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Cyclization of *N*,*N*-diethylgeranylamine N-oxide in one-pot operation: preparation of cyclic terpenoid-aroma chemicals

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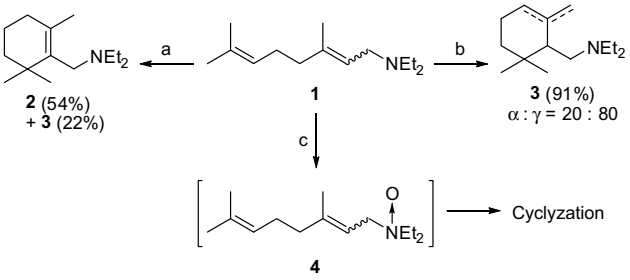
ABSTRACT

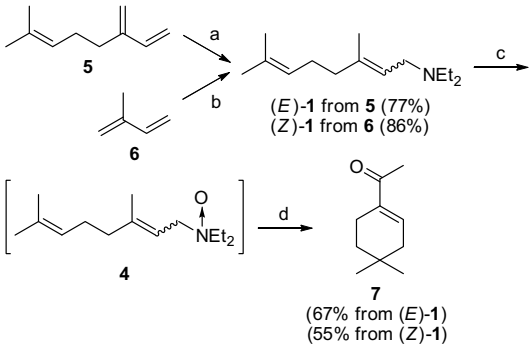
Acid promoted cyclization of the geranylamine N-oxide (*E*)-**4** followed by base-catalyzed intramolecular aldol condensation afforded 1-acetyl-4,4-dimethyl-1-cyclohexene (**7**) in one-pot operation. Reduction of **7**, which possess strong fruity odor, followed by lipase-catalyzed kinetic resolution furnished the acetate (*R*)-**26** (>49.9% yield, >99% ee) and the recovered alcohol (*S*)-**25** (>49.9% yield, >99% ee, herbal odor).

N,*N*-Diethylgeranylamine ((*E*)-**1**)[1a,b] and *N*,*N*-diethylnerylamine ((*Z*)-**1**)[1c] are key intermediates for the preparation of industrially important acyclic and cyclic monoterpenes such as linalool,[2] geraniol,[3] citral,[4] citronellal,[5] *l*-menthol,[6] and liral.[7] Previously, we reported sulfuric acid promoted regioselective cyclization of (*Z*)-**1** to *N*,*N*-diethyl β-cyclogeranylamine (**2**), in contrast, cyclization of (*E*)-**1** with $BF_3{\cdot}OEt_2$ afforded a 20:80 mixture of *N*,*N*-diethyl α- and γ-cyclogeranylamine (**3**) (Scheme 1).[8] As a continuation of our studies into the use of **1** in organic syntheses,[9] we wondered whether *N*,*N*-diethylgeranylamine N-oxide (**4**) could behave like **1**. Although terpenoid N-oxides are well known as a good substrate for Meisenheimer rearrangement,[10] to our best knowledge, cyclization involving C–C bond formation as well as C–C bond fission has not been studied previously. Herein, we report an acid promoted cyclization of the N-oxide **4** and lipase-catalyzed kinetic resolution of the odorous cyclized derivative **7**.

N,*N*-Diethylgeranylamine ((*E*)-**1**)[11] and *N*,*N*-diethylnerylamine ((*Z*)-**1**)[12] were stereoselectively prepared by a simple, one-step procedure from myrcene (**5**) and isoprene (**6**), respectively (Scheme 2). Oxidation of (*E*)-**1** with 31% H_2O_2 followed by addition of PtO_2 to decompose excess oxidizing agent gave the N-oxide **4**. Cyclization of the crude N-oxide **4** was carried out by the following manner.[13] To a colorless solution of the crude N-oxide **4** in H_2O was added 50% H_2SO_4 aq, then the mixture changed from colorless to pink. After the acidic reaction mixture was made strongly basic with NaOH pellets, the mixture gradually separated into pale yellow aqueous layer and dark brown organic layer. Interestingly, this dark brown liquid gave off good fruity odor. The structure of product was confirmed as 1-acetyl-4,4-dimethyl-1-cyclohexene (**7**) in comparison with alternatively synthetic enone **7**.[14] Similarly, the enone **7** was obtained from *N*,*N*-diethylnerylamine ((*Z*)-**1**) in 55% yield. Both of regioisomers **1** resulted in the formation of the same enone **7**. This outcome indicated that cyclization progressed through the same intermediate.



Scheme 1. Reagents and conditions: (a) 40% H_2SO_4, 120 °C, 20 h; (b) $BF_3{\cdot}OEt_2$, AcOH, 30 °C, 6 h; (c) H_2O_2, MeOH, rt, 48 h, then PtO_2, rt, 24 h.



Scheme 2. Reagents and conditions: (a) Et_2NH, Li, 55 °C, 5 h; (b) Et_2NH, *n*-BuLi, 5–65 °C, 13 h; (c) H_2O_2, MeOH, rt, 48 h, then PtO_2, rt, 24 h; (d) (i) H_2SO_4, H_2O, 100 °C, 24 h; (ii) NaOH, H_2O, 100 °C, 24 h.

Cyclization of *N*,*N*-diethylfarnesylamine (**8**) was also examined. The crude N-oxide **9** was obtained by oxidation of **8** with 31% H_2O_2.

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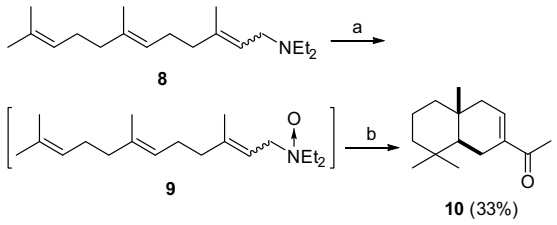
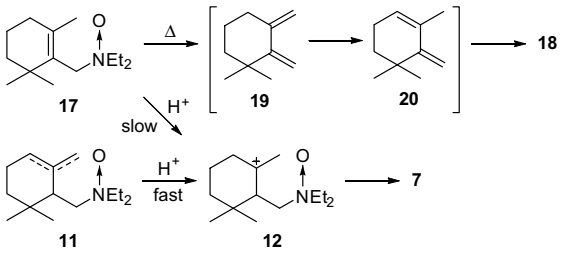


Scheme 3. Reagents and conditions: (a) H_2O_2, MeOH, rt, 48 h, then PtO_2, rt, 24 h; (b) (i) H_2SO_4, H_2O, 100 °C, 24 h; (ii) NaOH, H_2O, 100 °C, 24 h.



Scheme 6. Proposed reaction sequence.

One-pot operation under the same procedure gave the bicyclic enone **10** in 33% yield as a single diastereomer (Scheme 3).[15]

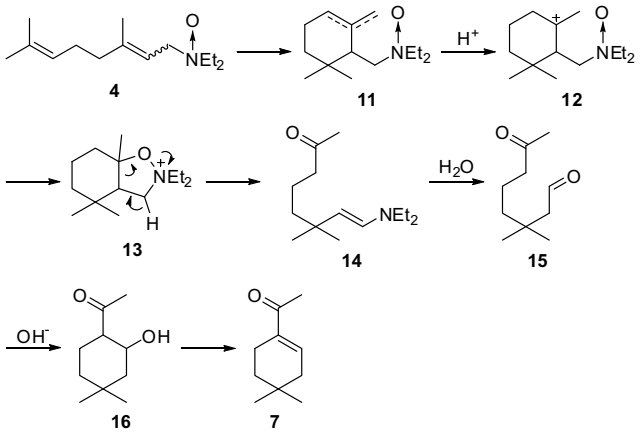
The proposed reaction mechanism for cyclization of the N-oxide **4** is shown in Scheme 4. Acid promoted cyclization of the N-oxide **4** formed a mixture of *N*,*N*-diethyl α- and γ-cyclogeranylamine N-oxide (**11**), which readily protonated to give the cation intermediate **12**. Nucleophilic cyclization of **12** furnished the bicyclic intermediate **13**, which was transformed to the keto-enamine intermediate **14** with C–C bond fission. Hydrolysis and base-catalyzed intramolecular aldol condensation of keto-aldehyde **15** afforded the desired enone **7**.

Following experiments have been performed to prove the above proposed reaction mechanism. The N-oxide **17** derived from β-cyclogeranylamine **2** was reacted in the same way to cyclization of the N-oxide **4** to give 1,2,3,4-tetramethylbenzene (**18**) in 53% yield through sequential elimination, isomerization, and migration (Scheme 5). Thermal elimination of **17** gave 1,1-dimethyl-2,3-dimethylenecyclohexane (**19**),[9b] which was isomerized to the diene **20**. Aromatization of the cyclic end group with concomitant regioselective migration of one methyl group from the geminal dimethyl functionality afforded the product **18** (Scheme 6).[16] On the other hand, in the case of α- and γ-cyclogeranylamine **11,** the cyclic enone **7** was formed in 41% yield (Scheme 5). These results indicate that the cyclization progressed through α- and γ-cyclogeranylamine N-oxide intermediate **11** not through β-intermediate **17**.

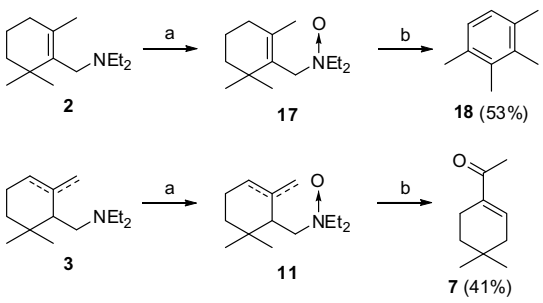
The reactive difference between N-oxide **11** and **17** was illustrated by the protonation ability. Terminal and/or trisubstituted olefin intermediate **11** is better proton acceptor than tetrasubstituted olefin intermediate **17**. Therefore, the N-oxide **11** was easily protonated to give the cyclized product **7** through the intermediate **12**, in contrast, thermal elimination preferentially proceeded in the case of **17** (Scheme 6).

Cyclization of the terminal olefin **21** and/or internal olefin **22** gave the same ketone **24** in 34–35% yields; therefore, location of double bond did not affect the reactivity (Scheme 7). In addition, C–C bond fission proceeded selectively at between β and γ position to the nitrogen atom. These experiments (Schemes 5 and 7) support that the cyclization of the N-oxide **4** includes (1) acid promoted cyclization, (2) nucleophilic cyclization of N-oxide, and (3) selective C–C bond fission as shown in Scheme 4.

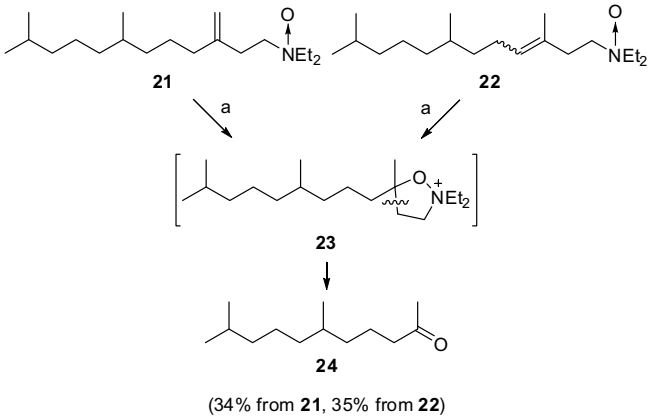
Since the cyclic enone **7** is strong fruity, odor of the derivatives from **7** should be interesting. Sodium borohydride reduction of **7** gave the racemic alcohol **25** in 99% yield. Lipase-catalyzed kinetic resolutions of **25** were carried out using 0.5 equiv of vinyl acetate in diisopropyl ether at 25 °C. All of lipase tested except M-10 and Newlase F provided the enantiomerically pure acetate **26** with *R* configuration and the recovered alcohol **25** with *S* configuration determined by derivation to the Mosher ester.[17] Especially, lipase AK (*Pseudomonas fluorescens*, Amano Enzyme Co, Ltd) was the best catalyst to afford (*R*)-**26** in >49.9% yield with excellent *E* value.[18,19] Both enantiomers of the acetate **26** and alcohol **25** were prepared



Scheme 4. Proposed reaction mechanism for cyclization of the N-oxide **4**.

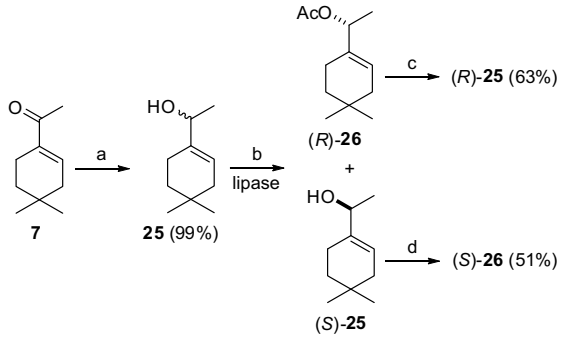


Scheme 5. Reagents and conditions: (a) H_2O_2, MeOH, rt, 48 h, then PtO_2, rt, 24 h; (b) (i) H_2SO_4, H_2O, 100 °C, 24 h; (ii) NaOH, H_2O, 100 °C, 24 h.



Scheme 7. Reagents and conditions: (a) (i) 40% H_2SO_4, 100 °C, 24 h; (ii) NaOH, H_2O, 100 °C, 24 h.

Table 1
Lipase-catalyzed kinetic resolution of the racemic alcohol **25**



Entry	Lipase	Conversion (%)	(*R*)-**26** ee (%)	*E* value
1	M-10	0	—	—
2	Newlase F	0	—	—
3	A-6	4.4	>99	208
4	PEG	4.5	>99	208
5	MY	9.7	>99	221
6	OF	13.8	>99	232
7	CHIRAZYME® L-2	30.9	>99	308
8	PSA-30	35.4	>99	344
9	PS-D	38.2	>99	373
10	NOVOZYME®	38.3	>99	374
11	PL	48.9	>99	738
12	AK	>49.9	>99	992

Reagents and conditions: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 2 h; (b) vinyl acetate (0.5 equiv), lipase (100 mg/mmol), *i*-Pr_2O, 25 °C; (c) K_2CO_3, MeOH, 25 °C, 6 h; (d) Ac_2O, Et_3N, DMAP, Et_2O, rt, 2.5 h.

by standard hydrolysis ((*R*)-**26** → (*R*)-**25**) or acetylation ((*S*)-**25** → (*S*)-**26**). Interestingly, odor of (*S*)-isomers **25** and **26** is stronger and more sensory active than those of (*R*)-isomers, particularly, (*S*)-alcohol **25** shows good herbal odor (see Table 1).[20]

In summary, we have developed acid promoted cyclization of geranylamine N-oxide (*E*)-**4** followed by base-catalyzed intramolecular aldol condensation afforded the cyclic enone **7** in one-pot operation. Reduction of **7**, which possess strong fruity odor, followed by lipase-catalyzed kinetic resolution furnished the acetate (*R*)-**26** (>49.9% yield, >99% ee) and the recovered herbal alcohol (*S*)-**25** (>49.9% yield, >99% ee). Further studies focusing on the use of acid promoted cyclization of N-oxide derivatives are currently under investigation and will be reported in due course.

Acknowledgments

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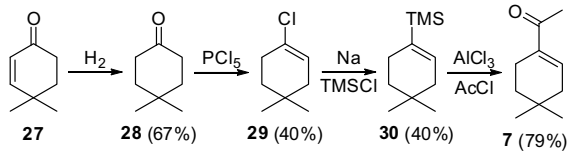
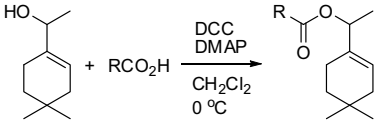
References and notes

1. (a) Takabe, K.; Katagiri, T.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 222–225; (b) Fujita, T.; Suga, K.; Watanabe, S. *Chem. Ind. (London, U.K.)* **1973**, 231–232; (c) Takabe, K.; Katagiri, T.; Tanaka, J. *Tetrahedron Lett.* **1972**, *13*, 4009–4012.
2. Takabe, K.; Katagiri, T.; Tanaka, J. *Tetrahedron Lett.* **1975**, 3005–3006.
3. Takabe, K.; Katagiri, T.; Tanaka, J. *Chem. Lett.* **1977**, 1025–1026.
4. Takabe, K.; Yamada, T.; Katagiri, T. *Chem. Lett.* **1982**, 1987–1988.
5. (a) Tani, K.; Yamagata, T.; Otsuka, S.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R. *J. Chem. Soc., Chem. Commun.* **1982**, 600–601; (b) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, *106*, 5208–5217; (c) Tani, K.; Yamagata, T.; Otsuka, S.; Kumobayashi, H.; Akutagawa, S. *Org. Synth.* **1989**, *67*, 33–43.
6. (a) Akutagawa, S. *Organic Synthesis in Japan: Past, Present, and future: in Commemoration of the 50th Anniversary of the Society of Synthetic Organic Chemistry, Japan*; Noyori, R. (Ed.), Tokyo Kagaku Dojin, 1992; pp 75–82; (b) Otsuka, S. *Acta Chem. Scand.* **1996**, *50*, 353–360.
7. Kumobayashi, H.; Mitsuhashi, S.; Akutagawa, S.; Ohtsuka, S. *Chem. Lett.* **1986**, 157–160.
8. (a) Takabe, K.; Yamada, T.; Sato, T.; Katagiri, T. *Nippon Kagaku Kaishi* **1980**, 776–778; (b) Takabe, K.; Yamada, T.; Katagiri, T. *Chem. Ind. (London, U.K.)* **1980**, *13*, 540. see also Ref. 9b.
9. (a) Takabe, K. *Koryo* **1983**, *139*, 41–45; (b) Yamada, T.; Takabe, K. *Chem. Lett.* **1993**, 29–30. See also references cited therein.
10. Albini, A. *Synthesis* **1993**, 263–277. See also references cited therein.
11. Takabe, K.; Katagiri, T.; Tanaka, J.; Fujita, T.; Watanabe, S.; Suga, K. *Org. Synth.* **1989**, *67*, 44–47.
12. Takabe, K.; Yamada, T.; Katagiri, T.; Tanaka, J. *Org. Synth.* **1989**, *67*, 48–51.
13. *Typical procedure*: To a solution of *N*,*N*-diethylgeranylamine ((*E*)-**1**, 2.1 g, 10 mmol, 1.0 equiv)) in methanol (10 mL) was added 31% H_2O_2 aq (3.3 mL) at room temperature. The mixture was stirred for 48 h, and then PtO_2 (3 mg) was added to decompose excess oxidizing agent. The reaction mixture was filtrated through the Celite and washed with MeOH. The filtrate was evaporated under reduced pressure to give the crude N-oxide **4**. To a colorless solution of the crude N-oxide **4** in H_2O was added 50% H_2SO_4 aq (V/V, 9.8 mL). The mixture changed from colorless to pink during stirring for 24 h at 100 °C. After cooling to 0 °C, NaOH pellets (10 g) and crushed ice (10 g) were added to the reaction vessel. Stirred for 24 h at 100 °C, the mixture was gradually separated into pale yellow aqueous layer and dark brown organic layer. The mixture was quenched with 10% HCl aq (10 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL). The organic extracts were concentrated to give the crude enone **7**, which was purified by flash column chromatography (silica gel 60 g, hexanes only → hexanes/ethylacetate = 80:20) to give 1-(4,4-dimethylcyclohex-1-enyl)ethanone (**7**, 0.96 g, 63%) as a pale yellow liquid: registry number 5773-37-5; R_f = 0.61 (hexane/AcOEt = 70:30); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.84 (ddd, *J* = 5.4, 3.7, 1.4 Hz, 1 H, –CH=C–), 2.29 (s, 3H, CH_3CO–), 2.21–2.32 (m, 2 H, $-CH_2-$), 2.04 (td, *J* = 4.2, 2.3 Hz, 2H, $-CH_2-$), 1.40 (t, *J* = 6.5 Hz, 2 H, $-CH_2-$), 0.92 (s, 6H, 2 × $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.24 (C=O), 140.04 (CH), 138.46 (C), 39.89 (CH_2), 34.68 (CH_2), 28.21 (C), 27.93 (CH_3), 25.08 (CH_3), 20.64 (CH_2).
14. The cyclic enone **7** was prepared from commercially available enone **27** in four step transformations: Fleming, I.; Pearce, A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2485–2489.



15. Acid promoted cyclization of farnesyl derivatives generally gave *trans*-decalyl derivatives. See: (a) Ohloff, G.; Näf, F.; Decorzant, R.; Thommen, W.; Sundt, E. *Helv. Chim. Acta* **1973**, *56*, 1414–1448; (b) Corbier, B.; Ehret, C.; Giraudi, E.; Pelerin, G. *Dev. Food Sci.* **1988**, *18*, 483–494.
16. Valla, A.; Andriamialisoa, Z.; Valla, B.; Labia, R.; Le Guillou, R.; Dufosse, L.; Cartier, D. *Eur. J. Org. Chem.* **2007**, 711–715.
17. (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519; (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
18. The enantiomeric ratio *E* is generally accepted as an adequate parameter to quantify the enantioselectivity in biochemical kinetic resolutions: Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
19. Enantioselectivities of the acetate **26** were determined by chiral capillary GC using InertCap CHIRAMIX. (130–180 °C, 2 °C/min, R_t: 20.953 min for (*S*)-**26**, 22.008 min for (*R*)-**26**.
20. We further synthesized ester derivatives **31** using DCC coupling agent. All of ester derivatives possessed sweet odor; however, odor of **31** was weaker than that of **26**.



R = Et (85%), Pr (81%),
i-Pr (94%), (*R*)-*sec*-Bu (98%)