 4.18 (dd, 1H, $J_1 = 11.5$ Hz, $J_2 = 6.0$ Hz), 4.06 (dd, 1H, $J_1 = 11.5$ Hz, $J_2 = 3.5$ Hz), 2.03 (s, 3H), 1.97 (br m, 2H), 1.79 (br s, 1H), 1.73 (s, 3H), 1.47 (m, 1H), 1.20 (m, 1H), 0.94 (s, 3H), 0.92 (s, 3H): ^{13}C NMR: $\delta =$ 171.09, 132.24, 123.17, 64.29, 48.74, 31.99, 31.73, 27.33, 27.00, 22.96, 22.87, 21.16.

1c: ^{1}H NMR: $\delta = 4.34$ (br d, 2H), 2.47 (br s, 1H), 2.07 (s, 3H), 1.78 (m, 1H), 1.62 (m, 2H), 1.42 (m, 3H), 1.27 (m, 1H), 1.23 (s, 3H), 1.03 (s, 3H), 0.88 (s, 3H); ^{13}C NMR: $\delta = 170.96$, 72.66, 63.52, 54.83, 42.42, 41.82, 34.14, 32.72, 24.04, 21.75, 21.26, 20.04.

2a: ^{1}H NMR: $\delta = 4.96$ (br s, 1H), 4.76 (br s, 1H), 3.73 (dd, 1H, $J_1 = 11.0$ Hz, $J_2 = 5.0$ Hz), 3.63 (dd, 1H, $J_1 = 11.0$ Hz, $J_2 = 11.0$ Hz), 2.12 (m, 2H), 2.04 (m, 2H), 1.20–1.58 (m, 3H), 0.96 (s, 3H), 0.87 (s, 3H).

2b: ^{1}H NMR: $\delta = 5.60$ (br s, 1H), 3.75 (s, 2H), 2.00 (m, 2H), 1.75 (s, 3H), 1.45 (m, 1H), 1.20 (m, 1H), 1.03 (s, 3H), 0.89 (s, 3H).

2c: ^{1}H NMR: $\delta = 3.94$ (m, 2H), 1.80 (m, 1H), 1.64 (m, 1H), 1.61 (m, 1H), 1.45 (m, 2H), 1.32–1.41 (m, 2H), 1.38 (s, 3H), 1.05 (s, 3H), 0.79 (s, 3H); ^{13}C NMR: $\delta = 74.87$, 62.03, 56.03, 43.23, 42.22, 33.53, 32.87, 23.46, 21.61, 20.22.

3a: ^{1}H NMR: $\delta = 5.37$ (br. t, 1H, $J = 7.0$ Hz), 4.96 (s, 1H), 4.85 (s, 1H), 4.60 (m, 2H), 4.02 (m, 1H), 2.17 (m, 2H), 2.05 (s, 3H), 1.77 (s, 3H), 1.74 (s, 3H), 1.63 (m, 2H); ^{13}C NMR: $\delta = 171.14$, 147.39, 142.29, 119.58, 111.04, 75.04, 61.06, 33.13, 28.00, 23.32, 21.06, 17.69.

5c: ^{1}H NMR: $\delta = 5.46$ (br s, 1H), 2.07 (dd, 2H, $J_1 = 13.0$ Hz, $J_2 = 2.0$ Hz), 2.00 (m, 2H), 1.84 (br s, 1H), 1.71 (m, 1H), 1.18–1.51 (m, 5H), 1.22 (s, 3H), 0.92 (s, 3H), 0.87 (s, 3H); ^{13}C NMR: $\delta = 137.36$, 122.01, 70.26, 49.82, 47.24, 38.95, 33.28, 31.10, 29.24, 28.00, 25.97, 25.02, 22.75.

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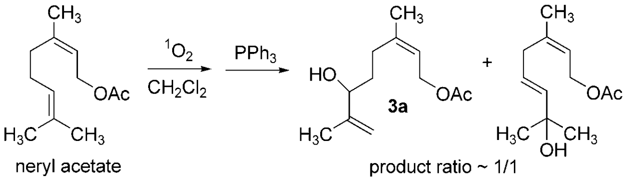

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