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Synthesis and odor description of optically active cyclopropanated analogues of geraniol, nerol, nor-leaf alcohol, and matsutake alcohol☆

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Abstract—Both enantiomers of cyclopropanated analogues of geraniol, nerol, nor-leaf alcohol, and matsutake alcohol were synthesized and their odor properties evaluated. Odor characters in enantiomeric pairs were similar in the geraniol series. The (+)-(2*R*,3*S*)-nerol derivative showed various odor aspects. From the results of nor-leaf alcohol derivatives, an interaction between the (2-*re*,3-*re*)-face of nor-leaf alcohol and the human olfactory receptor was suggested. The odor of (3*R*)-matsutake alcohol derivative was superior to the enantiomer.

1. Introduction

There has been a growing demand for new flavors and fragrances.[1] Chemical modification of known odorants can meet this need because a slight structural difference results in a drastic change in olfactory sense. Cyclopropane rings could be good biological substitutes for double bonds because of their isoelectrostatic and isostereochemical natures.[2] The first application for odorants was shown by Bajgrowicz et al. for santalol analogues.[3] We have also been developing new racemic odorants by cyclopropantion of known cyclic and acyclic compounds, such as jasmone,[4a] jasmonate,[4b,e] leaf alcohols,[4c,f] monoterpene alcohols,[4f] and unbranched aliphatic alcohols.[4d,f] However, examination using a single stereoisomer is required for precise olfactory analysis.[5] Thus, we synthesized and investigated the olfactory evaluation of the enantiomeric pairs of cyclopropanated geraniol **1**, nerol **2**, nor-leaf alcohol **3** [(*Z*)-2-penten-1-ol], and matsutake alcohol **4** (1-octen-3-ol). Herein, we report the results.

2. Results and discussion

2.1. Synthesis of optically active analogues

Preparation of the optically active analogues is summarized in Schemes 1 and 2. According to Charette's procedure,[6] the 2,3-double bond of geraniol (**1**) was cyclopropanated enantioselectively using (*R*,*R*)- and (*S*,*S*)-dioxaborolane ligands to afford (+)-**5** and (−)-**5**,[5] respectively. Nerol derivatives (−)-**6** and (+)-**6**,[7] and nor-leaf alcohol derivatives (−)-**7**[6] and (+)-**7** were prepared in a similar manner. Natural (*R*)- and unnatural (*S*)-enantiomers of matsutake alcohol **4**,[8] were cyclopropanated without the chiral ligands to afford (*R*)-**8** and (*S*)-**8**, respectively.

2.2. Odor evaluation

2.2.1. Geraniol and nerol derivatives. The odor of optically active geraniol and nerol derivatives were compared with the corresponding racemic compounds[4f] and (*R*)- and (*S*)-citronellols **9** (Table 1). Woody nuance is strengthened in both (−)- and (+)-**5** rather than (±)-**5**, but there is no marked difference between them. As for the nerol derivatives, odor characteristics of (±)-**6** were resolved: (+)-**6** was responsible for the odor of (±)-**6**. Furthermore, the 'spicy green' aspect disappeared and sulfrol and sandalwood like characteristics were added. 'Rosy' aspect can

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☆ Synthesis and odor description of cyclopropanated compound **7**. Part 6: See Ref. 4.

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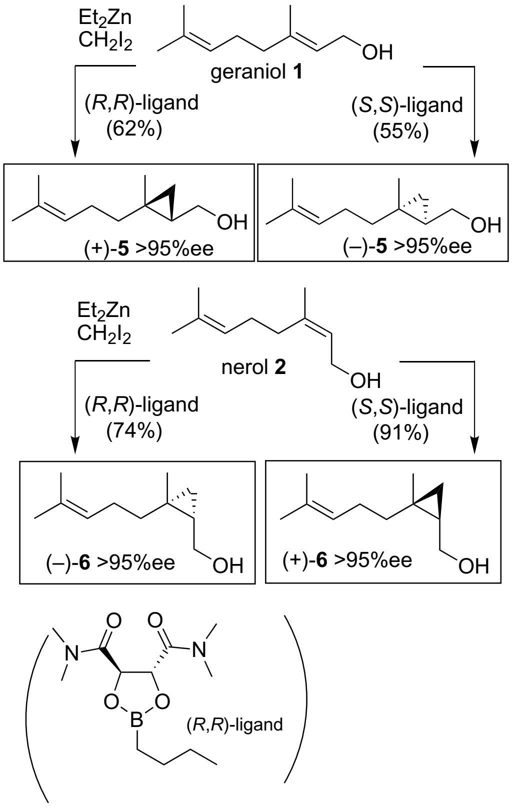
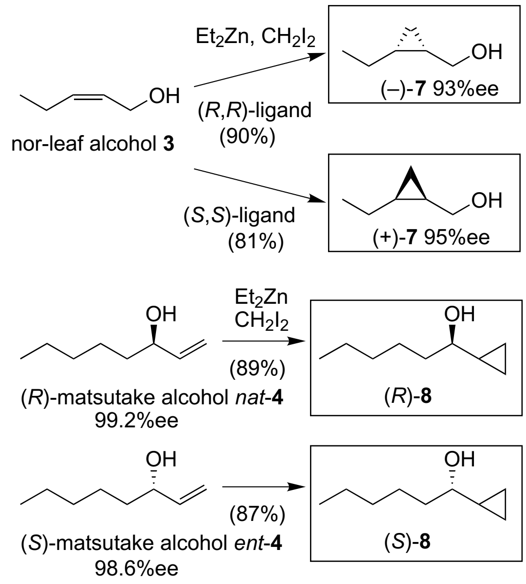


Scheme 1. Synthesis of optically active cyclopropanated analogues of geraniol and nerol.



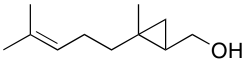
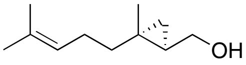
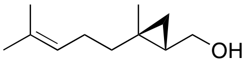
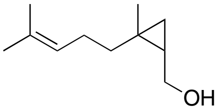
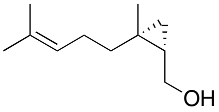
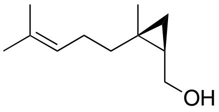
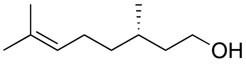
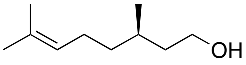
Scheme 2. Synthesis of optically active cyclopropanated analogues of nor-leaf alcohol and matsutake alcohol.

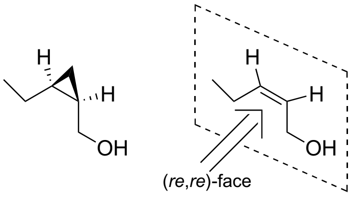
be attributed to the structural resemblance to (*R*)-citronellol **9**.

2.2.2. Nor-leaf alcohol and matsutake alcohol derivatives.

The resulting cyclopropanated aliphatic alcohols are summarized in Table 2. The 'acidic ether' odor of

Table 1. Odor evaluations of geraniol derivatives and related compounds

Entry	No.	Compounds	Odor description
1	(±)-**5**[4f]		Slightly woody, heavy rosy odor, less intensive and characteristic than geraniol **1**
2	(−)-(2*R*,3*R*)-**5**		Woody rosy odor close to (±)-**5**, a little bit more woody
3	(+)-(2*S*,3*S*)-**5**		Woody rosy odor with sweetness of nerol; similar to, but more woody than (±)-**5**
4	(±)-**6**[4f]		Floral-rosy odor with somewhat spicy green aspect, less intensive than nerol **2**
5	(−)-(2*S*,3*R*)-**6**		Nerol-like odor, but less intensive than (±)-**6**
6	(+)-(2*R*,3*S*)-**6**		Woody rosy odor with aromatic aspect reminiscent of sulfrol found in the top note of sandalwood oil
7	(*R*)-**9**		Diffusive rosy odor close to laevocitronellol with the odor aspects of Bulgarian rose and lily of the valley
8	(*S*)-**9**		Somewhat citronellal-like odor with woody aspect, less intensive than (±)- and (*R*)-**9**



(+)-**7** nor-leaf alcohol **3**

Figure 1. Plausible nor-leaf alcohol interaction with a human olfactory receptor.

(±)-**7** was found to be attributed to the (+)-**7** enantiomer. In (+)-**7** the 'ethereal' aspect as well as the 'green' note became stronger, while interestingly, (−)-**7** lost its green aspect like leaf alcohol. These results reveal the discrimination of the diastereotopic faces of nor-leaf alcohol. The (2-*re*,3-*re*)-face of double bond could be interacted with olfactory receptors (Fig. 1). Although the original matsutake odor was lost in (±)-**8**, it existed in the natural form (*R*)-**8**. Unnatural (*S*)-**8** which lacked mushroom character, would disturb it. The (*R*)-hydroxyl group was again responsible for the matsutake-like aspect, and the cyclopropane ring worked as a substitute for the double bond.

3. Conclusions

Both enantiomers of the cyclopropanated analogues of geraniol, nerol, nor-leaf alcohol and matsutake alcohol were synthesized and their odor descriptions were evaluated. Odor characters in enantiomeric pairs were similar in geraniol series. The (+)-(2*R*,3*S*)-nerol derivative showed various odor aspects. From the results of the nor-leaf alcohol derivatives, interaction between (2-*re*,3-*re*)-face of nor leaf alcohol and human olfactory receptor was suggested. The odor of (3*R*)-matsutake alcohol derivative was superior to the enantiomer. The results, especially of nor-leaf alcohol, could be of help to develop novel practical odorants and to study the mechanism of human olfaction.

4. Experimental

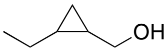
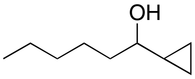
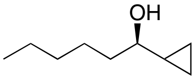
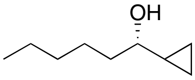
4.1. General

(*R*)- and (*S*)-1-Octen-3-ols (matsutake alcohol) and nor-leaf alcohol were provided by Nippon Zeon Co., Ltd. Geraniol was supplied by Kuraray Co., Ltd. (*R*)- and (*S*)-citronellols were purchased from Sigma–Aldrich Co. Nerol were purchased from Tokyo Kasei Kogyo Co., Ltd. Distillation: Shibata GTO-250 grass tube oven. Optical rotation: Horiba Sepa-300. GLC: Hitachi G-3500; column, HP-5 [cross-linked 5% PH ME Siloxane, 30 m × 0.32 mm × 0.25 μm, Hewlett–Packard. (A) Oven temp, 100–200 °C at +5 °C/min; injector temp; 250 °C, detector temp, 300 °C. (B) Oven temp, 110–200 °C at +5 °C/min; injector temp, 250 °C, detector temp, 300 °C. (C) Oven temp, 40–100 °C at +5 °C/min; injector temp, 140 °C, detector temp, 200 °C. (D) Oven temp, 100–200 °C at +5 °C/min; injector temp, 200 °C; detector temp, 240 °C]. IR: Jasco FT/IR-4100 (ATR, Zn–Se). ^{1}H NMR: Varian Gemini 3000 [300 MHz (δ_{TMS}: 0 ppm) in $CDCl_3$]. Mass spectra: Jeol JMS-700. Column chromatography: Merck silica gel 60 (70-230 mesh). TLC: Merck silica gel 60 F_{254} 0.5 mm. The enantiomeric purities of (+)- and (−)-**5**, **6**, and **7** were determined by ^{19}F (**5** and **6**) and ^{1}H NMR (**7**) spectra of the corresponding MTPA esters according to Charette.[6] '>95% ee' means the peak of another diastereomer is under the detection limit. Those of (+)- and (−)-**8** were reflected by the values of the parent compounds (98.6% and 99.2% ee, respectively).

4.2. (+)-(2*S*,3*S*)-2,3-Methano-3,7-dimethyl-6-octen-1-ol (+)-5

According to Charette's report,[6] using (*R*,*R*)-dioxaborolane ligand (193 mg, 0.71 mmol), geraniol **1** (100 mg, 0.64 mmol) was converted to (+)-**5** (66 mg, 0.39 mmol, 62%, >95% ee) as a colorless oil, bp: 65 °C/20 mmHg (oven temp), $[\alpha]_D^{25} = +3.0$ (*c* 0.90 $CHCl_3$) {lit.[6] $[\alpha]_D^{25} = +2.16$ (*c* 5.83, $CHCl_3$)}. GLC (A): $t_R = 4.50$ min (95%). IR $\nu_{\max}$

Table 2. Odor evaluations of nor-leaf alcohol and matsutake alcohol derivatives

Entry	No.	Compounds	Odor description
1	(±)-**7**[4f]		Acidic ether fruity odor, less green than nor-leaf alcohol **3**
2	(+)-**7**		Diffusive ether green odor, close to nor-leaf alcohol, more green than (±)- and (−)-**7**
3	(−)-**7**		Weak rosy odor without characteristic green aspect found in (±)-**7**
4	(±)-**8**[4f]		Unpleasant sweet-sour, fatty, woody, rosy odor, lacking in mushroom-like aspect in natural (*R*)-matsutakeol *nat*-**4**
5	(*R*)-**8**		Sweet matsutake-like odor, close to natural (*R*)-matsutakeol *nat*-**4**
6	(*S*)-**8**		Humid mossy rosy odor, no mushroom character found in (±)-**8**

(film) cm^{-1}: 3350 (s), 3050 (m, cyclopropyl C–H), 2950 (s), 1650 (w), 1450 (m), 1380 (m), 1090 (w), 1030 (s), 830 (w). ^{1}H NMR spectrum was in good agreement with that reported.[6] HR-EIMS *m/z*: calcd for $C_{11}H_{20}O$ (M^+), 168.1512; found, 168.1515.

4.3. (−)-(2*R*,3*R*)-2,3-Methano-3,7-dimethyl-6-octen-1-ol (−)-5

In the same manner as described for (+)-**5** using (*S*,*S*)-dioxaborolane ligand, **1** (100 mg, 0.64 mmol) was converted to (−)-**5** (59 mg, 0.35 mmol, 55% yield, >95% ee) as a colorless oil, bp: 65 °C/20 mmHg, $[\alpha]_D^{25} = -3.1$ (*c* 0.30, $CHCl_3$). GLC (A): $t_R = 4.50$ min (95%). HR-EIMS *m/z*: calcd for $C_{11}H_{20}O$ (M^+), 168.1512; found, 168.1512.

4.4. (−)-(2*S*,3*R*)-2,3-Methano-3,7-dimethyl-6-octen-1-ol (−)-6

Nerol **2** (155 mg, 1.00 mmol) was converted to (−)-**6** (124 mg, 0.739 mmol, 74% yield, >95% ee) as a colorless oil, bp: 65 °C/20 mmHg (oven temp), $[\alpha]_D^{25} = -8.3$ (*c* 1.0, Et_2O). $R_f = 0.40$ (pentane/Et_2O = 1:1). GLC (B): $t_R = 2.64$ min (95%). IR ν_{max} (film) cm^{-1}: 3350 (s, OH), 2920 (m), 1450 (s), 1380 (s), 1030 (s), 1010 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.14 (1H, t, $J = 4.9$), 0.48 (1H, dd, $J = 8.5$, 4.4), 0.98–0.88 (1H, m), 1.07 (3H, s), 1.40–1.34 (2H, m), 1.62 (3H, s), 1.69 (3H, s), 2.08 (2H, q, $J = 7.4$), 3.67–3.55 (2H, m), 5.14 (1H, m). HR-EIMS *m/z*: calcd for $C_{11}H_{20}O$ (M^+), 168.1514; found, 168.1509.

4.5. (+)-(2*R*,3*S*)-2,3-Methano-3,7-dimethyl-6-octen-1-ol (+)-6

Nerol **2** (155 mg, 1.00 mmol) was converted to (+)-**6** (152 mg, 0.905 mmol, 91% yield, >95% ee) as a colorless oil, bp: 65 °C/20 mmHg (oven temp). $[\alpha]_D^{25} = +7.7$ (*c* 1.0, Et_2O). GLC (B): $t_R = 2.64$ min (95%). HR-EIMS *m/z*: calcd for $C_{11}H_{20}O$ (M^+), 168.1514; found, 168.1521.

4.6. (−)-(2*S*,3*R*)-2,3-Methano-1-pentanol (−)-7

Nor-leaf alcohol **3** (376 mg, 4.36 mmol) was converted to (−)-**7** (392 mg, 3.92 mmol, 90%, 93% ee) as a colorless oil, bp: 60 °C/20 mmHg (oven temp), $[\alpha]_D^{25} = -17$ (*c* 0.10, Et_2O), $[\alpha]_D^{24} = -30$ (*c* 0.075, $CHCl_3$) {lit.,[6] 87% ee, $[\alpha]_D^{25} = -27.9$ (*c* 0.62, $CHCl_3$)}. GLC (C): $t_R = 2.24$ (99%). IR ν_{max} (film) cm^{-1}: 3350 (s, OH), 2970 (m), 1450 (s), 1030 (s), 1020 (s). ^{1}H NMR spectrum was in good agreement with that reported.[6] HR-EIMS *m/z*: calcd for $C_6H_{12}O$ (M^+), 100.0888; found, 100.0886.

4.7. (+)-(2*R*,3*S*)-2,3-Methano-1-pentanol (+)-7

Nor-leaf alcohol **3** (318 mg, 3.69 mmol) was converted to (+)-**7** (299 mg, 2.99 mmol, 81%, 95% ee) as a colorless oil, bp: 60 °C/20 mmHg (oven temp), $[\alpha]_D^{25} = +17$ ($c = 0.10$, Et_2O). GLC (C): $t_R = 2.24$ (96%). HR-EIMS *m/z*: calcd for $C_6H_{12}O$ (M^+), 100.0888; found, 100.0895.

4.8. (+)-(*S*)-1,2-Methano-3-octanol (*S*)-8

The flask was charged with dry CH_2Cl_2(15 ml) and dry DME (221 mg, 2.45 mmol) at −30 °C under N_2. To the solution was added diethylzinc in hexane (1.00 M, 2.45 ml, 2.45 mmol) followed by CH_2I_2 (1.31 g, 4.90 mmol) and a solution of (*S*)-**4** (78.5 mg, 0.613 mmol, 98.6% ee) in CH_2Cl_2 (5 ml) was added at −20 °C. Then the cooling bath was removed. After 2 days, the reaction was quenched by sat. aq NH_4Cl solution and the resulting mixture was extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$ filtered and concentrated under reduced pressure. Purification via silica gel chromatography and distillation with grass tube oven afforded (*S*)-**8** (76.5 mg, 0.546 mmol, 89%) as a colorless oil, bp: 85 °C/20 mmHg, $R_f = 0.60$ (pentane/Et_2O = 1:1), $[\alpha]_D^{25} = +0.45$ (*c* 4.3, Et_2O). GLC (D): $t_R = 1.51$ min (98%). IR and ^{1}H NMR were identical with those reported.[4f] HR-EIMS *m/z*: calcd for $C_9H_{18}O$ (M^+), 142.1358; found, 142.1350.

4.9. (−)-(*R*)-1,2-Methano-3-octanol (*R*)-8

(*R*)-**4** (78.5 mg, 0.620 mmol, 99.2% ee) was converted to (*R*)-**8** (75.9 mg, 0.542 mmol, 87%) as a colorless oil, bp: 85 °C/20 mmHg (oven temp), $[\alpha]_D^{25} = -0.3$ (*c* 0.65, Et_2O). GLC (D): $t_R = 1.50$ min (99%). HR-EIMS *m/z*: calcd for $C_9H_{18}O$ (M^+), 142.1358; found, 142.1376.

4.10. Odor evaluations

A mouliette (smelling blotter) was immersed in an unscented triethyl citrate solution (10% v/v) of each sample. Odor characteristics, strength, and persistence of them were observed for 24 h; then compared and appreciated by an experienced perfumer.

Acknowledgments

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