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Sniffing Out Chirality: Your Nose as a “Sides” Recognizer

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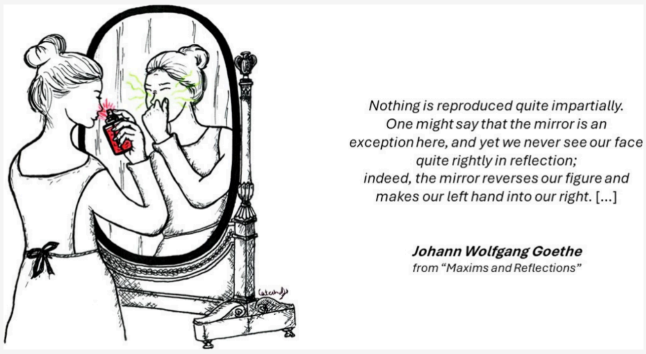
ABSTRACT: In this experimental investigation, final-year high school students and first-year university students were presented with a series of pairs of enantiomeric compounds for olfactory assessment. Five pairs of enantiomeric odorants (limonene, carvone, menthol, linalool, and dihydrocarveol) were presented at equal concentrations, and participants reported the perceived odor quality and intensity through an anonymous questionnaire. The collected data show that, for several compounds, students were able to discern distinct olfactory characteristics between enantiomeric counterparts, elucidating differential scent perception in agreement with literature descriptions. In other cases, the two enantiomers were perceived as being more similar and were more difficult to describe. Although the participants were not trained sensory analysts, the results indicate that olfactory tests can be used as an effective hands-on teaching activity to illustrate stereochemical concepts and connect chirality with sensory perception. This approach provides a simple and engaging way to integrate experiential learning into introductory courses in organic chemistry and stereochemistry.



KEYWORDS: *First-Year Undergraduate; Organic Chemistry, Hands-On Learning, Chirality*

INTRODUCTION

The sense of smell, or olfaction, plays a pivotal role in our daily lives, influencing our emotions, memories, and behaviors. Remarkably, the sensory experience of olfaction is intricately correlated to the molecular world, where even the slightest variations in the geometries of molecular structures can induce completely different olfactory experiences. Within the intricate relationship between olfaction and molecular chemistry, it is imperative to consider the role of chirality in smell recognition.[1−3] This characteristic, pervasive in many organic compounds, dictates distinct spatial configurations observed in their mirror-image forms or enantiomers.[4]

Enantiomers are nonsuperimposable mirror-image molecules[5,6] that have identical chemical and physical properties; however, when they interact with other chiral molecules, they can react at different rates. This behavior is at the basis of biological recognition processes because many biomolecules, such as enzymes and receptors, are chiral and interact differently (or not interact at all) with each enantiomer. Human receptors, typically composed of (*S*)-configured amino acids, have chiral binding pockets and can thus differentiate between enantiomers. For flavors, this enantiomeric recognition depends on the interaction efficiency between chiral flavor compounds and chiral enantiopure olfactory receptors in the nasal cavity epithelium.[7] Although the mechanisms of olfactory perception are well-understood,[8] efforts to correlate molecular structure and functional groups with perceived odor have not been successful.[9−11]

Many pairs of enantiomers and diastereoisomers have been described as having distinct qualitative aromas,[12−16] and four different categories of olfactory responses have been identified (Table 1), elucidating specific instances of odor activities among enantiomers.[17] A detailed analysis of each case is provided below. Although terms such as odor and aroma are often used interchangeably, international standards define odor as orthonasal perception and aroma as retronasal perception during tasting and drinking.[18,19]

Case #1: Selective Olfactory Response for a Single Enantiomer

In case #1, one enantiomer exhibits high affinity toward the binding pocket of the receptor, eliciting a robust olfactory response, while its counterpart exhibits either minimal or no olfactory activity. 3-(Methylthio)butanal exhibits this phenomenon, with the (*R*)-enantiomer having a distinct smell of potato, whereas the (*S*)-enantiomer is odorless.[20] Similarly, methyl jasmonate stereoisomers display this behavior: all (1*R*)-diastereoisomers have a typical floral, jasminic, slightly fruity scent, while both (1*S*)-configured diastereoisomers are almost

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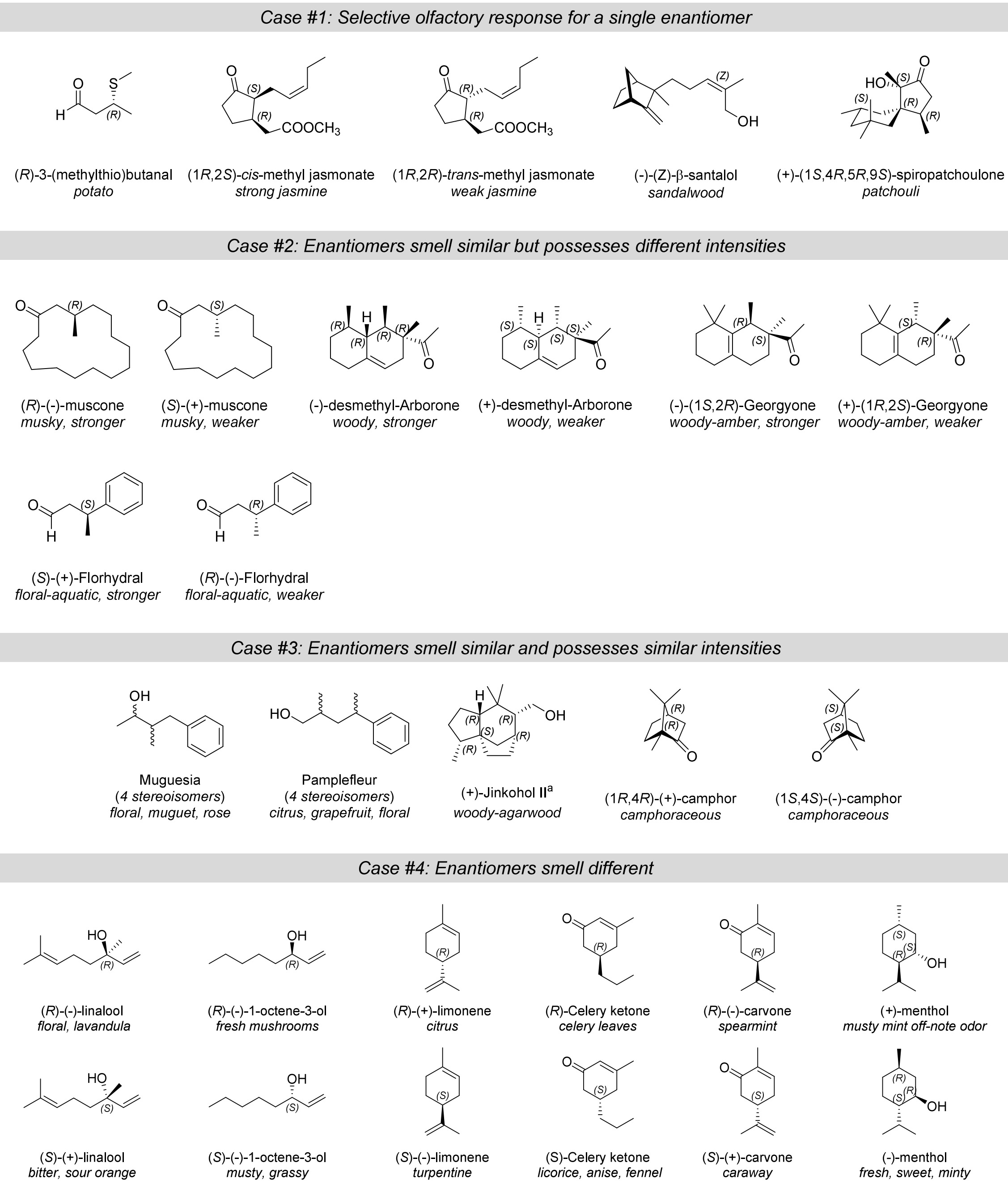
Table 1. Sensory Properties of Some Odorants



[a]The initial structure proposed for jinkohol II was wrong. See ref 27.

odorless.[17] A comparable pattern is observed with (−)-(Z)-β-santalol, found in sandalwood oil, which has a robust sandalwood fragrance, whereas its corresponding enantiomer lacks any scent.[21] Another example is (+)-spiropatchoulone (1-hydroxy-1,4,7,9-pentamethylspiro[4.5]decan-2-one), which imparts the woody odor of patchouli with an odor threshold of 0.067 ng/L in air for the racemate, whereas its (−)-counterpart remains scentless.[22]

Case #2: Enantiomers with Similar Scents but Different Intensities

More commonly, neither enantiomer fits perfectly with the chiral pocket, but both interact with the same receptor with varying affinities, leading to similar odors with different intensities. The differences between enantiomers pertain only to the intensity of the odor rather than its quality. This has been observed in the enantiomers of muscone, which share a similar odor profile (described as "powerful, musky") but exhibit intensity variation. For instance, the (*R*)-(−)-muscone enantiomer has an odor threshold of 0.43 ng/L in air (61 ppb in water), which is about 22 times higher compared to its (*S*)-(+)-antipode counterpart, which has a threshold of 9.5 ng/L in air (233 ppb in water).[14,17,23] Also, the enantiomers of desmethyl-arborone, characterized by a woody-amber odor profile, exhibit differing odor intensities: (+)-desmethyl-arborone has a weaker scent compared to its (−)-enantiomer.[24] In contrast, (+)-(1*R*,2*S*)-georgyone has a woody-amber odor with a threshold of 20 pg/L in air, compared to 3.5 ng/L for

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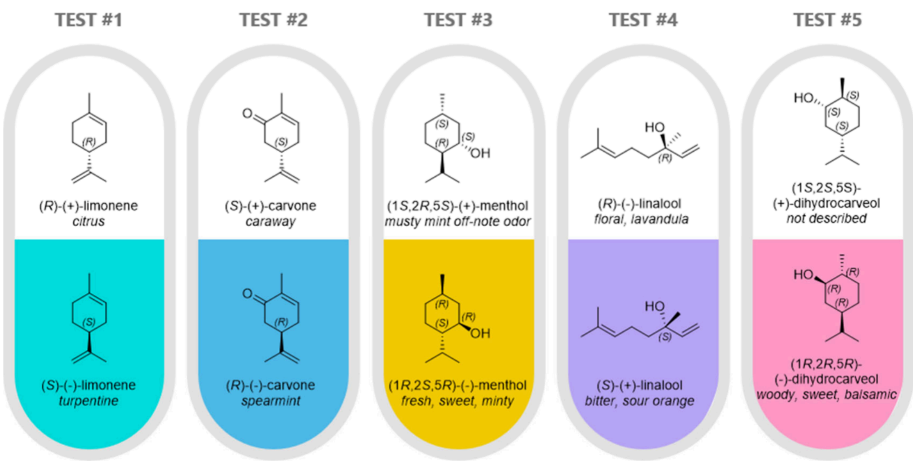

Figure 1. Odorants employed in olfactory tests with the documented odor for each individual enantiomer.

(−)-(1*S*,2*R*)-georgyone.[24,25] Moving to floral, aquatic scents reminiscent of lily of the valley, it must be noted that (*S*)-(+)-florhydral is about 25 times more potent, with an odor threshold of 0.035 ng/L in air, compared to 0.88 ng/L for the (*R*)-(−)-florhydral.[7,26,27]

Case #3: Enantiomers with Both Similar Scents and Intensities

If the stereogenic element of a molecule responsible for the smell is not differentiated by the receptor, then both enantiomers exhibit similar odors but with moderate intensity. One example is the odor of muguesia and pamplefleur: these structures contain multiple stereocenters, but in olfactory perception, no single stereoisomer predominates over the others. Instead, each stereoisomer distinctly contributes to the overall odor perception of the final blend.[28] Similarly, both enantiomers of jinkohol II exhibit a comparable intensity of a woody-agarwood odor.[29−31] Likewise, the two enantiomers of camphor cannot be distinguished by their odor.[32]

Case #4: Enantiomers with Different Scents

The most notable scenario occurs when each enantiomer fits different receptors, exhibiting very different olfactory characteristics. For example, enantiomers of linalool produce distinctly different smells:[33] (*R*)-(−)-linalool has a floral, woody lavender note and is the predominant isomer in authentic lavender oil,[17,34] whereas (*S*)-(+)-linalool has a petitgrain odor (bitter or sour orange) and is the major component of sweet orange oil (94−96%).[35] Another example pertains to the odors of 1-octene-3-ol: (*R*)-(−)-1-octene-3-ol exhibits the fragrance of fresh mushrooms, whereas (*S*)-(+)-1-octene-3-ol has a musty and grassy odor.[36] Moreover, the contrast in olfactory perceptions between enantiomers is evident in limonene[37] and celery ketone.[38] In their pure enantioenriched forms, they exhibit distinctly different scents: (*R*)-(+)- and (*S*)-(−)-limonene evoke citrus and turpentine notes, respectively. (*R*)-celery ketone offers odors reminiscent of celery leaves, while the (*S*)-form can be associated with licorice, anise, and fennel.

These examples demonstrate the substantial differences in the perception of optical isomers, highlighting the intricate relationship between molecular structure and olfactory perception. On the basis of these considerations and within the context of conducting outreach activities for our Chemistry Department, particularly in organizing seminars focused on chirality, we have decided to carry out olfactory tests of five pairs of enantiomers with various classes of last-year high school students as part of these outreach seminars. Additionally, first-year university students enrolled in the Natural Sciences B.Sc. degree program at the University of Milan were also involved in this activity. For high school students, the activity took place at the end of a seminar reviewing the basic concepts of stereochemistry and presenting examples of chirality in nature (e.g., spirals of snails), in human-made objects (e.g., screws and bolts), and in everyday actions (e.g., handshakes), with seminar materials distributed to all participants to provide teaching support. For first-year university students, the olfactory tests were integrated into the regular organic chemistry lectures during the semester. In this case, the relevant materials used were those already provided as part of the organic chemistry course, which are available in standard stereochemistry textbooks. The primary objective of these tests was to engage students in hands-on learning experiences and illustrate the concept of chirality in a tangible and memorable way. By having the students participate in olfactory tests, we aimed to demonstrate the practical implications of chirality, specifically, whether the human nose can distinguish between the fragrances of two enantiomers. This approach not only reinforces theoretical knowledge but also stimulates interest in chemistry through interactive and participatory methods.

■ ODOR TEST

Five pairs of enantiomers, commonly employed in the food and drink industry, were used in the olfactory tests.[39] Fragrances such as limonene, carvone, menthol, linalool, and dihydrocarveol were selected due to their easy availability in optically pure forms at a low cost (Figure 1). While this applies to most of the selected compounds, in the case of linalool, only the (*R*)-(−)-linalool enantiomer is commercially available in enantiomerically pure form. The opposite enantiomer is not readily available as a pure compound but can be obtained as a natural constituent of coriander essential oil, where it is typically present at levels exceeding 65%. For each test, two odor testers (absorbent paper strips) were presented to the students, who then used their smartphones to anonymously complete an online questionnaire via a QR code reporting their olfactory perceptions (see the Supporting Information). In the questionnaire, students were asked to rate the intensity of the two testers using a 1-to-5 scale and to select from a list of odors the one that most closely resembled what they perceived, with the option to write their own description if none of the suggested options fully matched their perception. It was stressed that there were no right or wrong answers but only the personal perception of each individual. Students were instructed to avoid discussing their perceived scents with each other until after they completed the survey to prevent mutual

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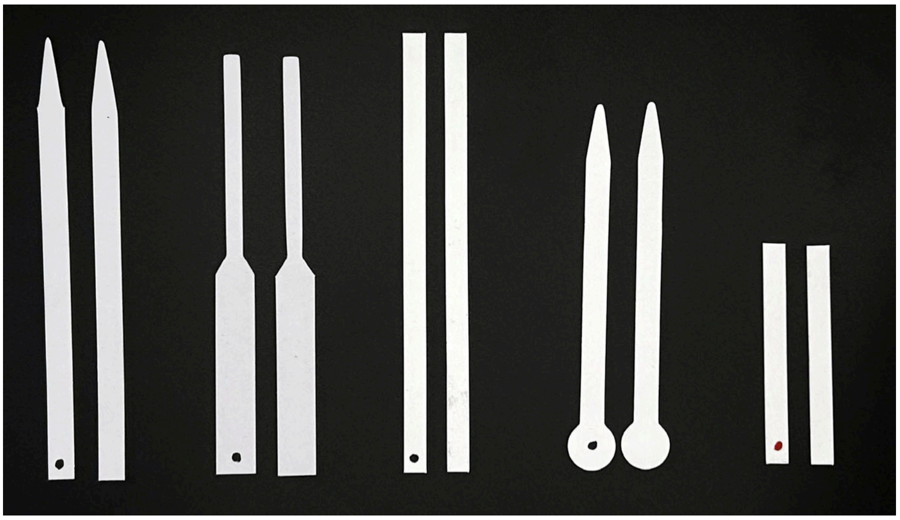

Figure 2. Individual testers used for olfactory evaluation. Within each pair, the two enantiomers were distinguished by the presence or absence of a dot mark. From left to right: limonene tester, carvone tester, menthol tester, dihydrocarveol tester, and linalool tester.

Table 2. Substances and Concentrations Used

Substance	CAS	Purity (GC)[a]	ee (%)[a]	Concentration (M)[b]
(*R*)-(+)-limonene	5989-27-5	99.4%	98.7%	0.1
(*S*)-(−)-limonene	5989-54-8	99.3%	96%	0.1
(*S*)-(+)-carvone	2244-16-8	99.7%	96%	0.05
(*R*)-(−)-carvone	6485-40-1	99.4%	98%	0.05
(1*S*,2*R*,5*S*)-(+)-menthol	15356-60-2	99.9%	99.1%	0.05
(1*R*,2*S*,5*R*)-(−)-menthol	2216-51-5	99.5%	99.9%	0.05
(*R*)-(−)-linalool	126-91-0	98.0%	≥97.0%	0.05
Coriander oil (containing (*S*)-(+)-linalool)[c]	-	89.1%	66.6%[c]	0.05
(1*S*,2*S*,5*S*)-(+)-dihydrocarveol[d]	22567-21-1	97.3%	≥95.0%	0.05
(1*R*,2*R*,5*R*)-(−)-dihydrocarveol[d]	20549-47-7	97.3%	≥95.0%	0.05

[a]These data are included in the certificate of analysis released by the seller. [b]Concentrations were chosen from what authors found to be a distinct intensity and selected according to previous data reported in the literature. [c]Determined by GC on chiral stationary phase. [d]Mixture of neo- and iso-isomers.

influence. Following the completion of the online survey by all students, discussion of individual olfactory perceptions was encouraged.

Each student received a set of individual testers, and to minimize confusion, the testers for each enantiomer pair had distinct shapes. Within each pair, enantiomers were differentiated solely by the presence or absence of a "dot mark" on the tester (see Figure 2). Students were kept uninformed about the specific compounds or the anticipated odors. Additionally, they were instructed to maintain a one meter distance from their peers. The experiments were conducted in a bright, quiet room. The windows of the room were opened to enhance the flow of fresh air.

Subjects

A total of four hundred healthy student volunteers, aged 17−19, participated in the study on an unpaid basis. Since the experiments were conducted at different times and across multiple educational institutions, not all participants underwent the same set of tests. As a general precaution, students exhibiting symptoms of a cold or allergies were excluded from the test (as a precautionary measure). Due to the nature of conducting olfactory tests during outreach activities across multiple educational institutions and relying on voluntary participation, the total number of participants for each test varied depending on volunteer availability and time constraints. All of the students were informed of the aim of the experiment and provided electronically written consent.

Odorants and Fragrance Preparation

A set of 5 odorants (5 pairs of enantiomers) was used (Figure 1). All substances had a nominal purity of at least 97% and were acquired from Merck (Merck, Life Science S.r.l.) except for (*S*)-(+)-linalool, which was purchased from AromaLabs with an optical purity of 66% (Table 2). The optical purity of linalool was confirmed by chiral GC analysis and by measuring its specific rotation (see the Supporting Information for further details). All samples were diluted using either ethanol (HPLC grade) or diethyl phthalate (flavor and fragrances grade) as the solvents. The choice between the two solvents was dictated by the safety regulations of the institution where the olfactory tests were performed, with diethyl phthalate being preferred whenever permitted, as it is nearly odorless, does not add alcoholic notes, and slows odorant evaporation, enhancing fragrance persistence. The enantiomers of each pair were presented at equal concentrations to evaluate any variations in perceived intensities. Before being distributed to the students, the odor testers underwent immersion in each alcoholic or diethyl phthalate solution and then exposed to fresh air to facilitate solvent evaporation. This process, aimed at removing any residual solvent, typically took around 5 min between the preparation of the tester and its distribution.

Test Procedure

All the students were instructed to smell the two testers of the same couple of the enantiomers in random order, in two or three sessions, allowing at least 2 min for consideration of each odorant. They were allowed to pause at any point if they felt tired or uncomfortable. Attendees were asked to position the olfactory tester near their nose (at a safe distance of 5 cm) and gently oscillate it during the test. There was no specified limit on the number of times students could smell the tester; however, a time limit of 15 min was set from the distribution of the tester to the completion of the questionnaire. After smelling each

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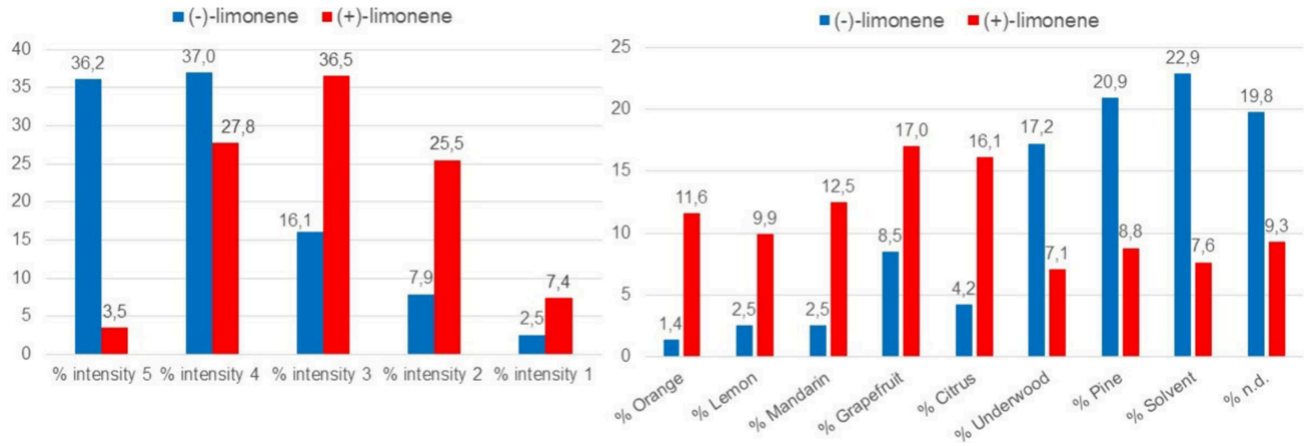

Figure 3. Olfactory perception of limonene enantiomers with a total of 353 participants. (Left) Distribution of perceived intensity ratings for (*S*)-(−)-limonene (blue color) and (*R*)-(+)-limonene (red color) on a scale from 1 (weak) to 5 (intense). (Right) Percentage of participants associating each enantiomer with specific odor descriptors; "n.d." indicates nonidentified odors.

couple of odorants, students were encouraged to complete the digital survey in which they could also rate the perceived intensity of the fragrance using a scale from 1 to 5, where 1 indicated a weak scent and 5 indicated an intense one. Each enantiomer couple was screened during the morning of the same day; the order of the enantiomer pairs was as follows: limonene was distributed during the initial session, carvone during the second, menthol during the third, dihydrocarveol during the fourth, and linalool during the fifth session.

Hazards

Ethanol, employed in the sample preparation, poses a flammability risk and can cause severe eye irritation. To mitigate these hazards, sample tests were meticulously prepared in a fume hood with researchers wearing appropriate gloves and eye protection. The same safety precautions were adopted when diethyl phthalate was used as the solvent. Furthermore, it was ensured that the odor samples were left in a well-ventilated area to allow for the complete evaporation of the solvent before testing.

■ RESULTS AND DISCUSSION

Before initiating the discussion of our results, it is crucial to highlight that our participants encompassed students from different backgrounds and none of them are professional analysts. Therefore, it is imperative to assess our findings in this context. As a result, participants were allowed to leave blank responses when they could not associate a scent with a given fragrance. For more insights into this topic, refer to the more specialized and rigorous studies reported in the literature, which are performed by professional analysts.[9,40,41] The aim of this activity is to demonstrate how the human nose can discern chirality by perceiving enantiomers differently and not to match a scent with a specific fragrance. Moreover, beyond simply showcasing this aspect, the activity aims to provide an understanding of chirality in organic chemistry and its real world implications. Additionally, it encourages critical thinking by prompting participants to consider how molecular structure influences scent perception. To incorporate statistical validation of our analysis, we have performed Chi-square multinominal tests (with equal expected proportions across categories) to analyze odor descriptor frequencies and implemented the nonparametric Wilcoxon signed-rank test to compare intensity ratings for each pair of enantiomers. Results have revealed highly significant differences in the distribution of odor classes for each compound ($p < 0.05$). Furthermore, the perceived intensity differences between enantiomer pairs were highly significant ($p < 0.001$), except for dihydrocarveol, which showed a marginal trend ($p = 0.087$). All statistical analyses were conducted using JASP[42] (version 0.95.4; 2019).

Olfactory Test #1: (*R*)-(+)-Limonene vs (*S*)-(−)-Limonene

For a long time, it has been commonly assumed that (*S*)-(−)-limonene is responsible for a lemon scent, while (*R*)-(+)-limonene is associated with an orange smell.[43] However, recent investigations have revealed that this information is incorrect[37] since it has been found that both pure orange and lemon oils exhibit dextrorotatory rotation of plane-polarized light, albeit with different angle values.[44] In a more precise analysis, it was reported that the fragrance of (*R*)-(+)-limonene is related to both lemon and orange odors, whereas the (*S*)-(−)-enantiomer is correlated with the scent of pine trees.[45−47]

A total of 353 healthy student volunteers, consisting of 134 males, 209 females, and 8 students who do not identify with these two genders, aged 17−19, participated in this test on an unpaid basis. Olfactory tests performed on limonene revealed that students were able to distinguish the smell between the two enantiomeric forms with an exceptional consensus among participants in identifying their respective characteristic notes ($p < 0.001$, $\chi^2(8) = 31.36$ for (*R*)-(+)-limonene and $\chi^2(8) = 203.6$ for (*S*)-(−)-limonene). The (*R*)-(+)-limonene enantiomer was predominantly described as having a citrus-like odor by the majority of participants (67.1%, Figure 3), in accordance with its well-known association with citrus fruits such as oranges and lemons. Besides the citrus note, a smaller portion of participants also detected pine or underwood scents (15.9%), and some students identified a solvent-like odor (7.6%). In contrast, (*S*)-(−)-limonene scent was more frequently associated with pine-like or woody (38.1%) scents and solvent-like notes (22.9%), while the perception of a citrus note dropped significantly to 19.1%. This distribution supports the revised view of enantiomer-specific odor profiles, consistent with the observations reported in recent literature.[37,46] Interestingly, the (*S*)-(−)-enantiomer was generally reported as more intense than the (*R*)-(+)-enantiomer ($p < 0.001$, $W = 38290.50$, $z = 10.91$). This suggests that the perceived difference is not only statistically valid but also remarkably pronounced across the students.

Olfactory Test #2: (*S*)-(+)-Carvone vs (*R*)-(−)-Carvone

It has been well-documented that the two enantiomers of carvone exhibit distinctly different odors. (*S*)-(+)-Carvone,

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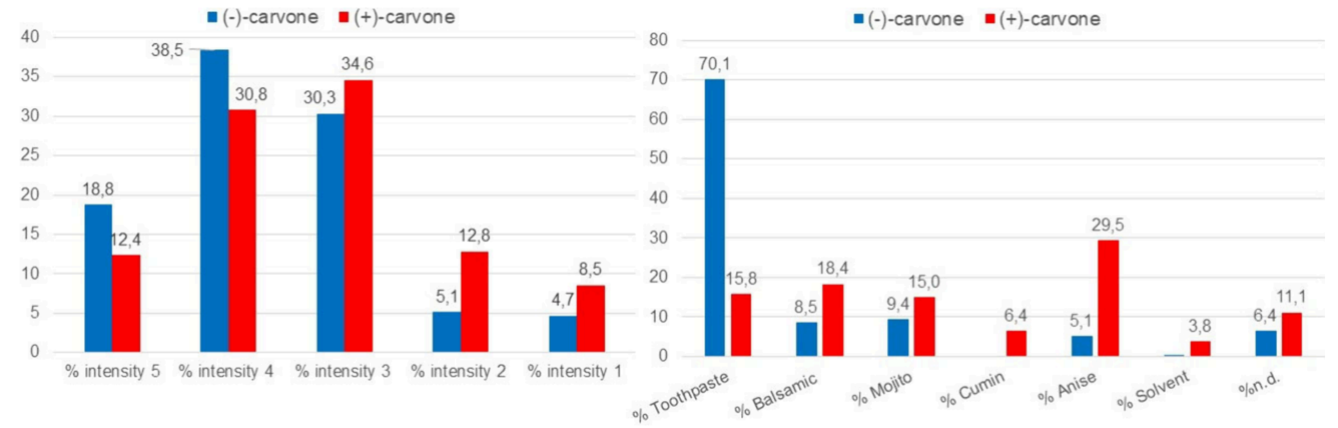

Figure 4. Olfactory perception of carvone enantiomers with a total of 234 participants. (Left) Distribution of perceived intensity ratings for (*R*)-(−)-carvone (blue color) and (*S*)-(+)-carvone (red color) on a scale from 1 (weak) to 5 (intense). (Right) Percentage of participants associating each enantiomer with specific odor descriptors; "n.d." indicates nonidentified odors.

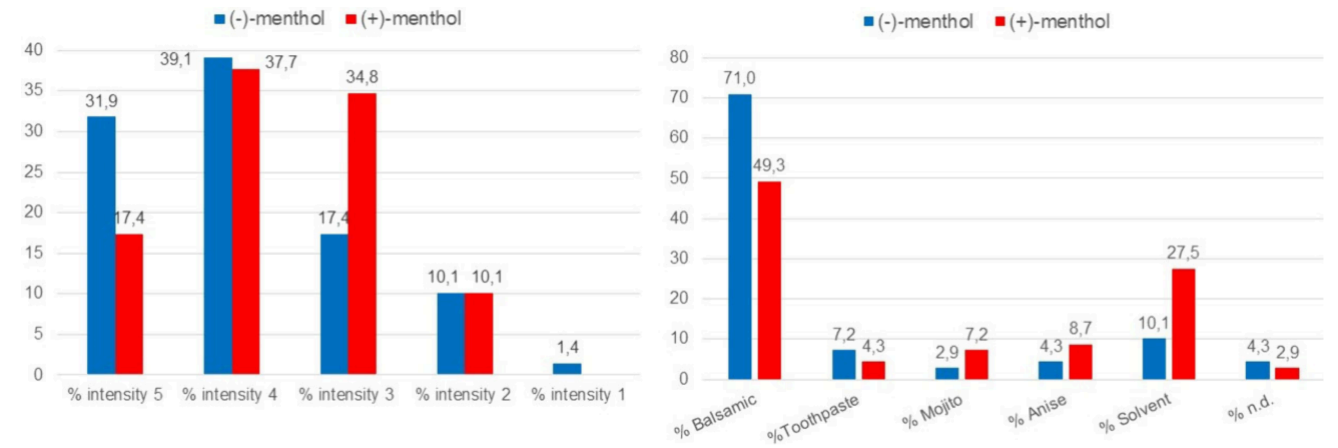

Figure 5. Olfactory perception of menthol enantiomers on a total of 69 participants (32 males, 34 females, and 3 identifying outside the binary gender categories). (Left) Distribution of perceived intensity ratings for (−)-menthol (blue color) and (+)-menthol (red color) on a scale from 1 (weak) to 5 (intense). (Right) Percentage of participants associating each enantiomer with specific odor descriptors; "n.d." indicates nonidentified odors.

isolated through the fractional distillation of caraway oil, has a characteristic odor reminiscent of caraway. On the other hand, (*R*)-(−)-carvone, derived from spearmint oil, has a scent strongly associated with spearmint.[39] The odors of these enantiomers reflect their natural origins, with (*R*)-(−)-carvone having a more intense smell than its counterpart. Due to its stronger scent, (*R*)-(−)-carvone is commonly used in dental care products, whereas the (*S*)-(+)-form is used in foods and beverages.[43]

The olfactory tests performed confirm these attributions: for (*R*)-(−)-carvone, the minty note predominates, with 88% of participants primarily associating it with aromas reminiscent of toothpaste, balsamic notes, or mint mojito ($p < 0.001$, $\chi^2(6) = 608.1$). In contrast, the olfactory profile of (*S*)-(+)-carvone does not exhibit a single dominant odor note, since different odor descriptions were collected ($p < 0.001$, $\chi^2(6) = 70.71$, Figure 4). While 50% of participants still perceive a minty scent, a significant portion (35.9%) also detects anise and cumin notes, which were neither identified nor predominant in the case of (*R*)-(−)-carvone. Interestingly, among the 234 students who participated in this olfactory test (97 males, 130 females, and 7 identifying outside the binary gender categories), both enantiomers were generally perceived as medium-intensity odors. However, within the subgroup of participants who rated the odors as more intense (scores of 4 or 5), (*R*)-(−)-carvone showed a slight predominance in higher-intensity ratings compared to its enantiomer, confirming what is reported in literature data ($p < 0.001$, $W = 8315.500$, $z = 3.705$).

Olfactory Test #3: (1*S*,2*R*,5*S*)-(+)-Menthol vs (1*R*,2*S*,5*R*)-(−)-Menthol

Menthol (2-isopropyl-5-methylcyclohexanol), a major component of peppermint and other mint leaves and oils, is widely used in medicines, flavors, and insect repellents. Because of the presence of three stereogenic centers, eight stereoisomers are possible (4 enantiomeric pairs).[48] The organoleptic properties and cooling strengths of all menthol stereoisomers (menthol, neomenthol, isomenthol, and neoisomenthol) have already been reviewed,[49−56] but only the (1*R*,2*S*,5*R*)-(−)-menthol enantiomer (the most abundant one) exhibits the desirable, fresh, sweet, minty odor and intense cooling properties. In contrast, the (+)-menthol enantiomer is less cooling and has a musty off-note odor, with bitter, phenolic, and herbaceous notes.[58] These derivates are extensively used in pharmaceuticals, cosmetics, toothpaste, chewing gum, personal care products, and cigarettes.

It has also been noted that mammalian odorant receptors are capable of distinguishing between the two enantiomeric forms of menthol.[40,57−60] Moreover, in humans, menthol can activate

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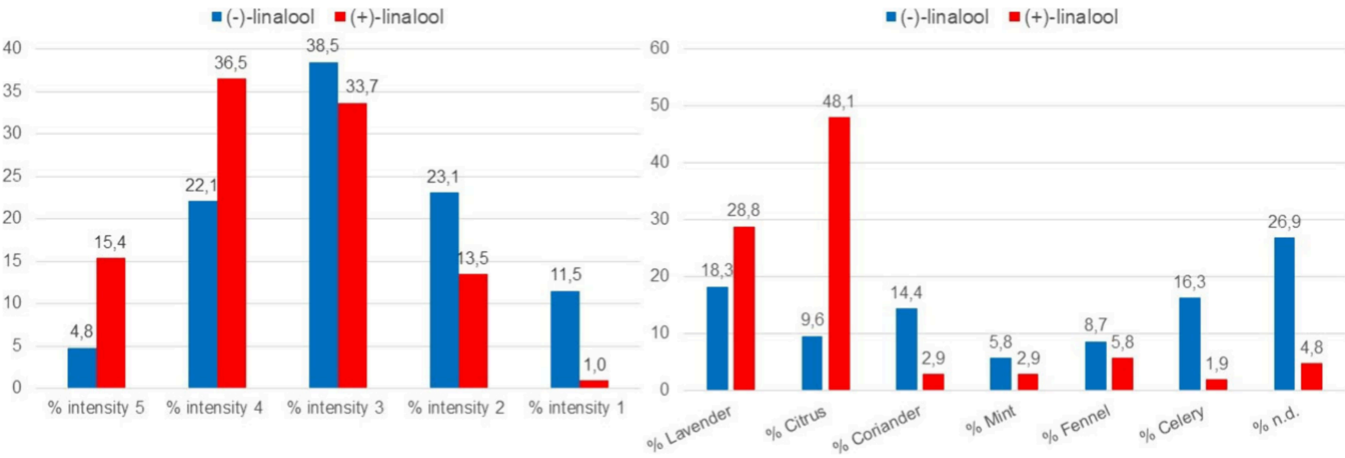

Figure 6. Olfactory perception of linalool enantiomers on a total of 104 participants (26 males, 76 females, and 2 identifying outside the binary gender categories). (Left) Distribution of perceived intensity ratings for (−)-menthol (blue color) and (+)-menthol (red color) on a scale from 1 (weak) to 5 (intense). (Right) Percentage of participants associating each enantiomer with specific odor descriptors; "n.d." indicates nonidentified odors.

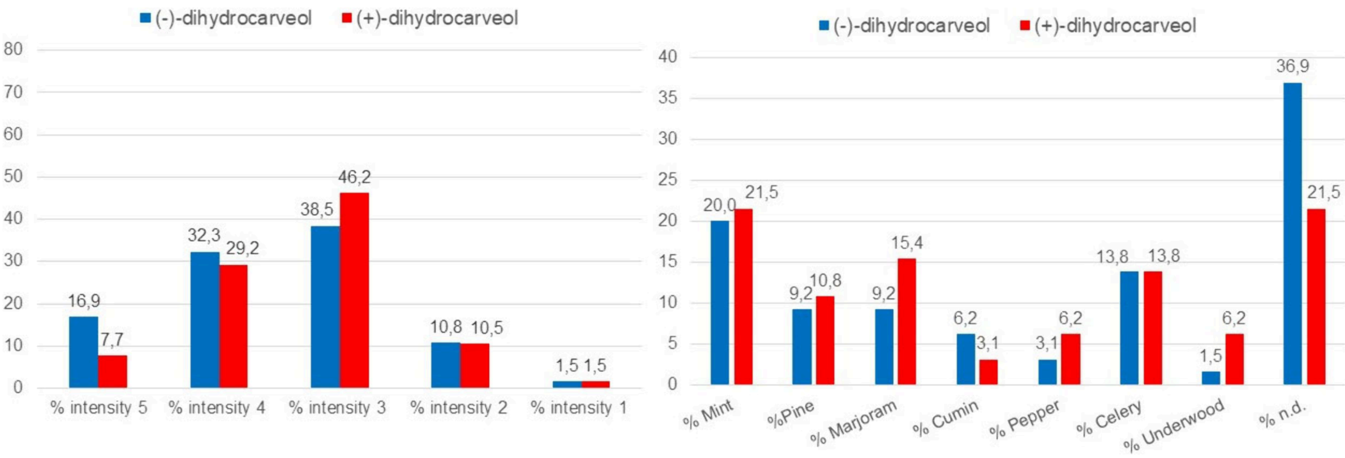

Figure 7. Olfactory perception of dihydrocarveol enantiomers on a total of 65 participants (33 males, 23 females, and 6 identifying outside the binary gender categories). (Left) Distribution of perceived intensity ratings for (−)-dihydrocarveol (blue color) and (+)-dihydrocarveol (red color) on a scale from 1 (weak) to 5 (intense). (Right) Percentage of participants associating each enantiomer with specific odor descriptors; "n.d." indicates nonidentified odors.

thermosensitive neurons, producing pleasant cooling sensations.[61,62]

The olfactory tests performed on menthol highlight the clear dominance of minty and balsamic notes in the olfactory perception of both menthol enantiomers (Figure 5). However, (−)-menthol was more frequently associated with the characteristic mint scent, as reported by 81.1% of participants ($p < 0.001$, $\chi^2(5) = 148.1$) compared to only 60.8% for (+)-menthol ($p < 0.001$ $\chi^2(5) = 69.35$). This suggests a moderate but noticeable olfactory difference in perception between the two enantiomeric forms, where the (−)-enantiomer was perceived as slightly more intense than its (+)-counterpart ($p = 0.018$, $W = 276.000$, $z = -2.194$).

Olfactory Test #4: (*S*)-(+)-Linalool vs (*R*)-(−)-Linalool

Linalool (2,6-dimethyl-2,7-octadien-6-ol) is an unsaturated acyclic monoterpene alcohol that naturally occurs in a wide range of aromatic plants. It is widely used in cosmetics, fine fragrances, and shampoos,[63] as well as in noncosmetic products such as household cleaners, detergents, and food additives; due to these applications, linalool consumption on a global scale exceeds 1000 t per year.[64] (*R*)-(−)-Linalool is the naturally occurring enantiomer, characterized by a lavender-like fragrance, whereas (*S*)-(+)-linalool exhibits a petitgrain-like scent, described as sweet, floral, and herbaceous, with citrus and fruity notes.[33,36,64,65] (*R*)-(−)-Linalool is predominantly found in rosewood oil, while (*S*)-(+)-linalool is primarily derived from coriander oil and orthodon oil. In recent years, linalool has also emerged as an interesting compound for pharmaceutical applications since it exhibits a broad spectrum of bioactive properties.[65−67]

In the olfactory test proposed to students, (*R*)-(−)-linalool of ≥97.0% purity was used, while the (*S*)-(+)-enantiomer could not be tested in its pure form and was instead presented as coriander oil, its main natural source. Results from the test are reported in Figure 6 and indicated that the lavender-like fragrance was more distinctly perceived with the (*R*)-(−)-enantiomer (18.3%), although a significant proportion of participants (26.9%) were unable to associate its scent with lavender ($p < 0.001, \chi^2(6) = 22.27$). In contrast, (*S*)-(+)-linalool was primarily characterized by a citrus note, as reported by 48% of participants, followed by a lavender note due to the presence of (*R*)-(−)-linalool as a contaminant in the coriander oil sample used ($p < 0.001$, $\chi^2(6) = 147.3$). Regarding intensity, (−)-linalool was generally perceived as having medium

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intensity, while (+)-linalool exhibited a stronger and more easily identifiable odor ($p < 0.001$, $W = 2269.500$, $z = 4.459$).

Olfactory Test #5: (1*S*,2*S*,5*S*)-(+)-Dihydrocarveol vs (1*R*,2*R*,5*R*)-(−)-Dihydrocarveol

Dihydrocarveol is a fragrance that has found application in the realization of decorative cosmetics, such as shampoos and toilet soaps as well as in household cleaners and detergents.[68] (+)-Dihydrocarveol is naturally found in caraway oil[69,70] and other aromatic plants,[71] whereas (−)-dihydrocarveol is a metabolite that can be extracted from actinomycetes.[72]

Regarding the scent, there are no data in the literature related to the smell of the individual enantiomers. However, the racemic mixture is described as having a minty,[73,74] cooling sweetness with camphor-like notes and fresh terpene nuances according to the Mosciano Flavor Library.[75,76] The IFRA Fragrance Ingredient Glossary reports that (−)-dihydrocarveol has a woody, sweet, balsamic fragrance, but unfortunately, no information is provided for the corresponding enantiomer.[77] Given the commercial availability of both enantiomers and the lack of descriptions for the individual enantiomers to date,[78] we chose to evaluate olfactory perceptions related to the recognition of this compound. Our aim was to determine whether the human nose can distinguish between (+)- and (−)-dihydrocarveol based on scent alone, allowing us to classify the substance accordingly.

Olfactory tests on dihydrocarveol revealed that both enantiomers were perceived with comparable and generally moderate intensity (Figure 7, $p = 0.018$, $W = 241.000$, $z = -1.667$). Similarly, the odor profiles were broadly similar, with no single descriptor emerging as predominant. For (−)-dihydrocarveol, the distribution of odor descriptors was highly significant ($p < 0.001$, $\chi^2(7) = 48.11$), while (+)-dihydrocarveol also showed a significant distribution pattern ($p = 0.011$, $\chi^2(7) = 18.25$). The most commonly reported notes included mint (approximately 20%), pine (approximately 10%), and various spices (approximately 10%). Notably, a celery-like odor was consistently recognized across both enantiomeric forms. Among all the tested compounds, dihydrocarveol proved to be the most difficult for participants to associate with a distinct olfactory profile, as a notable proportion of participants (36.9% for the (−)-enantiomer and 21.5% for the (+)-enantiomer) were able to perceive differences in odor but were unable to associate the scent with any familiar fragrance or descriptor. This observation confirms what has been reported in the literature, indicating that while the scents are distinguishable, it is not possible to associate a characteristic or definitive odor to them.[9]

■ ACTIVITY ASSESSMENT

Since students from two different educational contexts were involved in these olfactory perception tests (final-year high school students during outreach seminars and first-year university students enrolled in the Natural Sciences B.Sc. degree program at the University of Milan), the assessment strategies adopted were differentiated in accordance with the specific characteristics and learning objectives of each group. In the first case, due to the nature of the dissemination, no formal structured evaluation was applied, and the primary form of assessment was purely qualitative.

The high school teachers who attended the activity were asked to collect informal feedback from the students, and the responses were uniformly positive. The teachers reported that the activity was well received by the students and described it as "*engaging, informative, and rich in scientific content*". They emphasized the strong educational value of the experience, noting that the hands-on approach kept students interested during the activity, inspiring further discussion and facilitating the integration of concepts with topics addressed in their high school program. In particular, the integration between chemistry and sensory perception was considered an effective strategy to enhance the comprehension of stereochemistry. When olfactory perception tests were administered to first-year undergraduate students enrolled in the B.Sc. program in Natural Sciences at the University of Milan, the tests were conducted within the context of the regular course lectures and materials, which covered the fundamental concepts of stereochemistry, ensuring that all participants had a strong conceptual foundation to engage meaningfully with the hands-on activity. In this case, two distinct structured assessment methods were employed. First, general feedback was obtained from an anonymous survey (standardized across all university courses and carried out with students between the end of the course and the final exam date), which provided evaluations specifically for the chemistry course within the Natural Sciences B.Sc. degree program. In this survey, a specific question was dedicated to the evaluation of additional learning activities (such as hand-on experiments, tutorials, or extra seminars) beyond regular lectures. Student responses are collected in Figure 8 and show a strong positive trend, with the majority of students selecting "Strongly agree" (56%) and "Somewhat agree" (33%).

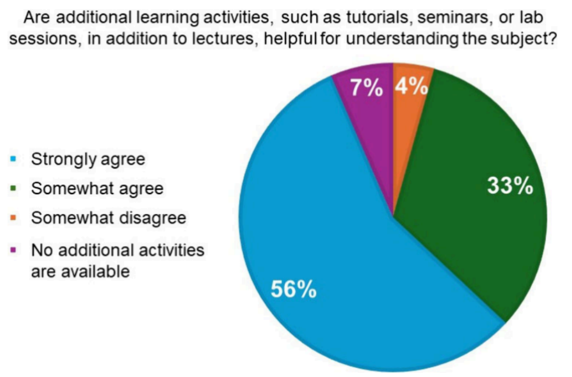

Figure 8. Student responses to a survey on the usefulness of additional learning activities (such as olfactory perception tests).

Additionally, in order to assess the impact of the olfactory tests on learning outcomes, a comparison between the academic performance of students from previous years (who were not involved in the olfactory testing activity) and the academic performance of students who attended the course of organic chemistry after the introduction of the olfactory tests was made. The assessment was performed on the basis of the scores obtained by students on the stereochemistry-related questions proposed during the final exam of the course. A correct answer was assigned 15 points with score reductions based on the deviation from the expected answer.

The mean score related to the question increased from 12.7 to 13.7 (Welch's t test, $\rho < 0.01$) after the proposed activity. This reflects an 8.1% improvement in the average evaluation, indicating a statistically robust impact of the activity. This increase was not observed in the other exam questions that were comparable in scope and content, whose average scores remained substantially unchanged. These results suggest that

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the integration of hands-on and sensory activities into the teaching process leads to improved conceptual understanding and promotes more effective learning of key principles in stereochemistry.

CONCLUSION

The results of these olfactory tests showed that students (who are not professional analysts) were able to discriminate between the enantiomer pairs of limonene, carvone, menthol, linalool, and dihydrocarveol based on their scent differences when presented at equal concentrations. In particular, in the case of limonene, it was demonstrated that the common perception associating one enantiomer with an orange scent and the other with a lemon scent is inaccurate. Based on evaluations from over 350 students, (*R*)-(+)-limonene was predominantly characterized by citrus notes, while (*S*)-(−)-limonene was associated with a resinous odor. Similarly, pronounced differences in the odor profiles were observed for the enantiomers of carvone, menthol, and linalool. In contrast, students showed difficulty in associating the smell of dihydrocarveol to familiar odors, although they confirmed that dihydrocarveol enantiomers present distinguishable odor profiles. The highly significant Chi-square result ($p < 0.05$) for odor descriptor frequencies provides robust evidence for the qualitative differentiation of the enantiomers. This suggests that the observed differences in perceived odors are not due to chance but reflect a consistent perception among the students, reinforcing the hypothesis that the olfactory system discriminates between these specific chiral structures. Furthermore, the Wilcoxon signed-rank test demonstrates that these compounds are perceived with significantly different intensities. However, it was clearly demonstrated that the differentiation of enantiomers through olfactory perception is possible, effectively contextualizing chirality within the sensory experience and supporting the integration of olfactory experiments into the teaching of stereochemistry concepts.

We believe that the integration of hands-on laboratory activities involving sensory perception helped students better understand concepts typically learned through traditional textbook methods. These olfactory experiments could offer an alternative approach to promote active student participation in learning chirality, favoring the development of a critical thinking approach derived from personal perceptions into the learning process. The interdisciplinary nature of this approach, which integrates laboratory practice and interactive learning (by combining chemistry with olfaction and perception), could offer a powerful way to stimulate student curiosity and to make chemical concepts more tangible and relevant to real-world experiences.

ETHICS

Before data collection, the activity was approved by the Director of the Department of Chemistry at the University of Milan and endorsed by the Chair of the Academic Board of the Department, by the coordinator of outreach and orientation activities, as well as authorized by the principals of the high schools involved in this activity (when required). All formal approval procedures at the university and at the high schools were completed, although these procedures are internal to the institutions and not publicly accessible.

All students participated voluntarily, and informed consent was obtained at the time of data collection (see Q1 of the General Statement provided to students before the olfactory tests in the Supporting Information). Students who declined to participate in olfactory tests were excluded from the activity. Prior to the survey, participants were informed of the purpose of the study and how the data would be used. It was assured that no personally identifiable information would be recorded and that the data collected would be used for research purposes.

Data from the olfactory tests were collected using Microsoft Forms questionnaires set to anonymous mode. The feedback on the activity (Figure 8) was obtained in accordance with the "*Code of Ethics and Research Integrity*" of the University of Milan. Data collection was coordinated by the University Quality Assurance Office (Presidio di Qualità), and the data obtained were processed exclusively for educational and quality assurance purposes. The statistical analyses of student academic performances were conducted on fully anonymized data, under the general institutional protocol for classroom activities, with all information potentially identifying individual students removed prior to analysis to ensure complete confidentiality.

ASSOCIATED CONTENT

Data Availability Statement

The raw data of olfactory tests supporting the findings of this study, along with the raw assessment data, have been deposited in Dataverse and can be accessed at 10.13130/RD_UNIMI/X482YK.

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.5c01032.

Additional experimental details, analysis on coriander oil, optical purity of essences, and olfactory test and response collection module (PDF, DOCX)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Franco Cozzi for his 75th birthday.

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(78) Interestingly, the Safety Data Sheets (SDS) for the pure enantiomers available from suppliers identified through the Reaxys platform do not include any fragrance information.

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