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Terpene cyclization catalysed inside a self-assembled cavity

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In nature, complex terpene natural products are formed by the so-called tail-to-head terpene (THT) cyclization. The cationic reaction cascade is promoted efficiently in complex enzyme pockets, in which cationic intermediates and transition states are stabilized. In solution, the reaction is hard to control and man-made catalysts able to perform selective THT cyclizations are lacking. We herein report the first example of a successful THT cyclization inside a supramolecular structure. The basic mode of operation in cyclase enzymes was mimicked successfully and a catalytic non-stop THT was achieved with geranyl acetate as the substrate. The results presented have implications for the postulated reaction mechanism in cyclase enzymes. Evidence indicates that the direct isomerization of a geranyl cation to the *cisoid* isomer, which so far was considered unlikely, is feasible.

Nature's extraordinary elegance when performing chemical reactions has fascinated and inspired chemists for a long time. Arguably, one of the most complex organic transformations performed in living organisms is the tail-to-head[1] terpene (THT) cyclization[2,3]. It allows the construction of the most diverse class of natural products, namely terpenes, through nature's version of combinatorial chemical synthesis. Thousands of different natural products are formed from just a handful of simple, acyclic starting materials: geranyl pyrophosphate (GPP) (**1** (Fig. 1a), monoterpenes), farnesyl pyrophosphate (**2**, sesquiterpenes) and geranylgeranyl pyrophosphate (**3**, diterpenes). Nature utilizes enzymes, termed cyclases or terpene synthases, to bind the acyclic terpene diphosphate in a hydrophobic reaction pocket. The reaction cascade is initiated by a metal(II)-triggered departure of the diphosphate leaving group, generating, in the case of GPP (**1**), the first carbocationic intermediate **4a** (Fig. 1b)[2–8]. A direct cyclization of cation **4a** into the α-terpinyl cation **6** is not possible; it has to be preceded by isomerization into the *cisoid* conformer **4b**. It was postulated that cation **4a** has to collapse to linalyl pyrophosphate (linalyl-PP) (**5a**) to allow the isomerization to the *cisoid* isomer **5b**, which is suitable for cyclization. It was argued that the free-energy barrier for the direct rotation of the allylic cation **4a** is relatively high (about 55 kJ mol^{-1}) and therefore unlikely[4,9]. We herein present evidence that such a direct isomerization is possible in an enzyme-like catalyst. The α-terpinyl cation **6**, formed by the cyclization of the *cisoid* cation **4b**, is a key intermediate in the biosynthesis. It is converted into a variety of different monoterpene products, depending on the properties of the cyclase. If a water molecule is present in the reaction pocket, α-terpineol (**7**) can be formed, which may be cyclized further into eucalyptol (**8**)[2,4,5,8]. Alternatively, a direct proton elimination of **6** would deliver terpinolene (**9**) or limonene (**10**). If, however, cation **6** is stabilized enough and nucleophiles excluded within the reaction pocket, it is able to undergo alternative intramolecular cyclizations or rearrangements. For example, it can rearrange into cation **11** via a hydride shift and then deliver α-terpinene (**12**). In any case, a wide selection of reaction pathways is available for the high-energy cationic intermediates: intra- or intermolecular substitution reactions, eliminations, rearrangements, oligomerizations and polymerizations. Not surprisingly, in solution THT reactions prove to be hard to control, and give mixtures of acyclic and, to a much lesser extent, cyclic products. Especially, the conversion of geranyl substrates in solution is problematic[4].

As the acyclic terpene alcohols geraniol (GOH), farnesol and geranylgeraniol are readily available, a direct selective conversion into cyclic terpenes is highly desirable. What are the main differences between THT cyclizations in solution and those in the hydrophobic enzyme pocket? (1) The initial ionization requires harsh conditions (a strong Lewis or Brønsted acid) in solution. In the cyclase, however, the pyrophosphate leaving group is removed under neutral conditions (optimum pH 6–7)[4] with the help of divalent metal ions. (2) In solution, high-energy cationic intermediates are susceptible to undesired side reactions (elimination or quenching by nucleophiles). In the enzyme pocket, cationic key intermediates are stabilized by cation–π and cation–dipole interactions. Specifically, it has been proposed that the aromatic side chains of phenylalanine, tyrosine and tryptophan play a key role in this regard[10,11]. In addition, the enzyme pocket blocks the access of undesired nucleophiles, and thereby prevents premature quenching.

Therefore, we explored the possibility of mimicking the complex cyclase reaction pocket using relatively simple aromatic supramolecular capsules[12–19]. Interestingly, although the field is quite active (for recent examples, see Bocokić *et al.*[20], Dydio *et al.*[21], Wang *et al.*[22], Zhao *et al.*[23,24] and Salles *et al.*[25]), no THT cyclizations in a supramolecular structure have been reported to date. The only reported example of a monoterpene-like cyclization was based on a Prins reaction, which is reproducible in solution[26]. The hexameric resorcinarene capsule **I**[27] (Fig. 2) (for catalysis within **I**, see Cavarzan *et al.*[28], Bianchini *et al.*[29] and Zhang and Tiefenbacher[30]), which is readily available by self-assembly of the monomer **13** in apolar solvents, seemed promising for this study. (1) It forms a large hydrophobic cavity (~1,400 $Å^3$) that is suitable for accommodating acyclic terpenes. (2) Owing to its aromatic walls, **I** is known to complex cationic guests, such as alkylammonium ions, via cation–π interactions[31,32]. In analogy to the aromatic residues in a terpene cyclase enzyme pocket, the aromatic walls of **I** could potentially stabilize cationic intermediates and transition states. (3) We recently reported that capsule **I** is a mild Brønsted acid (pK_a ~5.5–6) and can function as a catalyst for simple acetal hydrolysis[30]. (4) Guest exchange is facile and is believed to occur

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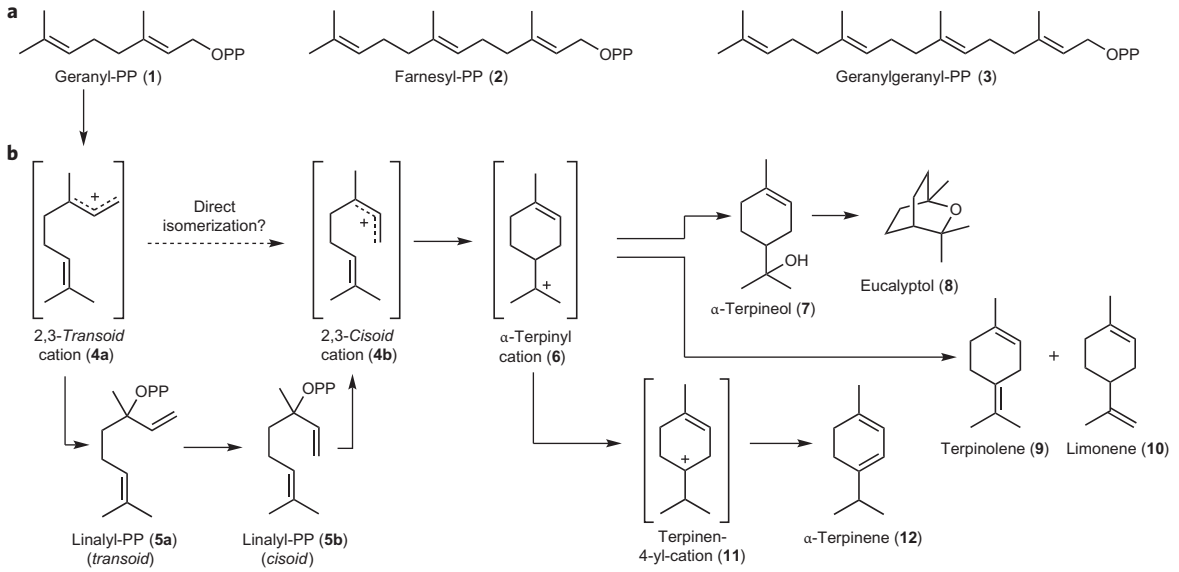

Figure 1 | Biosynthesis of cyclic terpene natural products. a, Structures of the natural terpene substrates. These are converted into cyclic monoterpenes (geranyl-PP), sesquiterpenes (farnesyl-PP) and diterpenes (geranylgeranyl-PP). **b**, Reaction pathways for the biosynthesis of a selection of monoterpene natural products via THT cyclization. Cleavage of the PP-leaving group forms the *transoid* cation **4a**, which has to isomerize to the *cisoid* form **4b** before cyclization can occur. A direct isomerization is considered unlikely in the literature and therefore a step-wise isomerization that involves reattachment of the pyrophosphate group was proposed. After cyclization to the α-terpinyl cation (**6**), a variety of different reaction paths are available. An attack of water forms α-terpineol (**7**), which can further cyclize to eucalyptol (**8**). Alternatively, elimination delivers terpinolene (**9**) or limonene (**10**). Rearrangements can also occur. A hydride shift, for instance, delivers cation **11**, which yields α-terpinene (**12**) after elimination.

via dissociation of one resorcinarene unit[33]. We speculated that it could potentially activate a suitable leaving group on an acyclic terpene by protonation, and thereby initiate a THT cyclization cascade inside the cavity. Indeed, the system is able to biomimetically catalyse THT cyclizations and herein we report these findings.

Results and discussion

We first investigated the cyclization of monoterpene alcohols. Treatment of a solution of GOH (**14**) in $CDCl_3$ (33 mM) with 10 mol% capsule **I** at 30 °C led to complete conversion of the starting material within 28 hours (Fig. 3a). Identification of the products formed was achieved by comparison with standard solutions of monoterpenes (gas chromatography, ^{1}H NMR spectroscopy). Initially, in analogy to the proposed biosynthesis (Fig. 1b), linalool (LOH) (**15**) was formed as the main product (for the initial rates of formation, see Supplementary Table 9), which indicates that, after protonation of GOH (**14**) and ionization to give cation **4a**, the cleaved water molecule attacked the allylic carbocation. The other two main products formed within the first ten hours were the cyclic α-terpinene (**12**) and α-terpineol (**7**). With progressing reaction time, the concentrations of LOH (**15**) and α-terpineol (**7**) decreased, and eucalyptol (**8**) started to form (for the final yields after 72 hours, see Supplementary Table 4). Alkylation of the phenol groups of monomer **13** (for details, see Supplementary Figs 13–15) and dimerization were observed as side reactions, as evidenced by a multitude of smaller gas chromatography peaks in the diterpene region. For dimerization inside the cavity, two substrates have to be encapsulated simultaneously. It was reported that six chloroform molecules occupy the cavity space if no other guests are present[34]. According to size considerations (see Supplementary Table 8), one substrate would replace two or three of the six chloroform molecules. Several control experiments were performed. When catalyst **I** was omitted, no conversion was observed (12 days). When the catalyst's cavity was blocked with a strongly binding guest (nBu$_4$NBr), no cyclization was observed, although the acidity of the system was thereby increased (see Supplementary Tables 5 and 6). These experiments provide strong evidence that the cyclization reaction is, indeed, only taking place inside the cavity. Additionally, substrate internalization was evidenced by ^{1}H- and diffusion-ordered NMR spectroscopy (see Supplementary Figs 6–8).

Conversion of nerol (NOH) (**16**) under similar conditions produced contrasting results (Fig. 3b): the conversion was much faster and the dominating product within the first 20 hours was α-terpineol (**7**), which was then converted into eucalyptol (**8**) with good selectivity. Besides α-terpinene (**12**), terpinolene (**9**) was also formed in considerable amounts. Side reactions were greatly reduced.

The product profile of LOH (**15**) (Fig. 3c) could be interpreted as a combination of the GOH (**14**) and NOH (**16**) results to give a

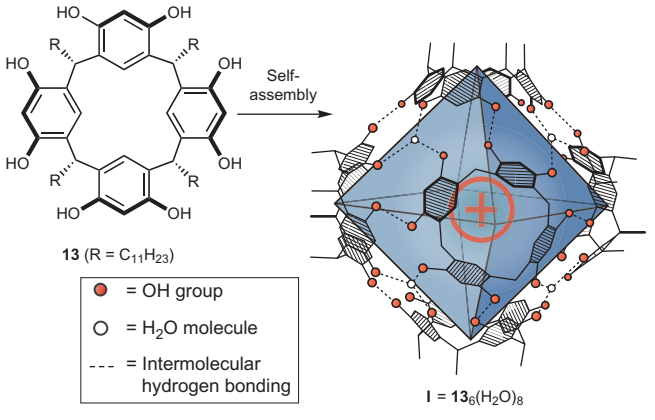

Figure 2 | Structure of the resorcinarene capsule I. This self-assembles via a hydrogen-bond network from six monomer units of **13** and eight water molecules in apolar solvents and encloses a volume of ~1,400 Å^3. Cationic guests, such as alkylammonium ions, are bound inside the cavity via cation–π interactions. Guest exchange is facile and probably occurs via dissociation of one monomer unit. Capsule **I** is a mild Brønsted acid (pK_a ~5.5–6).

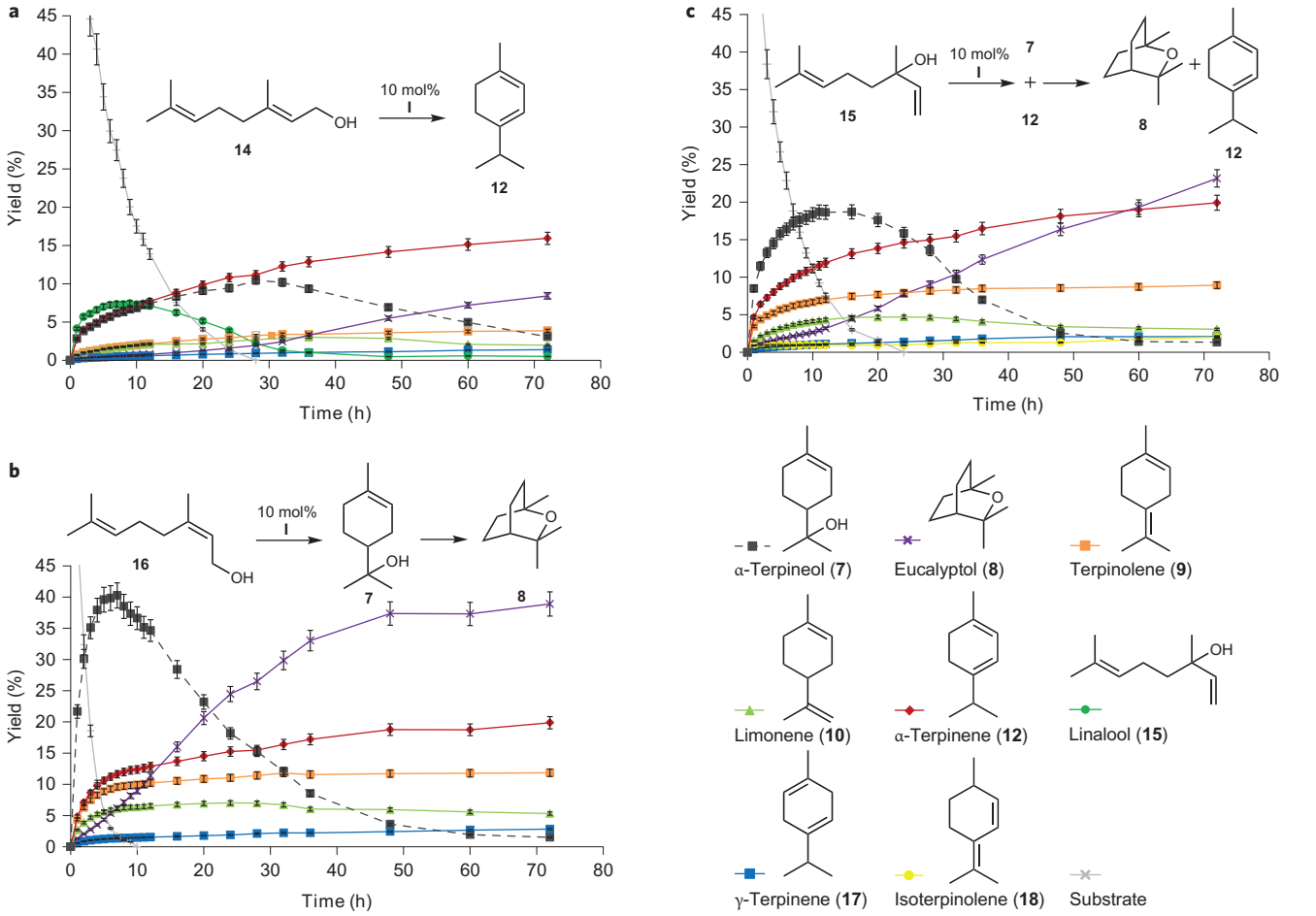

Figure 3 | Results of the THT cyclizations with catalyst I for the alcohol substrates. Products were identified by gas chromatography and ^{1}H NMR spectroscopy and quantified by gas chromatography. **a**, The cyclization of GOH (**14**) is rather unselective. Initially, in analogy to the proposed biosynthesis, LOH (**15**) was formed. The other main products formed within the first ten hours were α-terpinene (**12**) and α-terpineol (**7**). With progressing reaction time, the concentrations of LOH (**15**) and α-terpineol (**7**) decreased as eucalyptol (**8**) started to form. **b**, NOH (**16**) is first cyclized mainly to α-terpineol (**7**), which is then converted into eucalyptol (**8**). **c**, The reaction profile of LOH (**15**) appears to be a composite of the results from GOH (**14**) and NOH (**16**), and gives a less-pronounced initial maximum of α-terpineol (**7**) and a better selectivity of α-terpinene (**12**) over terpinolene (**9**) than in the case of NOH (**16**). Error bars indicate typical maximal errors (±5%) as evidenced by the experiment, which was run in triplicate (Fig. 4a).

less-pronounced initial maximum of α-terpineol (**7**) and a better selectivity of α-terpinene (**12**) over terpinolene (**9**) than in the case of NOH (**16**). In addition, side reactions were between the two extremes.

The cyclization results are remarkable; for example, eucalyptol (**8**) has not been formed in a cascade reaction from acyclic terpenes before. It was only accessible from cyclic α-terpineol utilizing a strong Brønsted acid[35] or Lewis acid[36], or in a two-step procedure via phenylselenoetherification[37]. Nevertheless, we wanted to suppress the interception of cationic intermediates by the cleaved leaving group, which resulted, for example, in the formation of α-terpineol (**7**) as an intermediate. We therefore tested leaving groups with a reduced nucleophilicity and found that the acetate proved to be well suited in that regard.

Submitting geranyl acetate (GOAc) (**14a**) to the described reaction conditions resulted in the selective formation of α-terpinene (**12**) (Fig. 4a). The interception of reactive cationic intermediates was suppressed successfully, as evidenced by the disappearance of LOH and α-terpineol derivatives. The α-terpinyl cation formed (**6**) (Fig. 1b) is not quenched by nucleophiles or elimination, but is able to propagate via a 1,2-hydride shift to form cation **11** in good selectivity. Therefore, this reaction represents a true 'non-stop'[38] THT cyclization cascade, which is hard to achieve in solution (for a different approach to 'non-stop' THT cyclizations, see Pronin and Shenvi[1]). As described for GOH (**14**), a series of control experiments were performed with **14a** and confirmed that the reaction did, indeed, only take place inside the cavity (see Supplementary Fig. 2 and Supplementary Table 6). Additionally, **14a** was converted selectively inside **I** in the presence of the extended derivative **19** (Fig. 4d) (for the details, see Supplementary Fig. 4 and Supplementary Scheme 1). For comparison, several Brønsted and Lewis acids were tested for the cyclization of GOAc (**14a**) and showed only traces of cyclic monoterpene products (see Supplementary Fig. 3).

In the case of neryl acetate (NOAc) (**16a**) (Fig. 4b), the product profile also changed dramatically. As expected, only trace amounts of α-terpineol (**7**) were observed. Nevertheless, a small fraction of α-terpinyl acetate (**7a**) was formed. More significantly, the initial product ratio between α-terpinene (**12**) and terpinolene (**9**) changed dramatically, with the latter dominating in the first 36 hours of the reaction. The product spectrum of linalyl acetate (LOAc) (**15a**), as in the case of the free alcohols, appears to be a composite of the results of GOAc and NOAc (Fig. 4c). Additionally, GOAc was formed initially, which could indicate an equilibration to the thermodynamically more stable isomer.

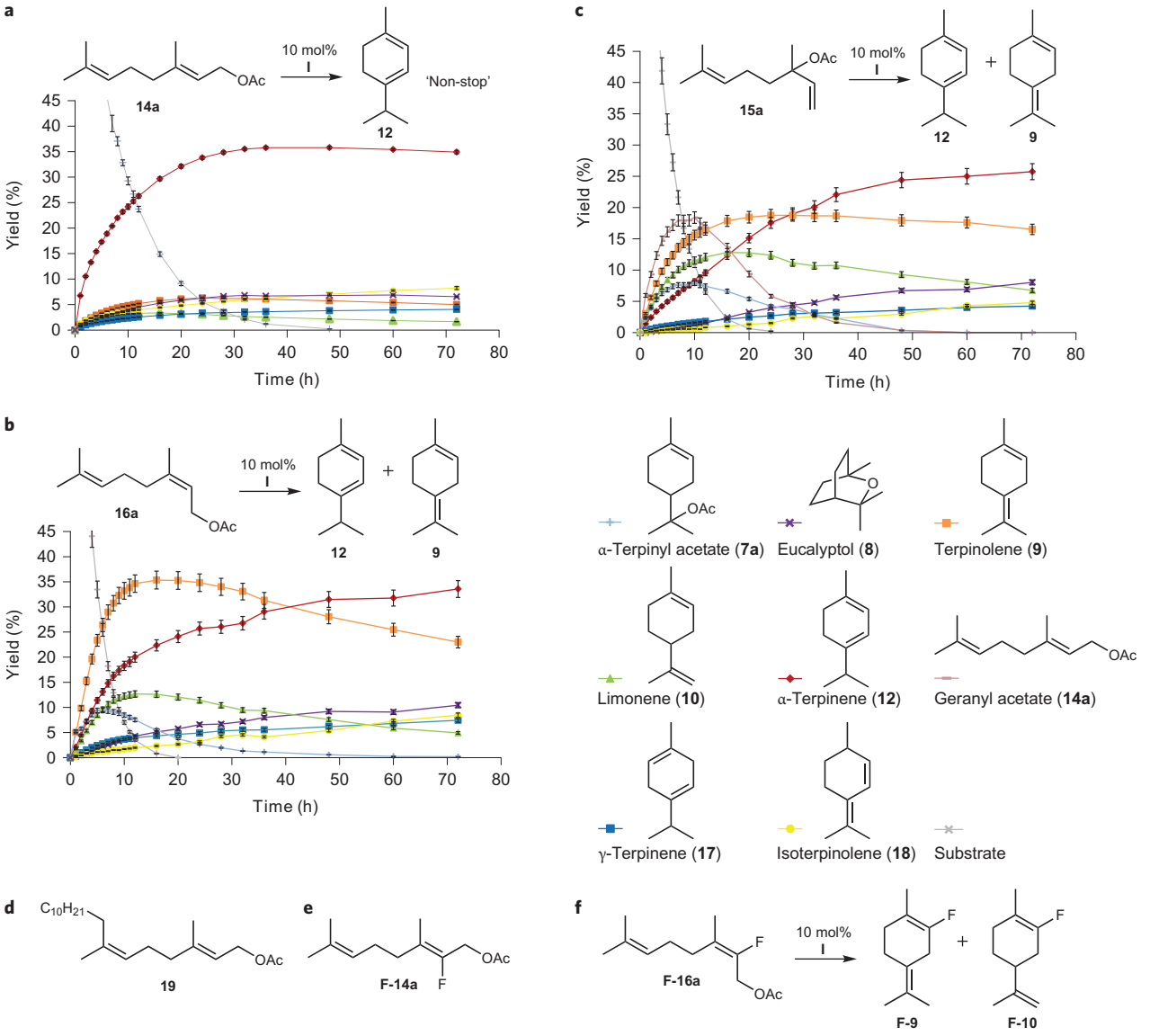

Figure 4 | Results of the THT cyclizations with catalyst I for the acetate substrates. a, The cyclization of GOAc (**14a**) led to α-terpinene (**12**) in good selectivity. It represents a 'non-stop' THT cyclization because the cationic intermediates were not quenched by nucleophiles or elimination—as evidenced by the disappearance of LOH and α-terpineol derivatives. **b**, NOAc (**16a**) cyclized mainly to α-terpinene (**12**) and terpinolene (**9**), with the latter dominating in the first 36 hours. **c**, The product profile of LOAc (**15a**) appears to be a composite of the results from GOAc (**14a**) and NOAc (**16a**). Initially, GOAc was formed, which could indicate an equilibration to the thermodynamically more stable isomer. **d**, The extended geranyl substrate **19** used for the control experiments. **e**,**f**, Fluoro derivatives explored in the cyclization. 2-Fluorogeranyl acetate (**F-14a**) did not undergo cyclization within **I** (**e**). 2-Fluoroneryl acetate (**F-16a**) produced fluoroterpinolene (**F-9**) and fluorolimonene (**F-10**) as the only main products (**f**), which indicates that these products are formed predominantly via a concerted (S_N2) mechanism, whereas α-terpinene (**12**) is formed predominantly via an S_N1-mechanism within **I**. Error bars in **a** represent the standard deviation from the mean value (the experiment was run in triplicate). Error bars in **b** and **c** indicate typical maximal errors (±5%), as evidenced by the results in **a**.

The dramatically different product profiles for GOAc (**14a**) and LOAc (**15a**) were striking. If GOAc (**14a**) formed the *cisoid* cation **4b** (Fig. 1b) via LOAc (**15a**) as an intermediate, as proposed in the biosynthesis, such a difference would not be expected. Additionally, no LOAc (**15a**) was observed as an intermediate in the cyclization of GOAc (**14a**). In contrast to natural enzymes, intermediates can be detected during cyclization in **I**, as can be seen in Figs 3a–c and 4b,c. Based on these results, we propose that the allylic cation **4a** is, indeed, directly undergoing the *transoid–cisoid* isomerization into **4b** inside **I**. As there is no direct evidence for the formation of linalyl-PP as an intermediate in cyclase enzymes[4] and the isomerization energy barrier of 55 kJ mol^{-1} (gas phase)[9] can be overcome relatively quickly at ambient conditions (half-life < 0.5 milliseconds, short compared to typical turnovers of every 1–100 seconds in cyclase enzymes[4]), a direct isomerization should no longer be excluded in cyclase enzymes.

Compared to NOH (**16**) and LOH (**15**), the reactions of NOAc (**16a**) and LOAc (**15a**) led to an increased initial formation of terpinolene (**9**) and limonene (**10**), respectively, as compared to α-terpinene (**12**). This may be attributed to the presence of the acetate/acetic acid leaving group in the reaction pocket, which could function as a general base to deprotonate the α-terpinyl cation **6** (Fig. 1b)[1]. The high degree of deprotonation in the cases of NOAc (**16a**) and LOAc (**15a**), as compared with the results of GOAc (**14a**), might seem surprising at first because all the substrates have to converge to the common intermediate α-terpinyl

cation **6**. We speculated that this may indicate a different reaction mechanism. In the case of GOAc (**14a**), because of its 2*E*-alkene geometry, ring formation has to be preceded by ionization and isomerization. Thereby, the leaving group is cleaved in a distinct step before the α-terpinyl cation **6** is generated. As the isomerization is considered a slow step[4,9], the leaving group may be able to diffuse away from the reaction centre. LOAc and NOAc, however, can react in a concerted fashion (S_N2'/S_N2-like). In these cases the leaving groups would be liberated simultaneously with the formation of the α-terpinyl cation **6**, and thus they have a greater probability to assist in deprotonation. Evidence in this direction was obtained by the investigation of the cyclization behaviour of 2-fluoro derivatives.

The electron-withdrawing fluoro substituent suppresses the formation of neighbouring cationic species. Thereby, ionization-dependent reaction pathways are efficiently slowed down, whereas concerted (S_N2-type) displacements remain viable. In cyclases, 2-fluorogeranyl-pyrophosphate and 2-fluorolinalyl-pyrophosphate were utilized to elucidate the reaction mechanism[39].

When submitting 2-fluorogeranyl acetate (**F-14a**) (Fig. 4e) to catalyst **I**, no formation of the corresponding cyclic products was observed (19 days), which confirms that, indeed, ionization is required to initiate the reaction cascade in this case. 2-Fluoroneryl acetate (**F-16a**), however, showed conversion, although at a reduced rate (8%; see Supplementary Table 7), to produce fluoroterpinolene **F-9** and fluorolimonene **F-10** as the only main products (see Supplementary Fig. 5). The reduced rate can be explained by the decreased uptake in the catalyst (fluoro-containing substrates have generally shown a lower degree of encapsulation) and by the inhibition of the S_N1 reaction path. The observed rate reduction, both in absolute terms as well as in comparison with 2-fluorogeranyl acetate (**F-14a**), does not indicate an ionization-dependent (S_N1-type) reaction path. In contrast to regular NOAc (**16a**), only traces of α-terpinene (**12**) were formed. These results indicate that terpinolene (**9**) and limonene (**10**) are formed predominantly via a concerted mechanism (S_N2' in the case of LOAc, and S_N2 in the case of NOAc), whereas α-terpinene (**12**) is formed predominantly via an S_N1 mechanism within **I**. These results are in line with the hypothesis that the local concentration of the leaving group influences product selectivity. Interestingly, these results are in contrast with solvolysis studies of neryl mesylate, in which a 160-fold rate reduction was observed for the 2-fluoroneryl substrate[40]. As, in that case, the rate decrease was comparable to that observed with the 2-fluorogeranyl substrate, it was argued that both react via an ionization (S_N1) mechanism. As expected, 2-fluorolinalyl acetate (**F-15a**) also produced fluoroterpinolene (**F-9**) and fluorolimonene (**F-10**) as the only main products. Additionally, these results could explain the different degrees of side reactions (alkylation of phenolic groups of monomer **13** and dimerization) observed during cyclization. Geranyl derivatives, which require the formation of acyclic cations, displayed the highest degree. Linalyl and neryl derivatives, able to react in a concerted fashion and thereby avoid acyclic cationic intermediates, displayed a much lower tendency.

To compare the catalytic efficiency of the system to that of natural cyclase enzymes, the kinetics of the conversion of GOAc (**14a**) inside capsule **I** were investigated (see Supplementary Figs 9–12 and Supplementary Table 10). The obtained k_{cat} value of $0.00079 \pm 0.00006\ s^{-1}$ is only about two orders of magnitude lower than that observed in natural cyclase enzymes ($0.01–1\ s^{-1}$)[4]. However, a large difference can be seen when comparing the K_m values (0.078 ± 0.007 M inside **I**, as compared to low micromolar values in natural cyclase enzymes[4]). As K_m is related to the inverse of the binding constant, this translates into a much weaker binding of the substrate in the presented capsule catalyst than in natural enzymes. One reason for the much higher affinity of natural substrates to cyclase enzymes may be the strong interaction of the pyrophosphate group with magnesium ions in the enzyme pocket[4].

Conclusions

Two main conclusions can be drawn from this work. (1) The presented evidence indicates that direct isomerization of the *transoid* cation **4a** into the *cisoid* form **4b**, considered unlikely in the biosynthesis[4,9], is possible inside cavity **I**. Therefore, a direct isomerization should also be considered in the biosynthesis. (2) It was demonstrated for the first time that a relatively simple aromatic cavity is catalytically competent in complex THT cyclizations. The catalytic power of the system relies, as with enzyme pockets, on the stabilization of the cationic intermediates and transition states. These findings set the stage for the development of catalysts able to revolutionize the total synthesis of complex terpene natural products.

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Author contributions

K.T. conceived the project and wrote the manuscript with Q.Z. Q.Z. planned and carried out the experiments. K.T. and Q.Z. discussed the experiments and results.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to K.T.

Competing financial interests

The authors declare no competing financial interests.