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Geraniol: Semester Assignment

Chemistry 4220

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## I. Geraniol

Geraniol, a monoterpenoid alcohol, is a naturally occurring essential oil. This natural product is a geometric isomer of citral and can be found alongside other terpenes in a wide variety of fruits, vegetables, and herbs. It is recognized as a key product within the global flavour and fragrance industry, and recent research has exhibited significant pharmacological properties that can aid in cancer research. Most of the geraniol commercial production consists of extraction and partial chemical syntheses, however with the rise of new technology allowing for genetic engineering, methods for increased geraniol production in microorganisms are being researched. In whole, this extensive review analyzes the natural product geraniol, specifically its structure, applications and manufacturing processes.

## II. Terpenes

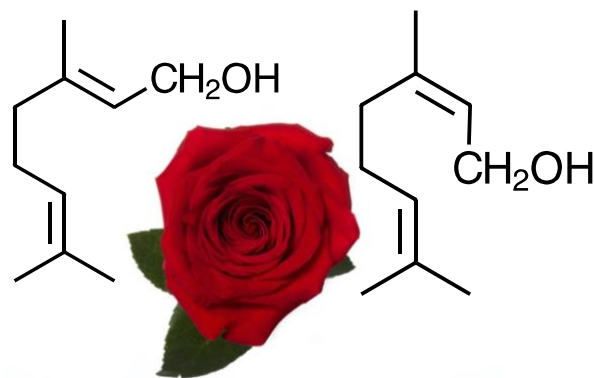
Within the class terpenes, which to date comprises more than 30,000 compounds, monoterpenes demonstrate the fusion of two isoprene molecules arranged in various structures such as cyclic, straight and branched. The analysis of terpenes began in 1884, when German chemist Otto Wallach isolated terpenes from essential oils and conducted extensive structural derivatization and elucidation.<sup>1</sup> On account of Wallach's significant contribution to terpene chemistry, this chemist was granted a Chemistry Nobel Prize in 1910. The properties of a few common terpenes are presented in Table 1. Since terpenes are built up hydrocarbons, they all have a similar chemical formula,  $(C_5H_8)_n$ , however can also be oxygenated as shown in the compounds of citral, geraniol, nerol and linalool. These compounds are also exceedingly aromatic and are commonly associated with the unique smells and tastes of numerous plants, such as pine, lavender, and rose. Further, due to the wide applicability of these compounds, terpenes are found in numerous consumer industries, such as cosmetics, pharmaceutical as well as food and beverage.<sup>2</sup>

**Table. 1** Properties of common terpenes.

Terpene	Formula	Odor	Essential Oil Appearance	Common Sources	CAS Number	Reference
Citral	C <sub>10</sub> H <sub>16</sub> O	Lemon	Pale yellow	Lemongrass oil	5392-40-5	PubChem <sup>3</sup>
Geraniol	C <sub>10</sub> H <sub>18</sub> O	Rose	Colorless to pale yellow	Rose/palmarosa oil	106-24-1	PubChem <sup>4</sup>
Nerol	C <sub>10</sub> H <sub>18</sub> O	Rose	Pale yellow-orange	Lemongrass oil	106-25-2	PubChem <sup>5</sup>
Limonene	C <sub>10</sub> H <sub>16</sub>	Orange or Lemon	Colorless	Citrus oil	5989-27-5	PubChem <sup>6</sup>
Pinene	C <sub>10</sub> H <sub>16</sub>	Pine	Colorless	Pine tree oil	1330-16-1	PubChem <sup>7</sup>
Linalool	C <sub>10</sub> H <sub>18</sub> O	Lavender	Colorless	Lavender	78-70-6	PubChem <sup>8</sup>

### III. Geometric Isomers: Geraniol and Nerol

As depicted in Figure. 1, the structure of geraniol, 3,7-dimethylocta-2,6-dien-1-ol, is acyclic with a hydroxyl group at its tail end resulting in it being a primary alcohol as well as the reason for the odor quality and potency.<sup>9</sup> Albert Verley is known as the French chemist who first elucidated the structure of geraniol in a paper published in 1919.<sup>10</sup> The geraniol product is understood to be a mixture of a pair of geometric isomers of citral, individually known geraniol, trans-citral, and nerol (neral), cis-citral, shown in Figure. 1. Citral, also a naturally occurring essential compound, is commonly associated with a strong citrus, or lemon, scent and can be identified by its yellow hue. This complex can be isolated through distillation from various essential oils, with lemongrass being most common.



**Figure. 1** Structure of geraniol (left) and nerol (right)

Similar to geraniol, nerol, the Z-isomer of citral, has a characteristic rose like scent, although considered to be less potent than its counterpart.<sup>9</sup> A study conducted in 2018, demonstrated this property as it reviewed the odor thresholds, OT, of both geraniol and nerol, finding that the former had an OT of 14 ng/L whereas the latter demonstrated an OT of 60 ng/L. The results of this study indicated the configuration of the compound, cis or trans, has a substantial effect on its respective odor capacity.

### IV. Sources of Geraniol



**Figure. 2** Fully matured spikelet of palmarosa.<sup>11</sup>

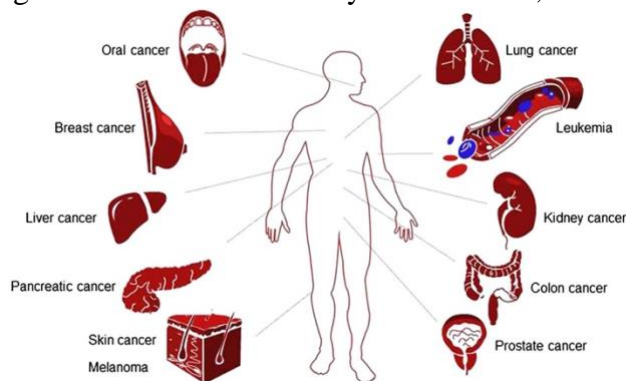
The sources of the compound geraniol vary widely, being found in various quantities within the essential oils of common plants, including fruits, vegetables, and herbs.<sup>4</sup> Studies have shown that geraniol is the main constituent of palmarosa oil, reaching 90.59 %, as well as one of the main components of rose oil, being 31.05 %.<sup>11,12</sup> However, it was found the yield of geraniol within essential oils is dependent on multiple factors, such as plant time, stages of harvesting, season and plant treatments.<sup>11,13</sup> Specifically, it was found in palmarosa (*Cymbopogon martini*, Roxb. Wats. var. motia) the highest yield of geraniol was within fully matured spikelets, as shown in Figure.

2.<sup>11</sup> The palmarosa plant is native to India, but can be found growing in Pakistan, Indonesia, and Brazil due to their tropical and humid conditions.<sup>13</sup> Possibly due to its high content of geraniol, the palmarosa plant is often utilized in aromatherapy as well as South-east Asian traditional medicines.<sup>15</sup>

## V. Application of Geraniol

This commercially important compound has applications in numerous industries, such as food, fragrance, pharmaceuticals, and pesticides, due to its characteristic sweet floral scent. Due to its wide applicability, geraniol is manufactured and marketed across the globe with major regions including North America, Latin America, Europe, Asia Pacific, and the Middle East.<sup>16</sup> Various chemical companies produce this compound, such as Symrise Co. and International Flavours and Fragrances, Inc., leading the industrial production of geraniol to exceed 1000 tons per year.<sup>17</sup>

The food industry employs geraniol as a flavouring agent, for flavours such as citrus, raspberry and watermelon, whereas the fragrance industry uses the compound as a scent ingredient in many common cosmetic products. Gas-chromatography and mass spectrometry quantitative analysis' have demonstrated geraniol to be one of the most common fragrances in cosmetic products. This compound was found in a range of 40-60 % within consumer products such as deodorants, skin care products, and perfumes, emphasizing its widespread use due to its aromaticity.<sup>18,19</sup> Additionally, geraniol has proven to be a success in the field of medicine due to its significant pharmacological properties. According to a review conducted by Yu Lei et al., the antioxidant, anti-inflammatory, anti-microbial and anti-tumor characteristics of geraniol allows this compound to be a remarkable drug candidate for various diseases.<sup>20</sup> Within the study, the discussion involving its anti-tumour applications indicated this natural product is able to promote anti-proliferation, and demonstrates significant beneficial results as a treatment for colon, liver, lung, pancreatic, prostate and skin cancer as well as endometrial carcinoma. A visual illustration of the various cancers that geraniol has



**Figure. 4** Cancer types which are sensitive to geraniol.<sup>21</sup>

demonstrated favourable effects against is shown in Figure. 4. These results are remarkable when considering the rise of cancer-causing deaths worldwide and the ongoing search for cancer treatments. Further, geraniol, among other essential oils, was suggested as a defence against the SARS-CoV-2 virus, or Covid-19.<sup>22</sup> This review, published in June 2020, proposed the penetration and disruption of viral membranes could be accomplished by essential oils due to their lipophilic nature. Although, due to the minimal preliminary results, involving computer aided simulations and in vitro studies, the use of geraniol as a potential treatment against Covid-19 remains inconclusive.

The ability of essential oils, and geraniol, to disrupt cell walls, membranes or organelles of microorganisms also allows this compound to be used in the pesticide industry as a mosquito, tick or mite repellent.<sup>17</sup> Geraniol is currently approved until 2023 as an active substance by the European Commission, who is deemed to have the most comprehensive pesticide regulations.<sup>23,24</sup> Despite its pesticidal use, the toxicity of geraniol is known to be low as reported by the U.S. Environmental Protection Agency, and as such deemed of minimal risk towards human health and the environment if used within labelled rates.<sup>17</sup> As illustrated in Table. 2, geraniol does not present a high LD<sub>50</sub> in rats, being 3600 mg/kg and is not persistent in the environment long after exposure, exhibiting the longest half-life in the soil. The compounds lengthy half-life in soil is due to its affinity to organic matter, which is demonstrated by its relatively large log K<sub>ow</sub> of 3.65. Further, although independently geraniol is considered a weak irritant/allergen, following an oxygenation process this compound has the potential to produce highly allergenic substances.<sup>25</sup> These compounds, identified in a study conducted by Lina Hagville et. al, were deemed to be hydroperoxide, aldehyde, geranial and neral.

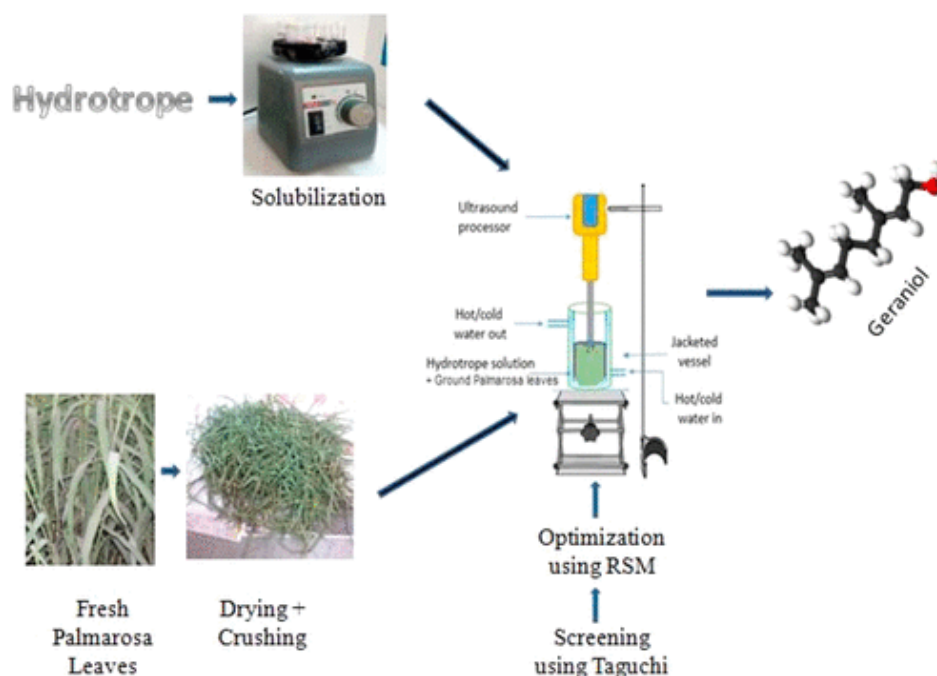
**Table. 2** Environmental and toxicological properties of geraniol.

Property	Value	Reference
LD50 (Rat)	3600 mg/kg	Thermo Fisher Scientific SDS <sup>27</sup>
WHO ADI	0.5 mg/kg	WHO 2004 <sup>28</sup>
Air half life	0.261 h	Cornell University <sup>17</sup>
Water half life	13.61 h (River) 10.53 days (Lake)	Cornell University <sup>17</sup>
Soil half life	30 days	Cornell University <sup>17</sup>
Persistence	18.4 days	Cornell University <sup>17</sup>
Octanol/Water Coefficient (K <sub>ow</sub> )	log K <sub>ow</sub> = 3.56	Cornell University <sup>17</sup>

## VI. Extraction of Geraniol

In 1871, geraniol was first extracted by German chemist, Oscar Jacobson.<sup>28</sup> Oscar Jacobson extracted this compound through fractional distillation of an essential oil obtained from geranium grass. Since then, there has been many unique methods that have been determined and utilized to extract this important compound from various essential oils. In general, essential oils from aromatic or medicinal plants are most commonly extracted utilizing the hydrodistillation method, which involves the evaporation of essential oils through the boiling of the essential oils in a solvent.<sup>29</sup> Specifically, a study in 2016 optimized the hydrodistillation extraction of geraniol, which resulted in a 1.4230 % w/w yield.<sup>30</sup> This research group utilized the leaves of the Palmarosa plant, which, as mentioned

previously, Palmarosa oil is known to contain the highest content of this natural product. Conversely, in an effort for a more sustainable approach in the extraction of geraniol from the Palmarosa plant, Miral R. Thakker et. al. developed an ultrasound assisted hydrotopic extraction method, as shown in Figure. 5.<sup>31</sup> Due to the insolubility of geraniol, as shown by its high  $K_{ow}$  in Table. 2, a hydrotope, which



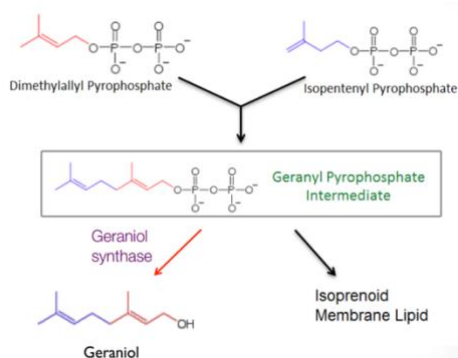
**Figure. 5** Ultrasound assisted hydrotopic extraction method.<sup>31</sup>

is a green solvent, can be employed to solubilize the hydrophobic components of a solution. However, utilizing the hydrotopic extraction technique often required extended extraction periods as well as a high concentration of hydrotopes. Therefore, this technique employed the use of ultrasonic waves to minimize the extraction time as well as the solvent needed, being the hydrotope. The yield of geraniol from this study was 1.8432 % w/w, and with the recycling of the hydrotopic solution only decreased to 1.8405 % w/w. Additionally, in 2014, a study confirmed the presence of geraniol in Java Citronella grass (*Cymbopogon winterianus*), which is also known to

contain a significant quantity of geraniol.<sup>32</sup> This research analysed the extraction of geraniol through a manual and crude extraction using various solvents, such as Methanol and *n*-hexane, and concluded Methanol was the best extractant due it producing the highest yield of oil.

## VII. Synthesis of Geraniol

Commercially, methods of geraniol synthesis include a mixture of natural extraction, partial synthesis from previously synthesized terpenes and total synthesis from various

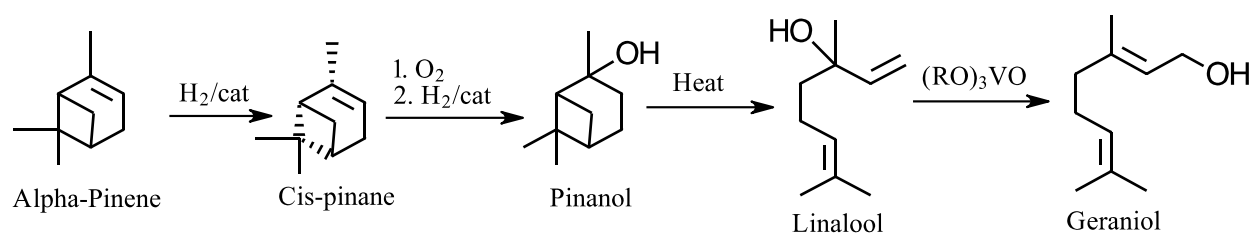


**Figure. 6** Common biosynthesis pathway of geraniol.<sup>41</sup>

petrochemicals. The biosynthetic pathway of geraniol, however, has been extensively studied for potential optimization strategies for commercial production. As shown in Figure. 6, geraniol can be derived through the mevalonate pathway using dimethylallyl pyrophosphate, IPP, and isopentenyl pyrophosphate, DMAPP. The head to tail condensation of these two five carbon units produce the intermediate geranyl pyrophosphate, GPP. Geranyl pyrophosphate, a ten-carbon compound, is known as the precursor to all monoterpenes or monoterpenoids. Although it was widely recognized that geraniol was synthesized by intermediate, geranyl diphosphate, it was not until 2004 the synthase that catalyzed the reaction was characterized.<sup>33</sup> Previously, it was suggested the synthesis involved the method of phosphatase, however Iijima et al. determined geraniol synthase was most similar to that of other monoterpene synthase-based catalysis.

Although extraction of geraniol from biological sources, such as the Palmarosa plant, have proven successful, this method is limited and is unable to fulfill the demands of the numerous industries geraniol is applicable to. As a result, chemical synthesis of this natural product has been employed by multiple manufacturing businesses. The total synthesis of geraniol has been researched since the mid 1900's, with a failed attempt being reported in 1954 by Kwart and Miller.<sup>34</sup> This method proposed the total synthesis of geraniol could be completed using starting material isoprene, however the product yielded was geranyl methyl ether, an alkyl ether of geraniol. It was not until twelve years later that Burrell et al. successfully synthesized geraniol by reducing *trans*-methyl geranate and purifying with calcium chloride.<sup>35</sup> This research also concluded that since the carbon- carbon double bonds were not affected through the reductions,

the previously suggested geometrical configuration of geraniol and nerol, being *trans* and *cis* respectively, must be accurate. Currently, various terpenoids are utilized as starting points for the “half-syntheses” commercial production of geraniol. As mentioned previously, geraniol is mass produced by Symrise Co., previously known as Glidco (SCM) and Millennium Specialty Chemicals. In 1988, Glidco (SCM) was the world’s largest supplier of geraniol and linalool, with manufacturing located in Jacksonville Fl.<sup>36</sup> This company employs an extensive process that begins with starting material  $\alpha$ -pinene, previously synthesized by fractional distillation of crude sulfate turpentine.<sup>37</sup> Crude sulfate turpentine is a foul-smelling by-product from the paper industry, where it functions as a fuel. The fractional distillation of this natural product results in a mixture of 60-70 %  $\alpha$ -pinene, which is then transformed into pinanol and linalool, as shown in Scheme. 1, before yielding a mixture of geraniol and nerol. Although lengthy, this technique produces geraniol with 99 % purity.



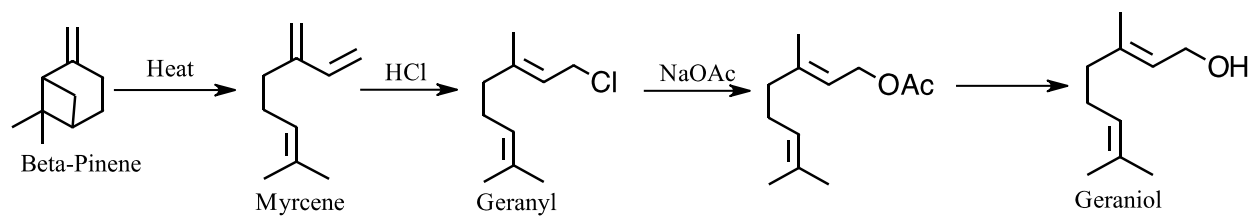
**Scheme. 1** Formation of geraniol from  $\alpha$ -pinene.

The functionalization of linalool to produce geraniol, as shown in Scheme. 1, involves an allylic rearrangement, often requiring a catalytic system,  $(RO)_3VO$ . Interestingly, a patent for an allylic rearrangement of linalool to geraniol was filed in 1979 by the SCM Corporation, emphasizing this companies’ chemical advances in terpenoid chemistry.<sup>38</sup> Alkyl orthovanadates have been widely utilized in the allylic rearrangement of linalool, and have been deemed the most selective catalysts for this isomerization.<sup>39</sup> A study published in 2003 within the *Journal of Molecular Catalysis* reported of catalytic system comprising of alkyl orthovanadate and tetrabutyl ammonium hydroxide,  $[(Bu)_4N^+][OH^-]$  that was very stable and selective towards the allylic rearrangement process of linalool and geraniol. The research concluded the reaction rate of the isomerization increases with increased catalyst concentration, however plateaus at a catalyst loading of 0.3-1.0 % mol.

Similarly, the fractional distillation of crude sulfate turpentine is also reported to produce 20-25 % of  $\beta$ -pinene.<sup>37</sup> Albeit produced at a lesser rate than  $\alpha$ -pinene,  $\beta$ -pinene can also be utilized for the synthesis of geraniol. As demonstrated in Scheme. 2, the formation of geraniol from  $\beta$ -



pinene involves the production of intermediate myrcene and geranyl. The use of  $\beta$ -pinene in the synthesis of other terpenes, however, is known to be inefficient and expensive. Impurities present within the reaction, such as chlorinated impurities, is known to inhibit the purity of products. Further, the process requires an exorbitant amount of energy in the form of heat, 500 °C, for the production of myrcene. Lastly, as mentioned previously, both  $\alpha$ -pinene and  $\beta$ -pinene are synthesized from crude sulfate turpentine, however the amount of  $\beta$ -pinene produced is significantly less than  $\alpha$ -pinene, effectively decreasing its availability.

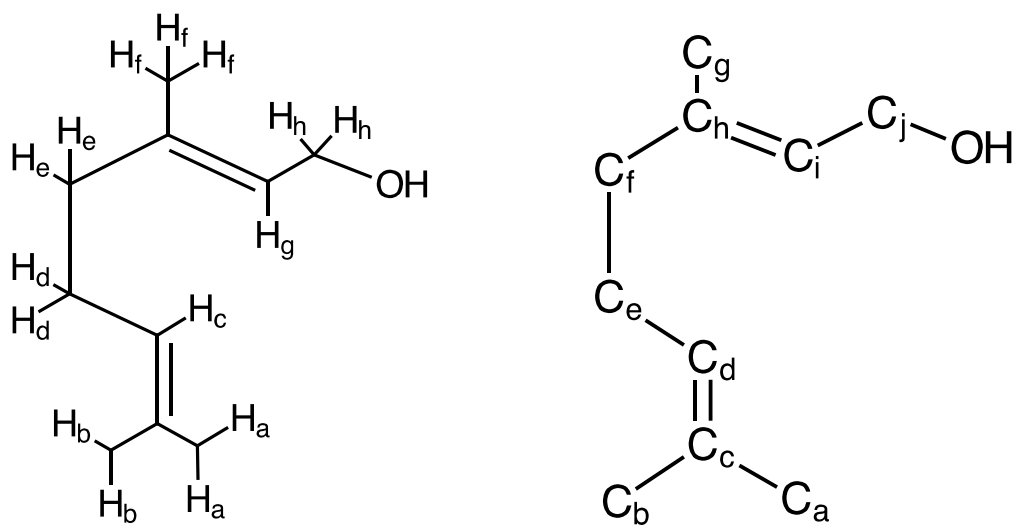


**Scheme. 2** Formation of geraniol from  $\beta$ -pinene.

The total synthesis of geraniol often involves other terpenoids, such as linalool, as intermediates. Beginning with an addition of acetylene to acetone a series of syntheses allows the formation of linalool, which can then be form geraniol using a catalytic system.<sup>36</sup> Further isoprene, the building block of all terpenes, can also be utilized in the formation of geraniol. Compared to the syntheses involving  $\alpha$ - and  $\beta$ -pinene, these process' involve an increased number of reaction steps, ultimately decreasing their associated efficiency.

A novel approach for the synthesis of terpenoids has been recently suggested which involves the genetically engineering of microorganisms. Research conducted by Liu et al. in 2016 presented a strategy involving the overexpression of pathway proteins in an *E. coli* strain.<sup>40</sup> As mentioned previously, GPP is produced as an intermediate in the synthesis of geraniol through the mevalonate pathway, however GPP synthase is not commonly found within most microorganisms. Mutations within a specific pathway, farnesyl diphosphate synthase, allows the release of GPP, which can therefore be utilized for the formation of geraniol. Through this method, the research successfully produced geraniol in a yield of 2.0 g/L. Comparatively, in 2020 Fabris et al. and George et al. preformed metabolic engineering on marine diatom *Phaeodactylum tricornutum* and concluded geraniol yields of 0.309 mg/L and 0.89 mg/L respectively.<sup>41,42</sup>

## VIII. Predicted Spectroscopic Data



**Figure. 7** <sup>1</sup>H NMR labelled (left) and <sup>13</sup>C labelled (right) structure of geraniol

**Table. 1** Infrared Predicted Data

Band Positions (cm <sup>-1</sup> )	Relative Intensities	Functional Group
3400	s broad	OH
1650	m stretch	C=C

**Table. 3** <sup>1</sup>H NMR Predicted Data

$\delta$ (ppm; multiplicity)	J (Hz)	Integration/Assignment
1.6; s	7	3H; H <sub>a</sub>
1.5; s	7	3H; H <sub>b</sub>
1.65; s	7	3H; H <sub>f</sub>
2.0; t	7	1H; OH
2.3; t	7	2H; H <sub>e</sub>
2.35; d of t	7	2H; H <sub>d</sub>
3.6; d of d	7	2H; H <sub>h</sub>
5.2; t	7	1H; H <sub>c</sub>
5.25; t	7	1H; H <sub>g</sub>

**Table. 4**  $^{13}\text{C}$  NMR Predicted Data

$\delta(\text{ppm})$	Assignment
18.3	C <sub>b</sub>
18.4	C <sub>a</sub>
18.7	C <sub>h</sub>
27	C <sub>e</sub>
28	C <sub>f</sub>
30	C <sub>d</sub>
32	C <sub>i</sub>
35	C <sub>c</sub>
37	C <sub>g</sub>
200	C <sub>j</sub>

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