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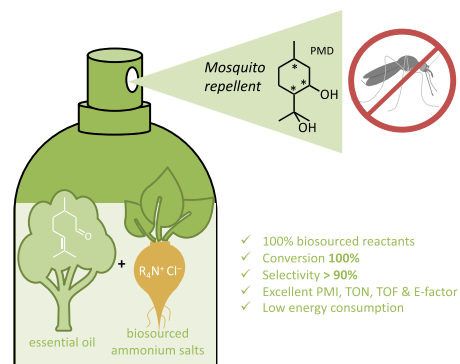
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# Efficient and Greener Process for the Production of *p*-Menthane-3,8-diols Using Biosourced Ammonium Salts as Catalysts

Andrii Stanovysh, Franck Pelissier, Claire M. Grison, and Claude Grison\*

**ABSTRACT:** *p*-Menthane-3,8-diol (PMD) is gradually dethroning the synthetic golden standard mosquito repellent, *N,N*-diethyl-*m*-toluamide (DEET), as PMD is natural and considered safer while displaying an excellent repellent activity. In this study, we revisited the synthetic route of PMD from citronellal in greener conditions, while maintaining the highest yield, and developed a sustainable post-reaction process. Biosourced ammonium salts were tested to catalyze the carbonyl-ene reaction-hydration transforming citronellal and essential oils rich in citronellal into PMD. Ammonium salts led to excellent conversions and selectivities toward PMD, better than previously reported, even at low catalytic loading and rapidly. Catalytic solution of ammonium salts could be directly reused, up to six times without any loss of activity. The sustainability of the methodology was evaluated using a holistic approach which gave excellent green metrics, such as the PMI (6), TON (708), TOF (17), and *E*-factor (0.68) in comparison to other processes. The repellent activities of PMD synthesized from citronellal and from essential oils were evaluated against *Aedes albopictus*, the most invasive mosquito in the world, and were as much or even more repellent than pure PMD.

**KEYWORDS:** *p*-menthane-3,8-diol, biosourced catalysts, sustainable process, catalyst recycling, green metrics, natural mosquito repellent



## INTRODUCTION

Almost half of the world population is exposed to mosquito-borne diseases, as malaria, dengue, chikungunya, yellow fever, and Zika virus disease, ranking mosquito as the world deadliest animal.<sup>1–3</sup> Also, this scenario is deteriorating, as mosquitoes' suitable habitats are expanding, mostly due to population growth, urbanization, connectivity, and climate change. Despite numerous efforts to control mosquito populations, the use of mosquito repellents remains an affordable approach for personal protection from mosquito bites.<sup>4</sup> *N,N*-diethyl-*m*-toluamide (DEET) is the gold standard of mosquito repellent, as it can provide a complete protection up to 8 h.<sup>5,6</sup> However, several studies have brought to light its potential adverse effects on human health<sup>7–11</sup> and clear hints of mosquito resistance.<sup>12–14</sup> Bio-sourced mosquito repellents are hence emerging for a safer use and for a better respect of the environment-friendly criterions defined by consumers' expectations. Although half as active as DEET, *p*-menthane-3,8-diol (PMD) is the most active natural repellent.<sup>6</sup> ( $\pm$ )-*cis*- and ( $\pm$ )-*trans*-PMD displaying a similar repellent activity against *Aedes albopictus*, the cyclization-hydration of citronellal became the commonly used synthetic route of PMD.<sup>15</sup> However, the selectivity toward PMD in this route is challenging as side products can be obtained. Four diastereomers of isopulegol can be formed by the carbonyl-ene reaction and acetals can be formed by the addition of PMD onto citronellal. Several catalysts, homogeneous or heterogeneous acid catalysts, have

been investigated to improve the selectivity of this reaction. Mineral homogeneous acids, as sulfuric acid, were mostly studied, despite a difficult separation from PMD and an impracticable recycling.<sup>16</sup> Following a green chemistry strategy, conventional hazardous acids were replaced by acetic acid<sup>17</sup> and citric acid.<sup>18</sup> However, similar technical issues of separation and recycling were encountered. Recently, new strategies were developed to overcome these difficulties. Carbonic acid in water was then used for the synthesis of PMD, but under 1–6 MPa pressure of CO<sub>2</sub>, which requires a specific handling.<sup>17</sup> A few studies have also investigated the use of heterogeneous catalysts as zeolite (ZSM-5) or pyrolyzed and acidified wastes of alkaline lignin.<sup>19</sup> Although these systems allow recycling of the catalyst, their catalytic efficiency remained limited.

The present work focuses on a new class of biosourced catalysts, ammonium salts derived from a natural origin. More usual ammonium salts have already been reported as acid catalysts for the formation of imines, enamines,<sup>20–22</sup> and acetals.<sup>23</sup> Here, ammonium salts were chosen, as their ionic

nature makes them less miscible to PMD, hence recyclable. Moreover, they were selected as natural, non-toxic, low-cost, and biodegradable with the purpose of following an eco-friendly approach: histidine methyl ester hydrochloride, glycine methyl ester hydrochloride, vitamin B1 hydrochloride, and betaine hydrochloride were used. We have investigated the catalytic activity of these four ammonium salts and compared it with another biosourced catalyst, citric acid. Their activity was tested in the synthesis of PMD from pure citronellal and from essential oils (EOs) rich in citronellal. The reaction conditions, workup procedures, and green metrics were compared to the literature. Also, the repellent activities of the synthesized PMD were determined and compared to standard repellents.

## EXPERIMENTAL SECTION

**Materials.** Ammonium salts (99%), citronellal (99%), and DEET (99%) were all purchased from Sigma-Aldrich. EOs of *Eucalyptus citriodora*, *Cymbopogon winterianus*, and *Citrus hydnifolius* were purchased from MyCosmetik Eko friendly, Nature & Decouvertes, and Dromessence, respectively. *trans*-PMD (95%) was purchased from Santa Cruz Biotechnology and a mixture of *cis*- and *trans*-PMD (98%) was purchased from Sigma-Aldrich.

**Synthesis of PMD from ( $\pm$ )-Citronellal. Procedure Using Citric Acid.** To citronellal (5.5 mmol, 1 mL) was added an aqueous solution of citric acid (0.2 wt %, 4 mL). No other solvent than water from the aqueous solution was added into the reaction. The resulting solution was stirred for 6 h at 70 °C. The aqueous solution was separated by decantation. The resulting organic layer was washed three times with brine (2 mL) to remove the residual citric acid, until pH of the organic layer reached neutrality.

**General Procedure Using Ammonium Salts.** To citronellal (5.5 mmol, 1 mL) was added an aqueous solution of ammonium salt (0.05–1 wt %, 4 mL). No other solvent than water from the aqueous solution was added into the reaction. The resulting biphasic solution was stirred for 6 h at 70 °C. The aqueous solution of ammonium salt was separated by decantation and could be directly reused in a new reaction. The resulting organic layer was composed of PMD at 90–93% of purity at best.

**General Procedure for the Synthesis of PMD from EOs.** To an EO (1 mL) was added an aqueous solution of ammonium salt (0.05–1 wt %, 4 mL). No other solvent than water from the aqueous solution was added into the reaction. The resulting biphasic solution was stirred for 6 h at 70 °C. The aqueous solution of ammonium salt was separated by decantation. The resulting organic layer was mainly composed of PMD.

**Analyses and Quantification.** Gas chromatography analyses were performed using a Thermo Scientific Trace 1300 device with H<sub>2</sub> as a vector gas coupled with an ISQ simple quadrupole mass detector. The column was a Trace TR-5MS column (30 m x 25 mm x 25  $\mu$ m) from Thermo Scientific.

In brief, 1  $\mu$ L of solution was introduced into the gas chromatography–mass spectrometry (GC–MS) system with an injector temperature of 260 °C; split mode was 1/25 with a flow gas of 1 mL/min. The column temperature was programmed as follows: initially, the temperature was kept at 100 °C for 1 min and then heated up to 130 °C with a rate of 40 °C/min and held at 130 °C for 3 min, then heated up to 160 °C with a rate of 15 °C/min and at last heated up to 260 °C with a rate of 50 °C/min and held for at 260 °C for 1.5 min.

The mass spectra of products were recorded using electron ionization in the positive ion mode. The transfer temperature was 300 °C. A full scan mode ( $m/z$  = 50–650) was used with centroid acquisition. Scan time was 0.05 s.

The quantification of the molecule concentration was monitored by GC–MS using external calibration. The most abundant fragment was selected for the quantification of each compound.  $m/z$  of each compound is given in ESI. We performed the calibration curve of commercially available *trans*-PMD and used it for the quantification of

*cis*- and *trans*-PMD. Acetal1 was isolated by column chromatography to perform its calibration curve that was also for acetal2. The limit of detection (LOD) and limit of quantification (LOQ) were calculated with the S/N > 3 method for LOD and the S/N > 10 method for LOQ. Equations of calibration curves, LOD and LOQ are given in ESI.

**Study of the Repellent Activity.** Behavioral tests of the Asian mosquito, *A. albopictus*, were conducted to evaluate the repulsive activity of each compound.

The tests were carried out at the Vectopole Sud in Montpellier (France), which is a WHO collaborating center for the evaluation of insecticides in public health.

Experiments were performed in climate-controlled insectary ( $T$  = 25 °C, RH = 55%). The tests were carried out on female mosquitoes aged of 5–9 days, after their evolution from nymph to adult. The mosquitoes had continuous access to a 10 wt % sucrose solution. On the day of experiment, female mosquitoes were introduced in cups and covered on the top by a net (10 mosquitoes per cup). Feeders, supplying sheep blood (300  $\mu$ L) maintained at 37 °C, were put over the net of the cups. Pig intestinal skin, mimicking the human skin, was placed and stretched over the feeders. Each compound was diluted at their ED<sub>50</sub> (100 mg/m<sup>2</sup> for DEET and 200 mg/m<sup>2</sup> for PMD) in ethanol and was deposited on the skin and spread over the entire surface. Experiments lasted for 1 h. For PMD control, a mixture of both diastereomers *cis*- and *trans*-PMD was used with the ratio 75/25 : *cis/trans*.

The cups were then put in a freezer at –20 °C for 40 min. The frozen mosquitoes were placed between two sheets of paper and were crushed with a Plexiglas plate. Blood-fed mosquitoes were determined using the number of red dots on the sheet of paper. The results were expressed as a percentage of repulsive activity (100% – X% of blood-fed). The percentage of saturation was defined relative to the negative control, ethanol.

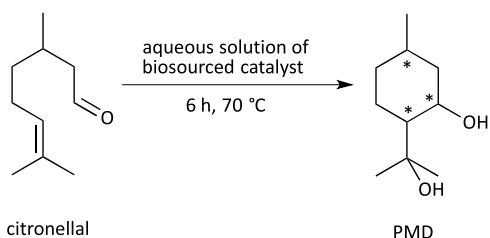
## RESULTS AND DISCUSSION

**Synthesis of PMD. Synthesis of PMD from ( $\pm$ )-Citronellal.** The synthesis of PMD was first performed following the commonly used synthetic route, the acid-catalyzed cyclization-hydration of citronellal.

The activity of different biosourced acid catalysts was evaluated starting from ( $\pm$ )-citronellal (Table 1). Citric acid was used to optimize the reaction conditions, as it has been previously reported as an efficient and biosourced catalyst by Drapeau et al.<sup>18</sup> Following a one-variable-at-a-time strategy (temperature, time, catalyst, stoichiometry, dilution, and catalytic loading), we were able to decrease the reaction time by two and decrease the catalytic loading by 35, while increasing the yield by 10%, reaching a satisfying yield of 76%. However, the purity of PMD was unsatisfying despite several washes, as in solution the pH was 3. This PMD could not be used as such for formulating mosquito repellents, as it could be irritating for a topical use. This acidity might be due to the presence of residual citric acid, which is highly soluble in PMD, hence difficult to remove.

Another class of biosourced and affordable catalysts was hence considered to allow an easier separation from the final product. Biosourced ammonium salts, such as vitamin B1 hydrochloride (VitB1, Cl-HCl), L-histidine methyl ester hydrochloride (H<sub>3</sub>N-His-OMe, Cl-HCl), glycine methyl ester hydrochloride (H<sub>3</sub>N-Gly-OMe, Cl), and betaine hydrochloride (Me<sub>3</sub>N-Gly-OH, Cl), were tested (Tables 1 and S1).

The activities of the ammonium salt catalysts were all excellent, at a catalytic loading of 1 wt %, and gave a conversion range of 91–100% and a selectivity range of 93–100% in only 6 h. The vitamin B1 hydrochloride catalyst led to higher conversion and selectivity toward PMD than the citric

**Table 1. Synthesis of PMD from Citronellal**

catalyst	catalytic loading (wt % and mol %)		conv. <sup>b</sup> (%)	select. <sup>b</sup> (%)
citric acid	0.2	0.001	84	91 <sup>a</sup>
Vit B1,Cl-HCl	0.4	0.001	91	94
H <sub>3</sub> N-His-OMe,Cl-HCl	1	0.003	91	93
	0.4	0.002	46	99
H <sub>3</sub> N-Gly-OMe,Cl	1	0.004	100	93
	0.4	0.003	51	100
Me <sub>3</sub> N-Gly-OH,Cl	1	0.008	96	94
	0.2	0.001	100	90
HCl	0.05	0.0003	83	95
	0.2	0.006	90	71

<sup>a</sup>PMD contains residual citric acid, as pH of its solution was 3.

<sup>b</sup>Conversions and selectivities were determined by GC-MS FID using external calibration.

acid catalyst at the same catalytic loading. Both solutions of amino acid methyl ester hydrochloride gave excellent or total conversion and selectivity toward PMD. Despite the chirality of L-histidine methyl ester hydrochloride, no change of the diastereomeric (*cis-trans*) ratio of PMD could, alas, be observed with L-histidine methyl ester hydrochloride compared to that with achiral glycine methyl ester hydrochloride. Overall, the best results were obtained with betaine hydrochloride, even at low catalytic loadings. Indeed, a solution of 0.001 mol % of betaine hydrochloride led to a total conversion and 90% of selectivity toward PMD, and a similar activity to citric acid was observed but with three times less of betaine hydrochloride (0.001 vs 0.0003 mol %).

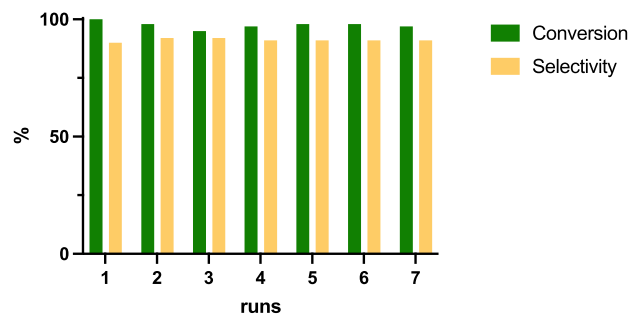
One might think that residual hydrochloric acid could catalyze the reaction, as ammonium salts derived from an HCl treatment post-production. A solution of 0.2 wt % of hydrochloric acid was tested as catalyst, but led to the lowest selectivity toward PMD and led to quite a few side products that were not observed with other catalysts. The catalytic activity of ammonium salts is explained by their own reactivity and is not due to the residual presence of hydrochloric acid.

**Workup Procedure.** The purification process is a key point in the synthesis of PMD. As mentioned previously for the citric acid catalysis, most catalysts are difficult to be separated from PMD, and require intense washes and/or extraction and hence cannot be recycled. The ammonium salts display no solubility in PMD and therefore are easy to remove from the crude reaction mixture by a simple decantation. The solution of ammonium salts could be recovered and reused directly for another reaction, generating no waste.

**Discussion on the Reaction Mechanism.** Using ammonium salts as catalysts led to a shorter reaction time with a lower catalytic loading compared to other syntheses, while the conversion and selectivity toward PMD were systematically better. One might wonder whether this high reactivity is due to the presence of an ammonium moiety showing Brønsted acidity and/or being able to form an intermediate iminium.

The formation of an intermediate iminium is unlikely due to the acidic aqueous reaction mixture at such a high temperature. Betaine hydrochloride was chosen to test this hypothesis, as it is an analogue of glycine methyl ester hydrochloride but with opposite protecting groups, bearing a protected amine as a quaternary ammonium and a free carboxylic acid. The use of a protected amine as a quaternary ammonium instead of a tertiary amine was deliberate to retain an ionic structure for the workup procedure. Betaine hydrochloride was surprisingly more active than the other primary ammonium salts. The carboxylic acid moiety of betaine hydrochloride can replace the role of ammonium moiety and works better than the citric acid catalyst because it exhibits a higher acidity. However, the use of HCl, a stronger acid than betaine hydrochloride, does not improve the yield since the presence of chloride ions led to the formation of side products.

**Recycling of the Catalyst.** Thanks to the ionic nature of the catalyst, all studied ammonium salts could be separated from the crude reaction by a simple decantation procedure. The recycling of the catalyst was studied with the most active, that is, the 0.2 wt % solution of betaine hydrochloride. After decantation, the solution of betaine hydrochloride was directly introduced into the next run. This process has been repeated six times and no decrease in conversion or selectivity was observed (Figure 1 and Table S2).



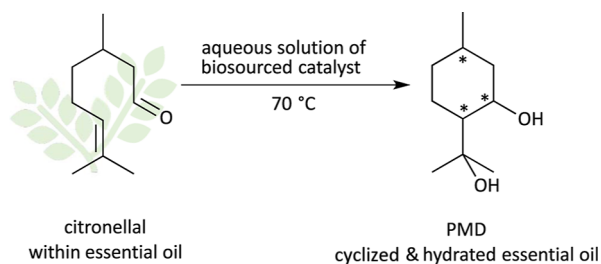
**Figure 1.** Recycling study of the 0.2 wt % solution of betaine hydrochloride for the cyclization-hydration of (±)-citronellal.

**Synthesis of PMD from EOs.** Instead of starting from pure citronellal, the synthesis of PMD was then envisaged using EOs naturally rich in citronellal (Tables 2 and S3). Using directly EO as a starting material avoids using citronellal that would have been extracted and purified, and hence decreases the environmental impact of the entire process of PMD production.

Eos of lemon-scented gum or *E. citriodora* (recently renamed *Corymbia citriodora*), java citronella or *C. winterianus*, and kaffir lime or *C. hystrix*, were selected, since they naturally contain 74, 36, and 81% of citronellal, respectively.<sup>24–26</sup>

Citric acid was first used as it has been previously reported.<sup>18</sup> However, due to its residual presence in the final product and its high catalytic loading (7 wt %), the biosourced ammonium salts—histidine methyl ester hydrochloride, glycine methyl ester hydrochloride, vitamin B1 hydrochloride, and betaine hydrochloride—were preferred. They were used at their ideal concentrations, determined in Table 1, for promoting the reaction. Ammonium salts acted as efficient catalysts, systematically better than citric acid, showing excellent conversion and high selectivity for the cyclization-hydration of citronellal within all EOs, and in only 6 h. The solution of 1 wt % histidine methyl ester hydrochloride led to the highest

**Table 2. Synthesis of PMD from EO**



essential oil	catalyst	catalytic loading (wt % and mol-%)		time (h)	conv. <sup>b</sup> (%)	select. <sup>b</sup> (%)
		wt %	mol-%			
<i>E. citriodora</i>	citric acid	7	0.036	15	86	90 <sup>a</sup>
	H <sub>3</sub> N-His-OMe,Cl	1	0.004	6	99	85
	H <sub>3</sub> N-Gly-OMe,Cl	1	0.008		90	83
	Vit B1,Cl-HCl	1	0.003		92	84
	Me <sub>3</sub> N-Gly-OH,Cl	0.2	0.001		98	87
<i>C. winterianus</i>	H <sub>3</sub> N-His-OMe,Cl	1	0.004	6	98	92
	H <sub>3</sub> N-Gly-OMe,Cl	1	0.008		92	92
	Vit B1,Cl-HCl	1	0.003		73	91
	Me <sub>3</sub> N-Gly-OH,Cl	0.2	0.001		93	96
<i>C. hystrix</i>	H <sub>3</sub> N-His-OMe,Cl	1	0.004	6	92	91
	H <sub>3</sub> N-Gly-OMe,Cl	1	0.008		89	91
	Vit B1,Cl-HCl	1	0.003		65	90
	Me <sub>3</sub> N-Gly-OH,Cl	0.2	0.001		89	93

<sup>a</sup>PMD contains residual citric acid, as pH of its solution was 3.

<sup>b</sup>Conversions and selectivities were determined by GC-MS FID using external calibration.

conversion of 98% of citronellal from the EO of *C. winterianus* and a selectivity of 92% toward PMD. Betaine hydrochloride was also the most active catalyst as it led to a similar activity in only a 0.2 wt % solution. As previously, the synthesized PMD from EOs did not display an acidic pH.

Overall, ammonium salts are excellent catalysts for the synthesis of PMD not only from pure citronellal but also from a mixture of citronellal and other natural compounds that is an EO.

**Comparison of the Ammonium Salt-Catalyzed Process with the Literature Using Green Metrics.** The reaction conditions using ammonium salts as well as the associated workup procedure were compared to selected types of processes from the literature: the industrial process from Takasago International Corporation,<sup>16</sup> and “greener” processes—one starting from an EO and using a biosourced catalyst,<sup>18</sup> one conducted under CO<sub>2</sub> pressure,<sup>17</sup> and one using pyrolyzed and acidified wastes of alkaline lignin (lignosulfonic acid) as catalysts<sup>19</sup> (Figure 2).

In Takasago International Corporation’s reaction,<sup>16</sup> the catalyst, sulfuric acid, is not biosourced and hazardous; for Drapeau et al.<sup>18</sup> and Kurnia et al.,<sup>19</sup> despite the effort of using a biosourced catalyst, the loading of the catalyst (citric acid or

lignosulfonic acid) is high (7 or 50 wt %) and the reactions are not rapid; and for Cheng et al.,<sup>17</sup> the use of CO<sub>2</sub> requires specific handling at 1 MPa. Here, much effort has been made on every parameter of the reaction, as the starting material is an EO hence biosourced, the catalyst is biosourced and used at a low loading, and the reaction is rapid and the temperature is moderate.

The workup procedure is a critical step for a process to be fully sustainable, by reducing the production of wastes and by recycling catalysts. In this study, no further purification step was performed, as the best reaction conditions led to good purities of PMD, varying from 86 to 93% depending of the starting material (EOs or pure citronellal). Although higher than the other green processes, we are aware that the purity of our PMD is not as high as the purity of Takasago’s PMD (99.5%). However, a compromise was made between a high purity and the quantity of generated wastes during the workup procedure.

Moreover, in our process and thanks to the chemical properties of the catalyst, the solution of ammonium salts could be reused in seven successive runs. Such recycling was not performed in Takasago’s process.

Green metrics for the sulfuric acid and the lignosulfonic acid catalytic processes could be calculated from the data available in the literature, allowing a holistic comparison of their sustainability with the process using citric acid, optimized by our group, and our process using betaine chloride. Details of calculation are included in the ESI. For an accurate comparison, only processes starting from citronellal were chosen.

Eight green metrics were calculated (Table 3): the optimum efficiency (OE) describing the efficiency of the reaction in terms of reactants by combining the atom economy (AE) and the reaction mass efficiency (RME), the process mass intensity (PMI) which has been detailed for solvents and workup, the TON representing the lifetime robustness of a catalyst and the TOF measuring its instantaneous efficiency, and the *E*-factor evaluating the production of wastes and the consumption of energy during the reaction. The solvents used during the reaction and the workup procedure were also considered and flag marked.<sup>27,28</sup>

In general, reported processes present good metrics in individual categories, but our strategy based on betaine hydrochloride catalysis led to the best green metrics in every category. In details, the OE of each process are similarly high (76–91%), as the four processes follow the same strategy of carbonyl-ene reaction-hydration from citronellal into PMD. Only the citric acid-catalyzed reaction displays a lower OE in connection with a lower yield, which would discourage an industrial development. The PMI, which is considered as one of the most important mass-based metrics by the chemical industry, shows significant differences between the processes (5–69), especially due to the workup procedures. The highest mass efficiency, or lowest PMI, was obtained for the sulfuric acid- and betaine hydrochloride-catalyzed reactions.

Betaine hydrochloride- and lignosulfonic acid-catalyzed reactions gave the highest TON values of 708 and 346, respectively, as these methodologies are the only examples of catalyst recycling. A similar TOF for citric acid, lignosulfonic acid, and betaine chloride displays the same instantaneous efficiency of these catalysts.

The *E*-factor, which varies between the processes in connection with the solvent use, workup, and recyclability of

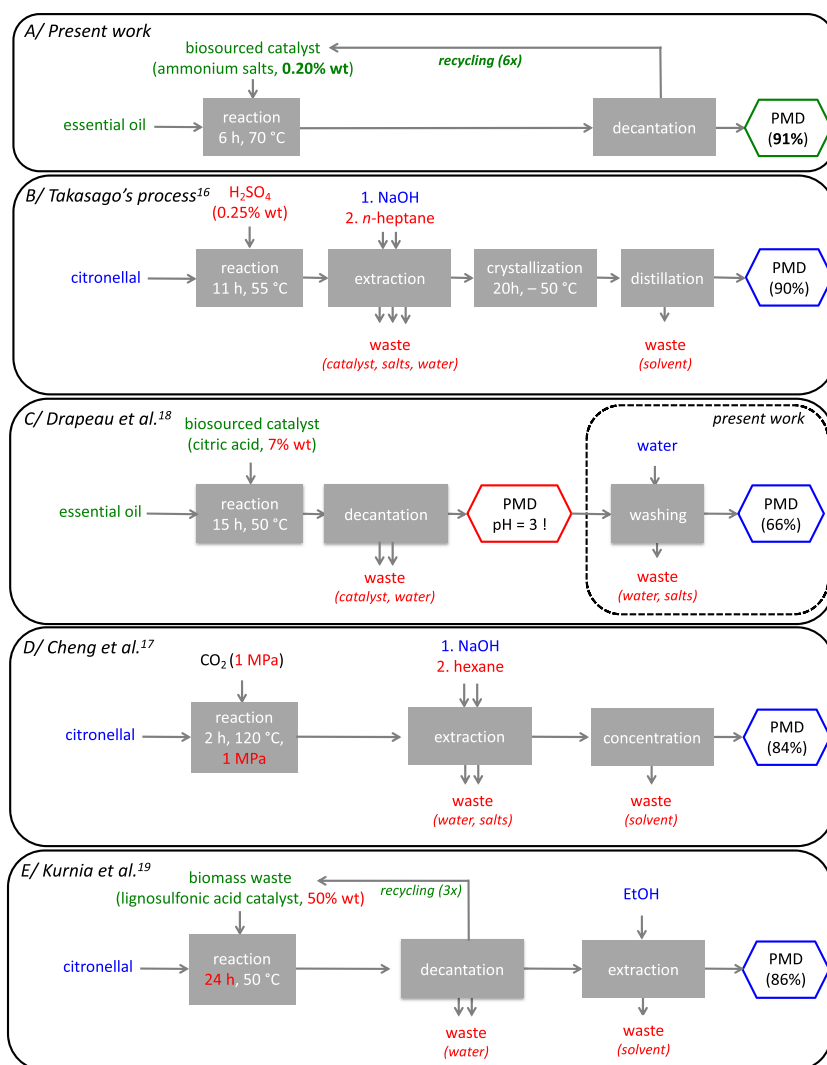


Figure 2. Comparison of processes for the synthesis of PMD.

Table 3. Comparison of the Green Metrics Calculated from Selected Processes of PMD Synthesis

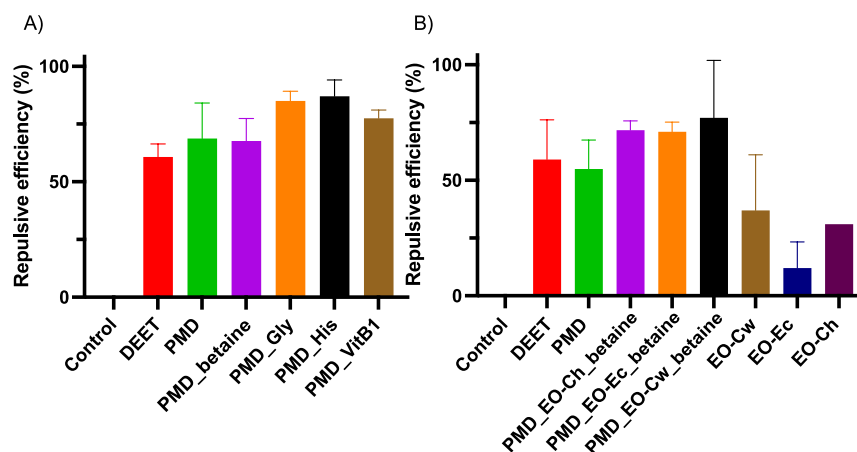
method	OE <sup>a</sup> (%)	PMI	PMI (solvents) PMI (workup)	TON TOF	E-factor	energy <sup>b</sup> (°C h)	catalyst flag (origin)	solvent flag	
citronellal and lignosulfonic acid <sup>19</sup>	86	69	26	346	49.7	1200	Green (recycled)	Green	
			41						4
			8						
citronellal and citric acid (present work)	76	15	6	100	13.9	420	Green (natural)	Green	
			17						
			8						
citronellal and sulfuric acid <sup>16</sup>	91	5	1	182	4.4	605	Amber	Amber	
			17						
			3						
citronellal and betaine chloride (present work)	90	6	5	708	0.6	420	Green (recycled)	Green	
			17						
			0						

<sup>a</sup>OE represents the optimum efficiency of the reaction and is calculated as  $RME/AE \times 100$ .<sup>27</sup> <sup>b</sup>The energy consumption was calculated as reaction temperature x reaction time, since data of electric power are not available.

the catalysts, is excellent for betaine chloride-catalyzed reaction thanks to the catalyst recycling and the generation of minimum of wastes.

The nature of the catalyst was scored using a green flag for the natural or recycled origin.<sup>27</sup> Lignosulfonic acid-, citric acid-,

and betaine hydrochloride-catalyzed reactions obtained a green flag, since catalysts were recycled from paper industrial wastes, derived from fermentation processes and recycled from sugar beet wastes.



**Figure 3.** Comparison of the repulsive efficiency of (A) PMD synthesized from pure citronellal and (B) PMD synthesized from EO versus commercial DEET and PMD. DEET and PMD (7S/2S : *cis/trans*) were used at their  $ED_{50} = 100$  and  $200$  mg/m<sup>2</sup>, respectively. Mosquito behavioral experiments were conducted in duplicates or triplicates. PMD\_EO-Ch\_betaine, PMD\_EO-Ec\_betaine, and PM\_EO-Cw\_betaine stand for PMD synthesized from EOs of *C. hystrix*, *E. citriodora*, and *C. winterianus* using betaine hydrochloride as the catalyst.

Although the reaction temperatures of all processes led to a green flag (less than 70 °C),<sup>27</sup> the energy consumption of the citric acid- and betaine chloride-catalyzed reactions was the lowest thanks to their rapidity.

The type of solvents used for the reaction and the workup led to a green flag for all processes except for the sulfuric acid-based reaction, due to the use of *n*-heptane for the crystallization step.

**Study of the Repulsive Activity.** The repulsive activities of PMD synthesized from pure citronellal (Figure 3A) and PMD synthesized from EOs (Figure 3B) were evaluated against the most invasive mosquito in the world, *A. albopictus*. The activity of the synthesized PMD was compared to a negative control, ethanol, and two positive controls, commercial PMD and commercial DEET, which are the mosquito repellent references. The mosquitoes were let for 1 h in the presence of a blood-feeder coated by intestinal pigskin, which has already been impregnated by the compound to be tested. The repellent activity of each compound was measured as the percentage of mosquitoes that have not consumed blood.

PMD synthesized from pure citronellal—PMD\_betaine, PMD\_Gly, PMD\_His, and PMD\_VitB1—gave a high repellent efficiency, regardless of the catalyst used for its synthesis. Their repulsive activity was similar or higher than the commercial PMD.

As the catalyst used for the synthesis did not impact significantly the repulsive activity of PMD, only EOs transformed in the presence of betaine, the best catalyst, were tested in the mosquito behavioral tests.

PMD synthesized from EO—PMD\_EO-Ch\_betaine, PMD\_EO-Ec\_betaine, and PMD\_EO-Cw\_betaine—gave a high repellent efficiency, regardless of the EO. The repulsive activity of each PMD synthesized from EOs was systematically higher than the non-transformed EO and was similar or higher than the commercial PMD.

PMD, that was synthesized here with a purity of 86 and 93%, was directly used without further purification in the mosquito behavioral tests, whereas the purity of the commercial PMD was 98%. However, as described previously PMD synthesized here was more repulsive than the purer commercial PMD. It is

important to emphasize that higher purity does not always lead to higher efficiency.

## CONCLUSIONS

The cyclization-hydration of citronellal or EOs rich in citronellal into PMD could be catalyzed by a new class of biosourced catalysts, ammonium salts. The use of such ammonium salts showed benefits for the synthesis and for the workup procedure. Especially betaine hydrochloride, due to its highest acidity, led to high conversion and selectivity toward PMD, in a short reaction time and even at a low catalytic loading. The workup procedure was simplified, as ammonium salts could be easily separated from PMD, avoiding the generation of wastes and allowing the recycling of the catalyst. Overall, the synthetic route of PMD was revisited in greener conditions thanks to the use of such ammonium salts, which also led to a higher catalytic efficiency than other processes. Eight green metrics of this strategy were quantified and showed excellent data in comparison to the literature.

Due to the novelty of the synthesis and workup procedure, the repellent activities of PMD synthesized here were evaluated against *A. albopictus*, the most invasive mosquito in the world, and were as much or even more repellent than pure standard mosquito repellents.

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A.S. and C.G. designed research; F.P., A.S., and C.G. performed research; F.P., A.S., C.M.G., and C.G. analyzed data; C.M.G. and C.G. wrote the paper. All authors have given approval to the final version of the manuscript.

## Notes

The authors declare no competing financial interest.

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## ABBREVIATIONS

DEET, *N,N*-diethyl-*m*-toluamide; EO, essential oil; GC–MS, gas chromatography–mass spectrometry; LOD, limit of detection; LOQ, limit of quantification; PMD, *p*-menthane-3,8-diols

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