



Solid-catalyzed synthesis of isomers-free terpinen-4-ol

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ABSTRACT

Terpinen-4-ol is a natural product with wide application in the fragrance and agrochemical industry, currently extracted from tea tree oil or synthesized from either base-promoted rearrangement of 1,4-cineol or acid-catalyzed hydration of limonene. However, these synthetic processes, based on aggressive, unrecoverable homogeneous reagents, are non-selective and give significant amounts of isomers, which severely complicate and make more expensive the purification of the active substance. Here we show the isomers-free synthesis of terpinen-4-ol, exclusively over solid catalysts such as alumina, nanotitania and Pd/C, in >60% yield, by selective epoxidation, isomerization of terpinolene epoxide and allyl alcohol hydrogenation. The synthesis can be performed either in batch or in flow mode for the isomerization of terpinolene epoxide. The use of bare nanotitania as a selective epoxide isomerization catalyst, here demonstrated, opens new ways for the synthesis of quaternary alcohols.

1. Introduction

1.1. Current synthesis of terpinen-4-ol from natural sources

Terpinen-4-ol **1** is a valuable commercial compound in the fragrance and agrochemical market, with a pleasing earthy-green note and a slightly peppery-woody undertone. **1** also possess antibacterial and antifungal properties, and it is used as a synthetic intermediate for other products of interest. **1** is isolated from the tea tree oil, and can also be found in synthetic essential oils such as geranium, lavender and rose oils. However, since unsustainable extracting processes do not provide the required amounts of **1** that industry demands, access to synthetic **1** has been sought for years, with limited success. The low availability from natural sources and the lack of a high yielding and highly selective synthetic process poses serious hurdles in the expansion of **1** in the fragrance industry, and also in its potential introduction into other business areas [1]. Besides, boiling points for the different terpineol isomers (Fig. S1) are very similar and, indeed, the current limited availability and high price of **1** is mainly due to the high costs associated to the distillation process. Thus, a selective synthesis of **1** is here paramount [2,3], moreover if it could be done with solid catalysts [4,5].

Three main synthetic strategies have been used so far for the

synthesis of **1**: a base-promoted rearrangement of 1,4-cineole, an acid-catalyzed hydration of limonene and a hydrogenolysis reaction of terpinolene epoxide. The synthesis of **1** by opening of 1,4-cineole with sodium amide and catalytic ferric nitrate (Fig. S2 and Table S1) [6], gives a mixture of alcohols in the final product, since the starting material contains a 60% of 1,4-cineole, a 20% of the 1,8 isomer, and also alpha-terpinene (10%), limonene (5%) and others. The synthesis of **1** from cineole has obvious disadvantages, not only the low selectivity towards the desired terpineol, but also the requirement of corrosive sodium metal and liquid ammonia at the early stages of the reaction. Alternative openings of 1,4-cineole have been attempted with synthetic zeolites [7] and mixed fused salts [8], however, in both cases, yields of **1** were <5%.

The hydration of limonene under diverse acidic conditions, including zeolites [9], gives yields of **1** as low as 2.7%, and a plethora of products can be formed (Figs. S3, S4 and Table S2) [10]. The formation of a complex mixture of products under acid-catalyzed conditions is not surprising, since the selective protonation of the tetra-substituted double bond in **1**, in the presence of another double bond, is a complicated task, even more considering that an internal carbon atom has to be hydroxylated. A plethora of carbocationic undesired process such as rearrangements, elimination, carbon-carbon or oxygen-carbon

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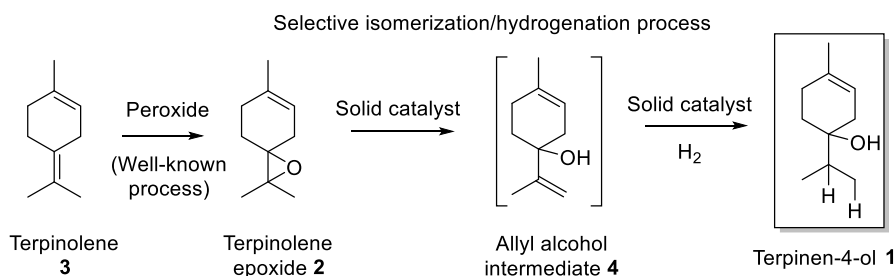


Fig. 1. The synthetic approach shown here for the synthesis of 1 with solid catalysts, without co-distilling alcohol by-products, either in batch or in flow.

couplings can easily occur in this type of substrates. Other approaches such as the intramolecular cyclization of neryl acetate [11] and some biocatalytic methods have shown very limited success and low industrial feasibility [12,13]. Therefore, all these approaches are far beyond a realistic industrial synthetic approach, either because of the required starting materials, techniques or selectivity they provide. It can be said that a high-yielding, selective and industrially feasible synthesis of 1 is of high interest and still required by industry.

1.2. Synthesis of terpinen-4-ol from terpinolene epoxide

Terpinolene epoxide 2 is an easy-to-prepare intermediate with a plethora of applications, produced by epoxidation of widely available terpinolene 3 either by standard epoxidation conditions with peroxides [14] or, perhaps more conveniently, with oxygen as a reagent [15,16]. Besides, heterogeneous catalysts such as Ti-MCM-41 [14] and $\gamma\text{-Al}_2\text{O}_3$ [17] can be used for the transformation, although pre-formed peroxides or the formic acid-catalyzed method are generally employed in industry [18].

The synthesis of 1 by hydrogenation of 2 with a mixture of $\text{LiAlH}_4\cdot\text{AlCl}_3$ provides a promising 67% yield of 1, but with an additional 22% of inseparable α -terpineol (Fig. S5) [7]. The same reaction can be carried out with modified copper oxide supported catalysts (silica gel, alumina, activated carbon, TiO_2 , diatomite, kaolin clay, Ba-kieselguhr) achieving 80–85% conversion and 75–80% selectivity towards 1, and also with Pd catalysts [19]. Notice that this process has a 100% atom economy.

Related to the above synthetic approach, a second way to obtain 1 from 2 is an isomerization/hydrogenation reaction sequence (Fig. S6). In this case, the synthesis of 1 is performed in two-steps, first converting the harsh-to-hydrogenate epoxide 2 to allyl alcohol, and then easily hydrogenating the allyl double bond. As the hydrogenolysis reaction commented above, this reactive sequence shows a 100% atom economy. Of course, the sequential approach presents challenges, such as the selective epoxide opening to the desired alcohol position and the hydrogenation of the allyl double bond in the presence of a second double bond. However, reported precedents made us confident of being successful. The isomerization of epoxides to allyl alcohols occurs with soluble stoichiometric reagents [20,21], metal catalysts [22] or solid inorganic oxides in batch mode [23–25], although generally with low selectivity. The use of modern non-metal nanosized solid catalysts for the direct isomerization of epoxides to allyl alcohols has apparently not been considered, despite some related reactions invite thinking that the use of a structurally well-defined, high surface area, simple and widely available solid catalyst will not only trigger the opening of epoxide 2 [26,27] but also would enable a higher selectivity for the desired allyl alcohol 4. The selective opening of epoxides is a topic of much current interest [28], and this solid-catalyzed synthetic approach opens the possibility of translating the batch to a more productive and industrially practical flow production process.

With all these data in mind, Fig. 1 shows our approach here to obtain terpinen-4-ol 1 without other alcohol isomers. The synthetic route consists in the selective isomerization of 2 over a nanosized solid

catalyst and hydrogenation of the corresponding allyl alcohol 3, to give the final product. These solid-catalyzed synthetic sequence can be run, in principle, either in batch or in flow mode.

This synthetic approach addresses the critical but unresolved problem of producing 1 without alcohol isomers in the final product, by selective opening of epoxide 2 and then, in a second step, hydrogenating the corresponding allyl alcohol 4. This second step has been reported in the literature with highly flammable Ni-Raney [18] but not with safer solid catalysts such as Pd-carbon. Thus, the present study not only provides a new, selective and high yielding method to open 2 to 4, but also manufacturing 1 by an in-flow method over solid catalysts.

2. Materials and methods

2.1. Synthesis of catalysts

The supported transition metal oxides were prepared by standard procedures [29–35], which consists in brief in: (1) impregnation of the metal oxide with an aqueous solution of the corresponding transition metal salt at either 0.5 or 1 wt% amount, (2) dry at 100 °C in an oven, and (3) calcination and reduction. Details can be found in the Supporting Information.

Zeolites are also commercially available or prepared by standard methods.[36,37] SnPt-SiO₂ was prepared following a 5-step reported procedure,[19] which consists in the incorporation of Pt on high surface area silica by exchange, calcination, incorporation of Sn by impregnation of an organostannane compound in organic solvent, evaporation of the solvent and treatment of the resulting solid on H₂ atmosphere at 200 °C. Pd-charcoal and Pd-Lindlar's catalyst are commercially available or prepared by standard methods [38,39]. Ti³⁺-enriched nTiO₂ was prepared by the ethanol method [40].

2.2. Reaction procedures

Synthesis of terpinolene oxide (2,2,6-trimethyl-1-oxaspiro[2.5]oct-5-ene) 2 with peracetic acid. Following a reported procedure [18], peracetic acid (40%, 76 g) was added dropwise to an agitating mixture of terpinolene 3 (54 g), methylene chloride (160 mL) and anhydrous sodium acetate (20 g) in a glass round-bottomed flask. The reaction temperature was held at about 6 °C by means of an external water/ice cooling bath. After addition of the peracid was complete, the reaction was stirred for 1 h and then neutralized with 30% sodium hydroxide. The organic layers were separated, washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give an essentially quantitative amount of crude epoxide which exhibited only a single major peak on vapor phase chromatography. A 3-gram sample was purified by flash column chromatography over silica gel (10% AcOEt in hexane, R_f= 0.17), to obtain 2 as a transparent oil. ¹H NMR (401 MHz, CDCl₃) δ (ppm) 5.30 (dq, $J = 3.1, 1.6$ Hz, 1H), 2.33–1.96 (m, 4H), 1.74–1.67 (m, 2H), 1.65–1.35 (m, 3H), 1.31 (s, 3H), 1.28 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ (ppm) 134.4 (-C-); 119.2 (-CH-); 64.4 (-C-); 62.4 (-C-); 30.7 (-CH₂-); 28.9 (-CH₂-); 27.0 (-CH₂-); 23.4 (-CH₃-); 20.9 (-CH₃-); 20.5 (-CH₃-). GC-MS (Calculated for

$C_{10}H_{16}O$): 152.1, found 152.1.

Synthesis of terpinolene oxide 2 with hydrogen peroxide. Following a reported procedure [17], hydrogen peroxide (50%, 2–4 equivalents) was added dropwise to an agitating mixture of terpinolene 3 (132 mg, 1 mmol) in AcOEt with solid alumina (25.7 mg), in a glass round-bottomed flask. The reaction was placed in an oil bath at 60 °C and magnetically stirred for 72 h. The reaction was neutralized and treated as above, to obtain the product.

Typical reaction procedure for the hydrogenolysis of terpinolene oxide 2. A solution of 2 (15.2 mg, 0.1 mmol) in the corresponding solvent (*o*-xylene or MeOH, 0.5 M) was added over the corresponding solid catalyst (10–100 wt%) in a reinforced double-walled 2 mL glass vial equipped with a magnetic stir and capped with a manometer connected via cannula. H₂ was flushed at room temperature twice to leave a final pressure of 8 bar of H₂ in the reactor. The resulting mixture was placed in a pre-heated bath oil at 120 °C for *o*-xylene and 50 °C for MeOH, under magnetically stirring. The mixture was periodically analyzed by GC, after dilution in dichloromethane of an aliquot and filtration.

Typical reaction procedures for the isomerization of terpinolene oxide 2 to allyl alcohol intermediate [4-methyl-1-(prop-1-en-2-yl)cyclohex-3-en-1-ol] 4.

In batch: A solution of 2 (15.2 mg, 0.1 mmol) in the corresponding solvent (200 µL, 0.5 M, or neat) was added over the corresponding solid catalyst (5–200 wt%) in a 2 mL glass vial equipped with a magnetic stir. The vial was sealed under atmospheric conditions and placed in a pre-heated bath oil at the required temperature under magnetically stirring. For gram-scale experiments, a 10 mL glass round-bottomed flask and a reflux condenser were employed. The mixture was periodically analyzed by GC, after dilution in dichloromethane of an aliquot and filtration. After the reaction was complete, the solid catalyst was removed by filtration and 4 was obtained as a yellow oil after removal under vacuum of the volatiles. ¹H NMR (401 MHz, CDCl₃) δ (ppm) 5.32 (s, 1H), 5.03 (d, *J* = 1.0 Hz, 1H), 4.84 (t, *J* = 1.5 Hz, 1H), 2.34 (d, *J* = 17.0 Hz, 1H), 2.18 (m, 1H), 1.99 (m, 2H), 1.83 (m, 1H), 1.81 (d, *J* = 1.5 Hz, 3H), 1.72 (m, 1H), 1.69 (s, 3H), 1.63 (s, 1H, -OH). ¹³C NMR (101 MHz, CDCl₃) δ (ppm) 150.2 (-C-); 133.6 (-C-); 118.1 (-CH-); 109.6 (-CH₂-); 72.1 (-C-); 37.0 (-CH₂-); 31.9 (-CH₂-); 27.2 (-CH₂-); 23.2 (-CH₃-); 18.7 (-CH₃-). GC-MS (Calculated for C₁₀H₁₆O): 152.1, found 152.1.

In flow: 50 mg of nTiO₂ sieved between 0.4–0.8 µm diameter were mixed with tungsten carbide and placed within a fixed-bed steel tubular reactor of 10 mm diameter and filled with more tungsten carbide [30]. Neat 2 was pumped through, at a rate of 500 mg per h, under a flow of N₂. The crude at the exit of the reactor was periodically collected in vials and analyzed by GC.

Typical reaction procedure for the hydrogenation of allyl alcohol intermediate 4 to terpinen-4-ol (1-isopropyl-4-methylcyclohex-3-en-1-ol) 1. A solution of 4 (370 mg, 2.5 mmol) in MeOH (1 mL) was added by syringe to a 10 mL glass round-bottomed flask equipped with a magnetic stir and containing a dispersion of Pd/C (10 wt% Pd, 3 mg, 0.2 mol%) in MeOH (1.5 mL, final 1 M solution of 4) previously flushed with H₂ and connected with a needle to a 7 cm diameter H₂ balloon. The resulting mixture was magnetically stirred at room temperature, and periodically analyzed by GC, GC-MS and NMR after dilution in dichloromethane of an aliquot and filtration. Solventless reactions were run at 150 °C. After the reactions were complete, the solid catalyst was removed by filtration and 1 was obtained as a slightly yellow liquid after removal under vacuum of the volatiles. ¹H NMR (401 MHz, CDCl₃) δ (ppm) 5.31 (dd, *J* = 5.0, 2.5 Hz, 1H), 2.18 (dd, *J* = 15.0, 5.0 Hz, 2H), 1.94 (dd, *J* = 15.0, 5.0 Hz, 2H), 1.75–1.69 (m, 3H), 1.68–1.64 (m, 1H), 1.60–1.56 (m, 2H), 0.96 (d, *J* = 10 Hz, 3H), 1.81 (d, *J* = 10 Hz, 3H). ¹³C-NMR (101 MHz, CDCl₃) δ (ppm) 133.86 (-C-), 118.45 (-CH-), 71.74 (-C-), 36.78 (-CH-), 34.61 (-CH₂-), 30.80 (-CH₂-), 27.06 (-CH₂-), 23.28 (-CH₃-), 6.85 (-CH₃-); 6.82 (-CH₃-). GC-MS (Calculated for C₁₀H₁₈O): 154.1, found 154.1.

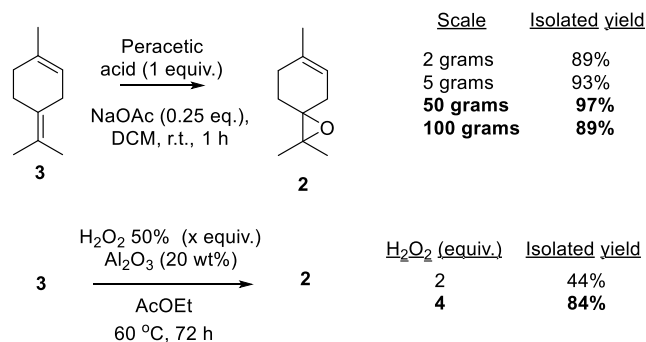


Fig. 2. Synthesis of terpinolene epoxide 2 from terpinolene 3 by epoxidation with peracetic acid (top) or hydrogen peroxide (bottom).

3. Results and discussion

3.1. Synthesis of terpinolene epoxide 2

The epoxidation of terpinolene 3 with peracetic acid, which is well-known in the literature with yields and selectivity >90%, was tested with peracetic acid as a reagent, since this method is, in principle, difficult to beat by other cheaper oxidizing agents in terms of efficiency and practicality (Fig. S7) [14,17]. Fig. 2 shows the results obtained in our hands. Terpinolene epoxide 2 could be obtained as a clear liquid in 97% yield from terpinolene 3 at 50 g scale, after simple water washings and without any distillation required. 100-Gram scale experiments were also performed, in both the ITQ and IFF installations, and the formation of epoxide 2 from terpinolene at 114 g scale yielded complete conversion and 89% selectivity in both laboratories. Thus, it seems that scaling up to 100 g can produce a small decrease of the final epoxide yield, however, this small decrease should not be a problem provided that the subsequent steps proceed well. A 3-gram sample was purified by flash column chromatography over silica gel and showed the same reactivity than the unpurified sample in all the reactions performed hereafter. The quality of the peracetic reagent is critical for the reaction performance, and fresh samples gave the best results.

A more adequate synthesis of 2 was then accomplished, since peracetic acid as a reagent and dichloromethane as a solvent are not environmentally acceptable. For that, we followed a reported procedure but avoiding a 20 atm pressure, [17] with hydrogen peroxide H₂O₂ as a reagent and alumina as a catalyst. The results, also depicted in Fig. 2, shows that a 84% yield of 2 can be obtained by this solid-catalyzed procedure. This result is close to that obtained with peracetic acid.

3.2. Hydrogenolysis of terpinolene epoxide 2

The direct synthesis of 1 by hydrogenolysis reaction of 2 over solid catalysts with H₂ as hydride source (and not LiAlH₄) was firstly attempted, in order to contextualize the next results in the two-step route (isomerization/hydrogenation reaction sequence). The results are shown in Fig. 3, using different inorganic oxides of general formula MOx (TiO₂, Al₂O₃, ZrO₂, Fe₂O₃) [29–31], also with supported transition metals (M-TiO₂, M= Fe, Ru, Pd, Pt, Cu, Au; M-Al₂O₃, M= Ru, Pd, Au; and M-ZrO₂, M= Fe, W); [35–38] bimetallics (SnPt-SiO₂ and CeZrO₂); [19] and Pd-charcoal and Pd-Lindlar's catalyst as commercially-available hydrogenating catalysts [38,39]. Reaction tests were performed with 1 M solutions of 2 under two different reaction conditions: at 50 °C (solvent MeOH) and at 120 °C (solvent *o*-xylene) for 1–5 h reaction time.

Gas chromatogram (GC) analyses indicated the absence of the target product 1 even at moderate conversions, and the appearance of many by-products. When the catalyst is used at 100 wt% the process is not catalytic, these high amounts of catalysts were tested just in case the

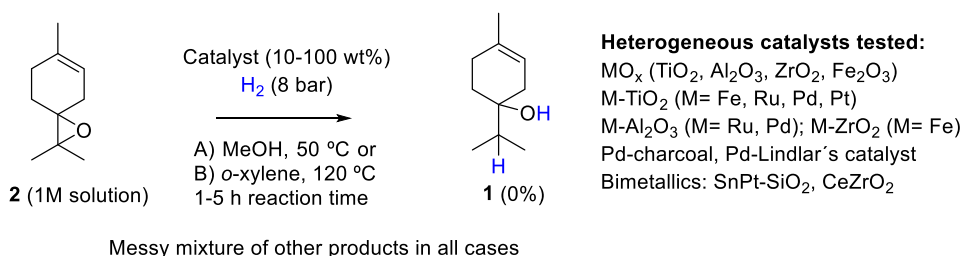


Fig. 3. Attempts for the selective hydrogenolysis of **2** to **1** with heterogeneous catalysts and H₂.

Table 1

Some of the results for the the formation of **4** from **2** (purified by column chromatography) with different solid catalysts and reaction conditions. See Table S3 for further results.

Entry	Catalyst (wt%)	Solvent (wt%)	Temperature (°C)	Time (h)	Conversion (%)	Yield to 4 (%) ^{a,b}	Selectivity (%) ^c
1 ^d	nTiO ₂ (200)	1,2-DCE (2000)	80	2	42	39	93
2 ^d		Toluene (2000)	110		100	76 [73]	76
3	Au-nTiO ₂ (200, 2 mol% Au)	1,2-DCE (2000)	80		12	11	96
4	Fe-nTiO ₂ (as above)				5	4	80
5	Au-ZnO (as above)				3	3	100
6	Au-CeO ₂ (as above)	DCE	80		2	2	100
7		Toluene	110		2	2	100
8	Au-nTiO ₂ (as above)	No solvent	80		10	9	90
9			110		100	70	70
10	Au-nTiO ₂ (as above)	Toluene (2000)	80		3	3	100
11			110		100	77 [71]	77
12	Au-nTiO ₂ (as above)	1,4-dioxane (2000)	80		5	5	100
13			110		100	25	25
14	TiO ₂ anatase (as above)	Toluene (2000)	110	16	16	14	88
15	TiO ₂ rutile (as above)				14	13	93
16	No catalyst				18	14	78
17 ^d	nTiO ₂ (100)	Mesitylene (300)	160	0.5	95	78	82
18	nTiO ₂ (70)				91	76	83
19	nTiO ₂ (40)				86	72	85
20		Mesitylene (200)			88	73	83
21		Mesitylene (100)			82	70	85
22		No solvent			92	71	77
23	nTiO ₂ (20)	Mesitylene (300)			67	62	95
24	nTiO ₂ (20)	No solvent	180	0.5	90	85 [83]	94
25			200	0.25	95	81	85
26	nTiO ₂ (10)		180	1.5	90	83	92
27			200	0.5	95	83	87
28	nTiO ₂ (5)		180	1.5	68	64	94
29			200	1	98	88 [86]	89
30	nTiO ₂ (2)		200	6	100	76	76

^a GC yields, using *n*-dodecane as an external standard.

^b Between brackets, isolated yields at 0.5-gram scale.

^c Selectivity refers to the relative amount of **4** respect to by-products **6**, since **5** was not found.

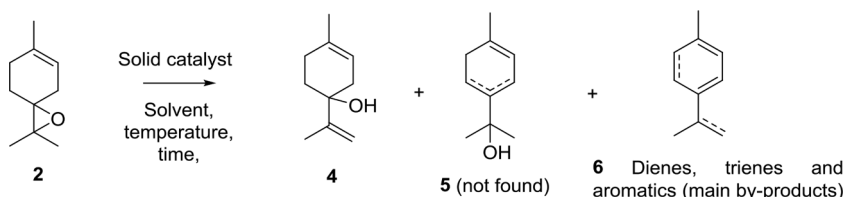
^d A large excess of TiO₂ was used.

reaction worked.

The bare metal oxides Al₂O₃, ZrO₂, Fe₂O₃, CeZrO₂, and also Au-Al₂O₃ and Fe- or W-ZrO₂, all give 0–20% conversions, with alkenes and some diols as products but without any trace of **1**. M-TiO₂ (M= Fe, Ru, Pd, Pt, Cu, Au or no metal) gives 100% conversion, without the presence of **1** but the appearance of some isomers of **2**. Other reactions such as rearrangements, aromatization and etherification reactions also occur. Pd-charcoal, Pd-Lindlar's catalyst, Ru-Al₂O₃, Pd-Al₂O₃ and

SnPt-SiO₂ give 100% conversion, and no trace of **1**. The main product is that coming from the hydrogenation of the alkene, but rearrangements, aromatization and etherification reactions also occur.

While these results were clearly discouraging, the formation of an isomer of **2** with TiO₂ catalysts was worthy of study [30]. Analysis of the reaction mixture by combining GC, GC-MS and NMR techniques unveiled that one of the products of the reaction was, precisely, allyl alcohol **4**.



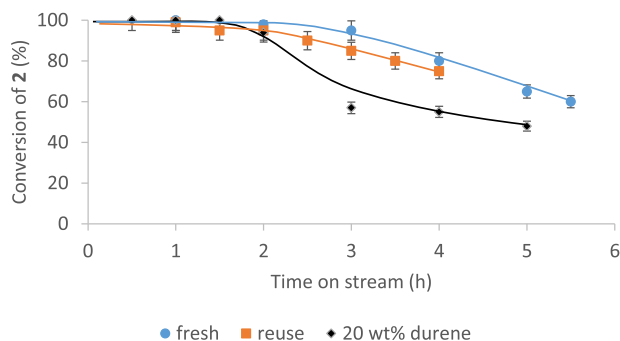


Fig. 4. In-flow isomerization at 200 °C of 10 g of **2** per gram of nTiO₂ per hour, under a N₂ flow. Error bars account for a 5% uncertainty.

3.3. Isomerization/hydrogenation of terpinolene epoxide **2**

3.3.1. Isomerization

In batch. The isomerization/hydrogenation strategy for the formation of **1** from **2** (purified by column chromatography) was studied, with the heterogeneous catalysts previously used for the hydrogenolysis. Some of the results for the first step (isomerization reaction) are shown in Table 1 (see Table S3 for further reaction data).

The results show that the desired vinyl alcohol intermediate **4** can be isolated in up to 86% yield (entry 29) at 0.5 g scale when heated neat during 1 h at 200 °C in the presence of 5 wt% of commercially available nanotitania (nTiO₂, average size = 25 nm, pure anatase phase). Remarkably, co-distilling alcohols, such as **5**, were not obtained as by-products. Other catalysts including metal-supported nTiO₂ catalysts (compare entries 1–4 and Table S3) and other metal oxides with metals, supported or not (entries 5–15 and Table S3), were mainly inactive, in the range of the thermal reaction (entry 16). Other solvents, concentrations, nTiO₂ catalyst amount and reaction temperatures worked well (entries 17–30), as long as the reaction time is properly set. The nTiO₂ catalyst could be recovered by simple filtration and reused 3 times without apparent loss of yield, and kinetic experiments at very low

catalytic amount (1 mol%) revealed that the used nTiO₂ catalyst preserves its intrinsic catalytic activity after use (Fig. S8).

The nTiO₂-catalyzed isomerization reaction is very robust and occurs regardless the purity of the starting epoxide **2**, since either the pure epoxide or samples with crescent amounts of terpinolene **3** and even terpineol **1**, observed impurities during uncomplete epoxidations, reacted similarly (Table S4). Indeed, terpinolene **3** samples from two different companies (IFF Co. and Sigma-Aldrich Co.) were tested in the isomerization reaction with 5 wt% nanotitania catalyst, to give exactly the same result (Table S5, experiments were made by duplicate and the results are in average, with less than 2% error). Gas chromatography analysis showed exactly the same composition. Thus, 114 g of epoxide **2** were submitted, without purification, to the isomerization reaction. First, 10 g of **2** with 500 mg of nanoTiO₂ catalyst were tested, and, in a second experiment, the rest of **2** (105 g) with 5 g of nanoTiO₂ catalyst were reacted (GC chromatograms of the product obtained in the 10 and 100 g experiments, respectively, can be found in Fig. S9). The results show that the reaction product is identical, with 86% purity of **4** after complete conversion. The mass balance was >99%, and 10 and 100 g were recovered, respectively, in the two experiments. Nuclear magnetic resonance measurements showed 85% purity for the product. Thus, the combined GC, NMR and weight results confirm that the isomerization proceeds in 86% yield at 10 and 100 g scale, exactly the same yield that at milligram scale. It is true that the reaction times long as the scale increases, thus 1 h reaction time was needed for 1 g, 1.5 h for 10 g, and 2 h for 100 g.

In flow. The use of nTiO₂ as a stable solid catalyst for the isomerization of **2** to **4** allows the potential implementation of a flow process [30,36]. After sieving nTiO₂ to a size between 0.4–0.8 μm, the reaction was run in a fixed-bed tubular reactor of 10 mm diameter under a N₂ flow at a rate of 10 g of neat **2** per gram of nTiO₂ catalyst per h, at 200 °C reaction temperature. Fig. 4 shows that the catalyst starts to deactivate after 3 h reaction time. Stopping the reaction and washing the catalyst with acetone and drying at 250 °C, basically reactivates the original activity of the catalyst. It must be noticed that significant amounts of aromatics are collected at the first 1–2 h of reaction, which means that the catalyst is excessively active and that the isomerization occurs at the very

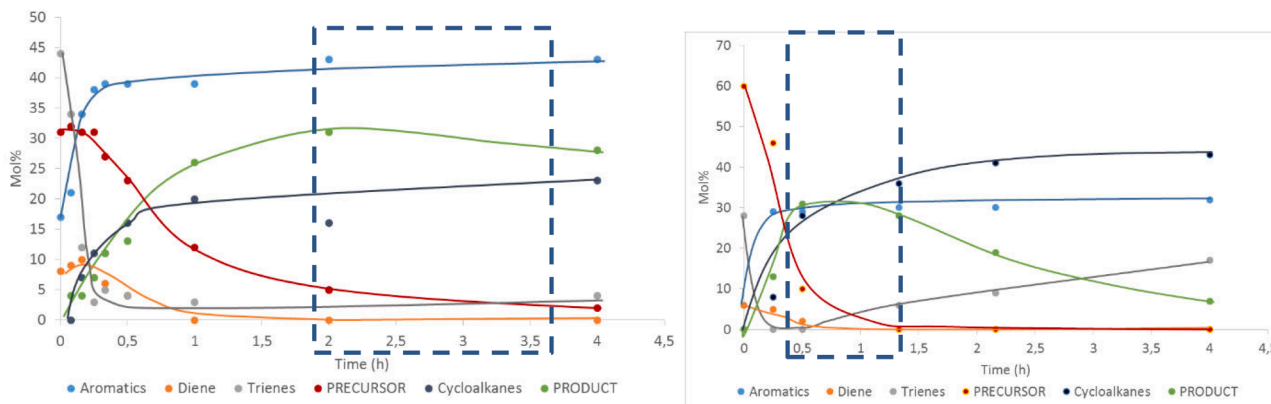
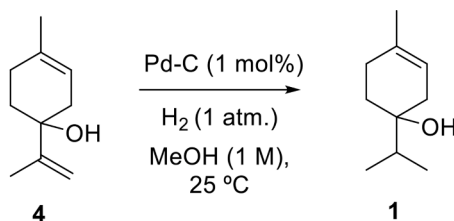


Fig. 5. Kinetic results for the Pd/C-catalyzed hydrogenation of two different mixtures of crude **4** under the indicated reaction conditions.

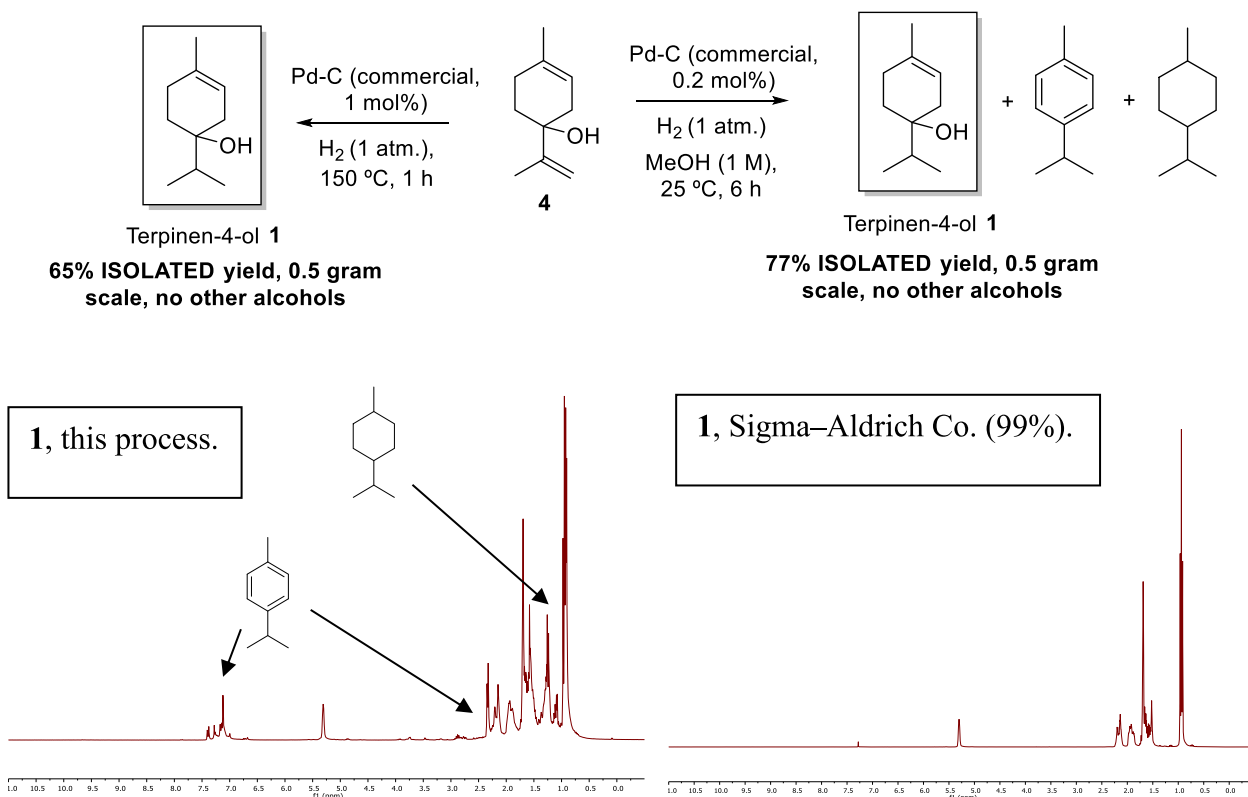


Fig. 6. Yield of 1 from 4 with the optimized Pd/C-catalyzed hydrogenation process, and comparison of the ¹H NMR spectra of obtained (left) and pure (Sigma-Aldrich Co.) terpinen-4-ol 1.

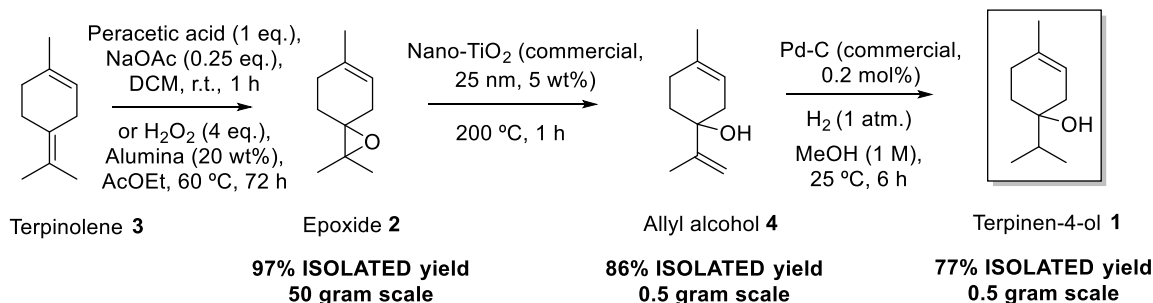
beginning of the catalyst bed, with time to dehydrate and aromatize. Thus, it is expected that a better control of the reaction, either by temperature of flow ramps, should lead to better results. A third experiment with 20 wt% of durene (1,2,4,5-tetramethylbenzene) mixed with the reactant gives a significant poorer result, which together with the successful regeneration of the catalyst activity after washings and the lack of deactivation observed in batch when aromatics are not formed, strongly supports that the generation of aromatics poisons the catalyst.

3.4. Hydrogenation reaction

Once vinyl alcohol intermediate 4 was readily obtained, the final hydrogenation of 4 to 1 was accomplished with Pd/C as a benchmark catalyst. In order to avoid the isolation of 4, the resulting mixture of the

isomerization process was directly used as a starting material. Fig. 5 shows the kinetic results for the Pd/C-catalyzed hydrogenation of two different mixtures of crude 4, one containing 30% of allyl alcohol 3 plus 70% of by-products 6 (45% trienes, 15% aromatics and 10% dienes), and another containing 60% allyl alcohol 3 plus 40% 6 (30% trienes, 5% aromatics and 5% dienes) in MeOH solvent at 25 °C and atmospheric pressure. Alcohols are the solvent of choice for hydrogenation reactions since reducible solvents (toluene, acetonitrile,...) are not suitable. A clear window of selectivity for target terpinen-4-ol 1 (squared) can be observed, after which 1 evolves to further hydrogenated products.

The results in Fig. 5 indicate that stopping the hydrogenation at the appropriate time can lead to a good yield of 1 from crude 4. Indeed, Fig. 6 shows that a 77% yield of 1 is obtained from a crude nearly pure in 4 (88%), and that the ¹H NMR spectrum of the obtained compound is



OVERALL YIELD= 66%
SELECTIVITY RESPECT TO OTHER ALCOHOLS >99%

Fig. 7. Overall yield of target terpinen-4-ol 1 from terpinolene 3.

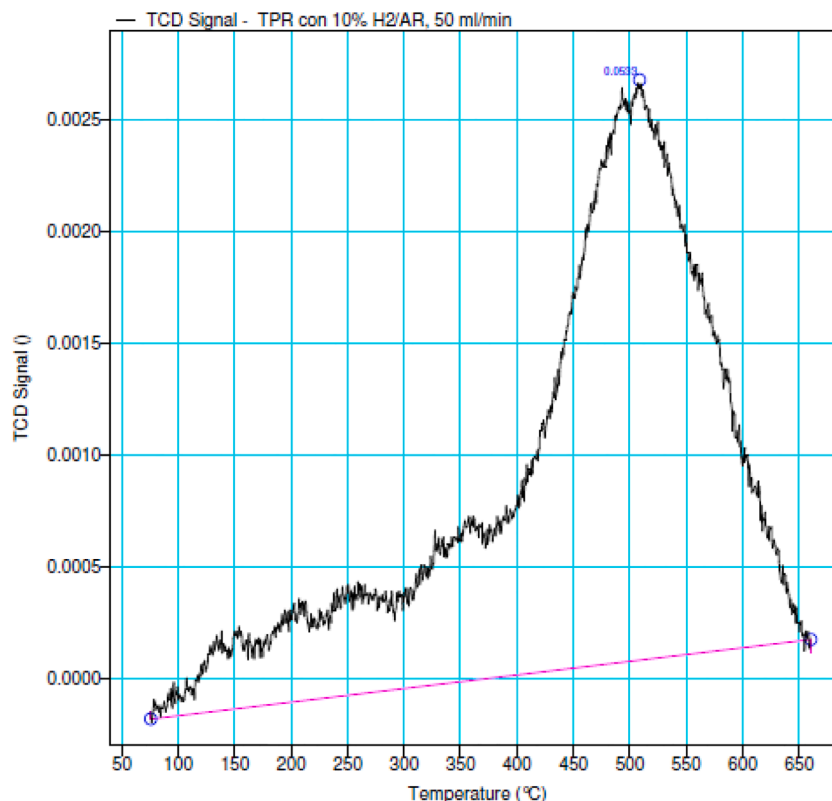


Fig. 8. Temperature-programmed reduction (TPR) of nTiO₂.

identical to that of commercially available (Sigma-Aldrich Co.) terpinen-4-ol **1**. The aromatic impurities observed in the spectrum are not counted in the final yield of **1**. Fig. 6 also shows that the reaction can be run solventless at higher temperature, with a slight decrease in yield [41].

3.5. Overall yield and rationalization of the isomerization/hydrogenation process

3.5.1. Overall yield

Fig. 7 summarizes the best results obtained. An overall 66% yield of target terpinen-4-ol **1** is obtained from terpinolene **3**, after the isomerization/hydrogenation process, without any other co-distilling alcohols present in the final mixture but just some lower boiling points aromatics and cyclic alkanes. The process is 100% atom economic and could be run exclusively with solid catalysts.

It must be noticed here that not all the steps were tested in-flow by different reasons. The first step, i.e. the epoxidation, is not amenable for in-flow conditions because the peroxide agent, either peracetic acid or hydrogen peroxide, are very corrosive agents that require special steel reactors to be handled, which makes extremely expensive the construction of an in-flow reactor. Even using the solid-catalyzed procedure with alumina as the catalyst, the reactor costs will be huge. This is not the case for the isomerization reaction. Regarding the last step, the hydrogenation reaction, a conventional multi-kilogram hydrogenating reactor in batch (i.e. Parr-type) is plausibly the best alternative here, since this type of reactor is very common in industry and allows to carefully control the selectivity.

3.6. Catalytic sites in nTiO₂

The uniqueness of nTiO₂ as active and selective metal oxide catalyst together with the dramatic loss of activity when transition metals are supported discards, in principle, an acid-catalyzed process and points to

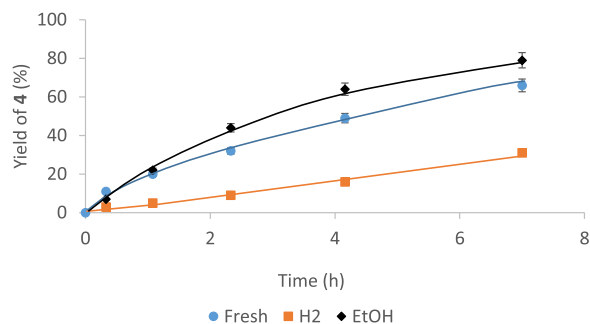


Fig. 9. Comparison of the catalytic activity of fresh nTiO₂, reduced under H₂ at 400 °C and reduced with EtOH at 250 °C. Error bars account for a 5% uncertainty.

a Ti³⁺-catalyzed radical process, with the assistance of the oxygen atoms of the solid. A Ti³⁺-radical mechanism will be in line with the reported opening of epoxides with stoichiometric Ti³⁺ complexes in solution [42] and the capability of nTiO₂ to generate Ti^{3+/4+} catalytic pairs. [35] To shed more light in the catalytic active species, and with the aim of getting more active catalysts, a temperature-programmed reduction (TPR) of nTiO₂ with H₂ was accomplished in order to know at which temperature the Ti⁴⁺ sites transform to Ti³⁺. Fig. 8 shows that the main reduction peak starts at 400 °C. Thus, in order to have some of the Ti⁴⁺ reduced to additional Ti³⁺ sites, we prepared a new nTiO₂ catalyst by reducing the solid at 400 °C on a 10% H₂ in N₂ stream, during 2 h.

The adsorption-desorption isotherm and pore volume distribution of the reduced nTiO₂ solid gives a specific surface area (S_{BET}) of 64 m²/g (Fig. S10), half of the fresh nTiO₂ (110 m²/g). This loss of surface area must be associated to the agglomeration of the nanoparticulated material at high temperature, which irreversibly drives to a loss of catalytic activity. For instance, non nanoparticulated TiO₂ is mainly inactive, as shown in Table 1 (entries 14 and 15), regardless if pure anatase or rutile

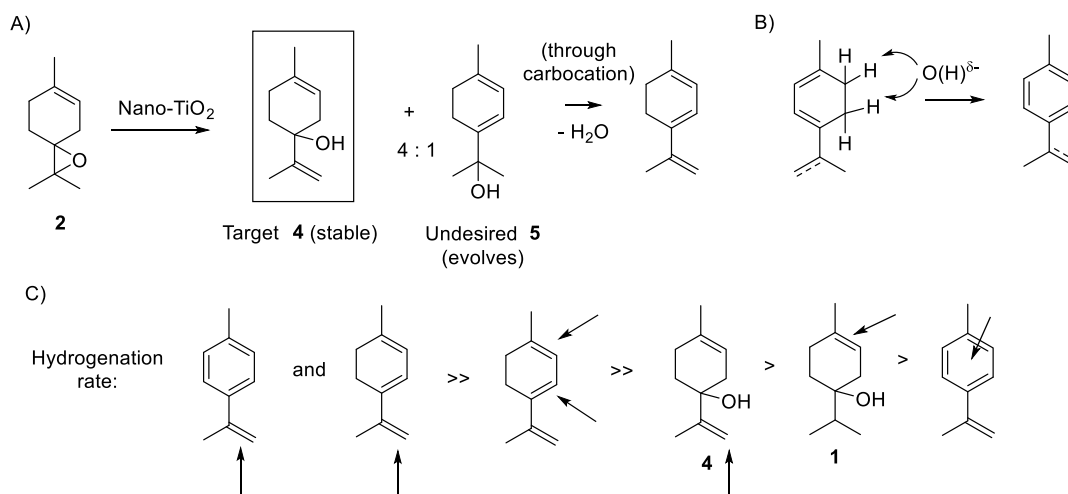
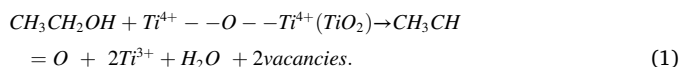


Fig. 10. Rationalization of the reactivity found for the intermediates during the isomerization/ hydrogenation reaction sequence, to give 1.

phases are used. In accordance, Fig. 9 compares the kinetic results for fresh and reduced nTiO₂, and a decrease of one order of magnitude in the catalytic activity is found for the reduced sample.

In order to avoid the agglomeration of nTiO₂ when increasing the relative Ti³⁺/Ti⁴⁺ ratio and, therefore, the amount of accessible Ti³⁺ sites, a milder method was employed, which consists in the treatment of the solid with minute amounts of EtOH at 250 °C [40]. Eq. (1) shows that, in this way, the concomitant oxidation of EtOH to acetaldehyde and reduction of Ti⁴⁺ to Ti³⁺ occurs, through hydrogen-borrowing mechanisms. The method gives coloured TiO₂ materials due to the formation of vacancies associated to the new Ti³⁺ atoms formed.



BET measurements confirmed that the new nTiO₂ material reduced with EtOH basically retained the original surface area (c.a. 100 m²/g) and the kinetic experiments in Fig. 9 above show that this material is more active than fresh nTiO₂. The addition of a 10 mol% of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as a radical quencher during reaction provokes a 10% decrease in the final yield, regardless the reaction conditions (from 78 to 70% at 160 °C in mesitylene solvent and from 86 to 82% in neat 2). These results, together, support that a Ti³⁺-catalyzed radical epoxide opening is operating during the process.

3.7. Reactivity of the intermediates

Fig. 10 shows some key issues which help to understand the process and why the desired terpinen-4-ol 1 is produced without other alcohols. First, Fig. 10A shows that the undesired exocyclic alcohol 5 is apparently formed in ca. 20% yield during the isomerization step, as assessed by kinetic experiments with GC-MS measurements, but dehydrates much more rapidly than the desired intermediate 4, since the elimination in 5 is more favoured by the easier formation of the corresponding intermediate bis-allylic carbocation.

Fig. 10B shows that the conjugated dienes and trienes 6 can aromatize in both steps under the aerobic conditions, probably by the combined action of the basic sites present in nTiO₂ and the hydrides formed with H₂, which may trigger the aromatization reaction. Fig. 10C shows the reactivity order of the different molecules in the hydrogenating mixture, according to GC-MS measurements. 1 is much more stable towards Pd/C-catalyzed hydrogenation than all the rest of alkenes, including terminal alkenes, conjugated alkenes (cyclic or not) and even aromatic alkenes. The stability of the carbon-carbon double bond in 1 can be explained because it is unconjugated, cyclic and substituted.

4. Conclusion

The synthesis of terpinen-4-ol 1 from terpinolene epoxide 2 has been achieved exclusively with simple commercial solid catalysts, alumina, nTiO₂ and Pd/C, in >60% yield and >99% selectivity respect to other co-distilling alcohols, by a 100% atom economic isomerization/hydrogenation process. The only by-products formed are low boiling points aromatic and cycloalkane molecules, easily removable. Implementation in flow has also been demonstrated for the isomerization of terpinolene epoxide. These results significantly improve any current synthetic methodology in the market [43,44], thus enabling the manufacturing of 1 in a safe process, over recyclable solid catalysts and without costly distillations. The active catalytic species during the isomerization reaction are Ti³⁺ atoms on the nTiO₂ catalyst, which gives still room for catalyst improvement [45].

Supporting information

Additional experimental details, Figs. S1-S10 and Tables S1-S5 are available at the end of the document.

CRediT authorship contribution statement

Francisco Garnes-Portolés: Investigation. Carlos López-Cruz: Supervision. Jorge Sánchez-Quesada: Supervision, Writing – original draft. Estela Espinós-Ferri: Supervision. Antonio Leyva-Pérez: Investigation, Supervision, Writing – original draft.

Declaration of Competing Interest

The authors have no competing interests to declare.

Data Availability

Data will be made available on request.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mcat.2022.112785.

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