*Tetrahedron* Vol. 49, No. 9, pp 1871-1878, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00


# SYNTHESIS OF (*S*)-α-DAMASCONE†

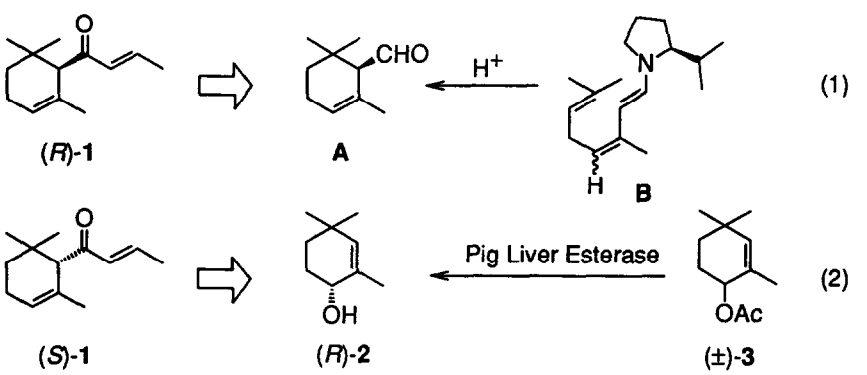
**Kenji Mori,* Masayasu Amaike†† and Masamichi Itou†††**

Department of Agricultural Chemistry, The University of Tokyo,
Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan.

(*Received in Japan* 1 *September* 1992)

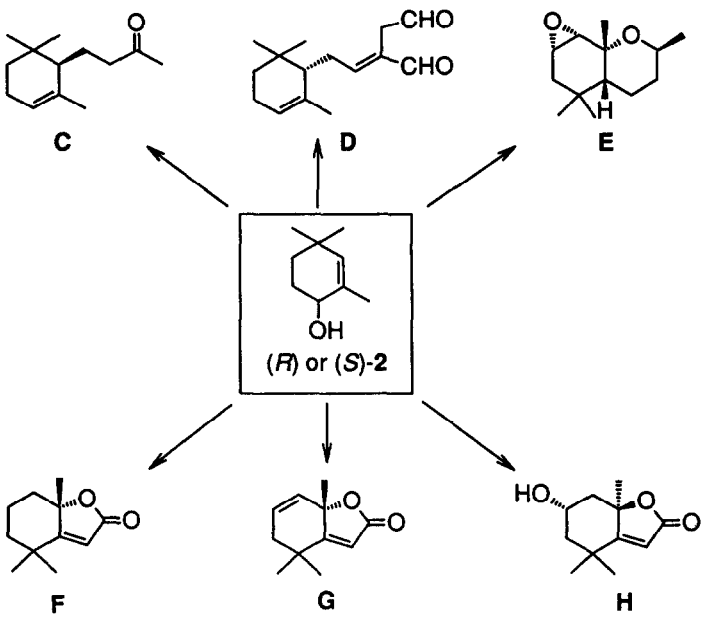
***Abstract:*** Enantiomerically pure (*S*)-α-damascone (**1**) was synthesized from (*R*)-2,4,4-trimethyl-2-cyclohexen-1-ol (**2**) by employing two different sigmatropic rearrangement reactions to transfer the chirality at C-1 of **2** to C-3. The starting material **2** could be prepared by either enzymatic asymmetric hydrolysis of (±)-**3** or chemical asymmetric reduction of **4**.

Since its discovery in 1970,[1,2] α-damascone (**1**, Scheme 1) is an important perfume compound which possesses a powerful fresh-fruity note with a rose-like character. In 1989, König *et al.* determined the absolute configuration of α-damascone (**1**) isolated from black tea as *S* by enantioselective capillary GC using octakis(3-*O*-methyl-2,6-di-*O*-pentyl)-γ-cyclodextrin as a chiral stationary phase.[3] In the same year, Pickenhagen reported that the detection threshold of (*S*)-**1** in water was as low as 1.5 ppb, while that of (*R*)-**1** was 100 ppb.[4] We therefore became interested in developing an efficient synthesis of (*S*)-**1**.




Scheme 1. Synthesis of α-damascone
(1) Yamada's synthesis in 1973. (2) The present synthesis.

† Dedicated in honor of the 77th birthday of Professor Shun-ichi Yamada, one of the pioneers in asymmetric synthesis. Carotenoids and Degraded Carotenoids—9. for Part 8, see ref. 12.
†† Research fellow on leave from T. Hasegawa Co., Ltd. (1991–1994).
††† Research fellow on leave from T. Hasegawa Co., Ltd. (1988–1991).

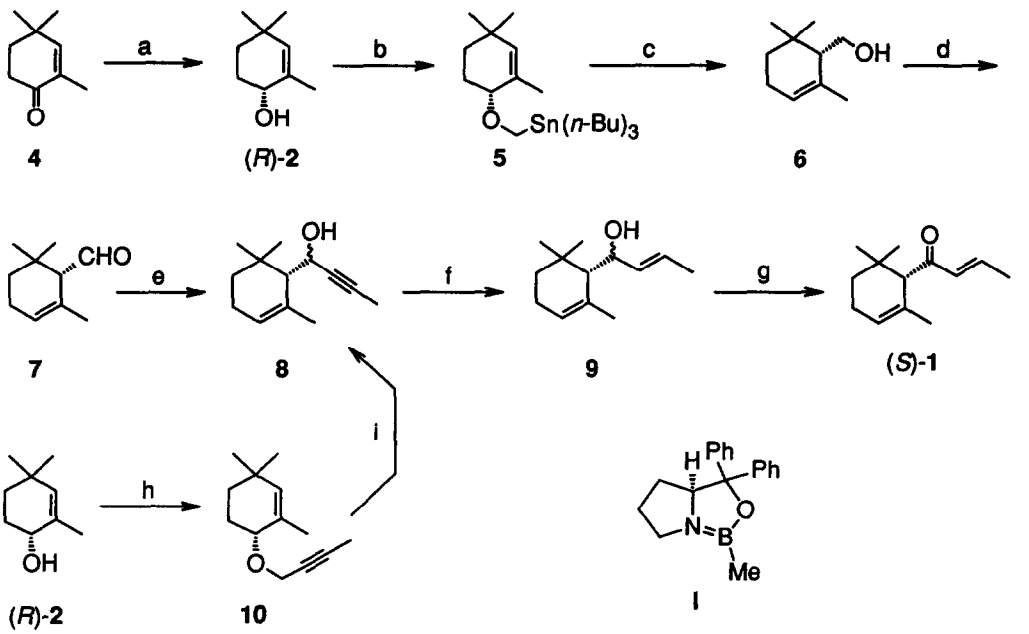



Scheme 2. Usefulness of **2** as a building block

Although there exist many different syntheses of (±)-**1**, only few syntheses of optically active **1** have been reported to date. The conversion of (*R*)-(+)-α-ionone to (*R*)-(+)-**1** (66% e.e.) by Ohloff and Uhde established the absolute configuration of **1** in 1970.[1] In 1973, Yamada *et al.* achieved an asymmetric synthesis of (*R*)-**1** via (*R*)-α-cyclocitral (**A**), obtained by acid-catalyzed cyclization of **B**.[5,6] This was indeed a remarkable pioneering work in the history of asymmetric terpene synthesis, although their (*R*)-**1** was of only 17.5% e.e. Fehr and Galindo were the first to synthesize enantiomerically pure α-damascone (**1**) in 1988 by a highly enantioselective protonation of a ketone enolate coupled with crystallization of **1**.[7]

Our own strategy to prepare (*S*)-**1** as shown in Scheme 1 is the use of an allylic alcohol (*R*)-2,4,4-trimethyl-2-cyclohexen-1-ol (**2**), which is readily available by enzymatic resolution of (±)-**3**.[8] Transfer of chirality from C-1 of **2** to C-3 by sigmatropic rearragement reactions will provide precursors to (*S*)-**1**. The usefulness of (*R*)- or (*S*)-**2** in asymmetric synthesis of terpenes has already been proved as illustrated in Scheme 2.[9] Namely, dihydro-α-ionone (**C**),[8] a marine sesquiterpene with antifeedant activity (**D**),[10] butterfly epoxide (**E**),[11] dihydroactinidiolide (**F**),[12] actinidiolide (**G**),[12] and loliolide (**H**)[12] were synthesized from either (*R*)- or (*S*)-**2**. It must be emphasized that both the enantiomers of **2** are easily accessible in enantiomerically pure state by the asymmetric hydrolysis of (±)-**3** with pig liver esterase (PLE) followed by purification via 3,5-dinitrobenzoate of **2**.[8]

Scheme 3 summarizes our synthesis of (*S*)-**1** by two different routes. Although our starting material (*R*)-**2** was prepared by our own enzymatic method,[8] we also examined Corey's asymmetric reduction (CBS reduction[13,14]) of **4**[15] by employing (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (**I**, Scheme 3) as a catalyst and borane in THF as a reductant. In a small-scale experiment with 2.0 mmol of **4**, (*R*)-**2** (95.8% e.e.) was obtained in 77% yield. The asymmetric yield of this process was excellent, but not




Scheme 3. Synthesis of (*S*)-α-damascone (**1**)

Reagents: (a) $BH_3$-THF, I, THF (77%).— (b) KH, $(n\text{-Bu})_3SnCH_2I$, THF, 0°C ~ r.t. (93%).— (c) *n*-BuLi, THF, −78° ~ 20°C (57%) — (d) $(COCl)_2$, DMSO, $CH_2Cl_2$, $Et_3N$ (96%). — (e) MeC≡CMgBr, THF (79%). — (f) $LiAlH_4$, NaOMe, THF (96%) — (g) $MnO_2$, $Me_2CO$ (79% of **1** from **9**, 17% of **1** from **10**) — (h) $MeC{\equiv}CCH_2Br$, $(n\text{-Bu})_4NI$, aq.NaOH (96%).— (i) *n*-BuLi, TMEDA, $Et_2O$, −85° ~ −30°C —

yet perfect. The enzymatic process was therefore considered to be a competitive alternative to the CBS reduction, especially in view of the simplicity of the experimental procedure.

In the first route (route A) shown in the upper part of Scheme 3, Still's [2,3] Wittig rearrangement[16] was employed as the key reaction. Treatment of (*R*)-**2** (~100% e.e.) with potassium hydride and tri(*n*-butyl)stannylmethyl iodide furnished stannyl ether **5**. Addition of *n*-butyllithium to **5** at low temperature initiated the rearrangement to give (*S*)-α-cyclogeraniol (**6**).[17,18] The alcohol **6** was oxidized under the Swern condition to afford (*S*)-α-cyclocitral (**7**). Addition of 1-propynylmagnesium bromide to **7** gave (*S*)-dehydro-α-damascol (**8**) as a diastereomeric mixture at C-1 in a ratio of 87:13. Reduction of the triple bond of **8** was executed with lithium aluminum hydride in the presence of sodium methoxide in THF to furnish **9** as a 91:9 diastereomeric mixture. Finally, **9** was oxidized with manganese dioxide to give (*S*)-α-damascone (**1**) $[\alpha]_D^{23}$ −514° (*c*= 4.03, $CHCl_3$) [ref.[7] $[\alpha]_D^{20}$ −488° (*c*= 4.0, $CHCl_3$)]. The overall yield of (*S*)-**1** was 30% based on (*R*)-**2** (6 steps). The enantiomeric purity of the synthetic (*S*)-**1** was estimated by GC analysis using heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (PMBCD-TH column) as the chiral stationary phase, and shown to be ~100% e.e.

In the second route (route B), (*R*)-**2** (95.3% e.e.) was converted to butynyl ether **10**, which was treated with *n*-butyllithium in ether in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) to effect [3,3]sigmatropic rearrangement. The resulting **8** (diastereomeric ratio at C-1 = 64 : 36) was an intermediate in route A (*vide supra*) leading to (*S*)-**1**. This type of rearrangement was previously employed by Schulte-Elte *et al.* in their synthesis of γ-damascone.[19] In the present case, however, unidentified by-products were also generated, which could not be removed at this stage. Accordingly, crude **8** was reduced to give crude **9** (diastereomeric ratio = 72 : 28), whose oxidation yielded (*S*)-α-damascone (**1**). Fortunately, the final product could be purified by chromatography and recrystallization to give pure (*S*)-**1**, $[\alpha]_D^{24}$ −510° (*c*= 1.92, $CHCl_3$). Its enantiomeric purity as estimated by GC analysis was 95.2% e.e. before recrystallization and ~100% e.e. after recrystallization. The overall yield of (*S*)-**1** by route B was 16% based on (*R*)-**2** after 4 steps.

In conclusion, the present synthesis of (*S*)-α-damascone (**1**) was efficient and selective enough to give enantiomerically pure **1** in good overall yield. Enantiomerically pure **2** was again proved to be a versatile chiral building block for synthesis of degraded carotenoids. At the time when the present synthesis was orally reported,[20] Dr. P. Werkhoff (Haarmann & Reimer Co., Germany) gave an important comment. According to him, reexamination of the enantiomeric purity using the same chiral stationary phase for their GC analysis as König *et al.* employed[3] revealed that natural α-damascone (**1**) isolated from tobacco and black tea was almost racemic: *R* / *S* = 53 : 47 = 6% e.e.[21] It sometimes happens that naturally occurring degraded carotenoids are almost racemic as in the cases of karahana lactone,[22] megastigmadiene relatives from *Osmanthus fragrans*,[23] and dihydroactinidiolide.[24] Although these facts as observed by Werkhoff *et al.*[21] have some negative impacts, the present asymmetric synthesis of α-damascone will assist solving the remaining problems in enantioselective odor perception in the case of α-damascone.

## EXPERIMENTAL

All m.p.s and b.p. were uncorrected. IR spectra were measured as films on a Jasco IRA-102 spectrometer. $^1$H-NMR spectra were recorded with TMS as an internal standard at 90 MHz on a JEOL JNM EX-90 spectrometer or at 300 MHz on a BRUKER AC-300 spectrometer. $^{13}$C-NMR spectra were recorded with $CDCl_3$ as an internal standard at δ=77.00 at 22.5 MHz on a JEOL JNM EX-90 spectrometer. Optical rotations were measured on a Jasco DIP-371 polarimeter. HPLC analysis was performed on a Shimadzu LC-6A with an SPD-6A as a detector. GC analyses were performed on a Shimadzu GC-14A with a flame ionization detector. Merck Kieselgel 60, Art. Nr. 7734 was used for $SiO_2$ column chromatography.

*(R)-2,4,4-Trimethyl-2-cyclohexen-1-ol* (*R*)-**2**. To a stirred and ice-cooled solution of (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (**I**, 55 mg, 0.20 mmol) and a solution of borane-THF complex in THF (1.0 *M*, 1.3 ml, 1.3 mmol) in dry THF (1 ml) was added dropwise a solution of **4** (0.28 g, 2.0 mmol) in dry THF (2 ml) between 0 and 5°C under Ar. After stirring for 30 min at this temperature, the reaction mixture was decomposed by the addition of water (2 ml). The mixture was poured into brine and extracted with ether. The extract was dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over $SiO_2$ (8 g). Elution with *n*-hexane-EtOAc (9:1~7:1) gave recovered **4** (24 mg, 8.7% recovery) and (*R*)-**2** (0.22 g, 77%; 85% based on the consumed **4**) as a colorless oil. Its IR and $^1$H-NMR

spectra data were identical with those reported[8].

In the same manner as previously reported manner[10], the enantiomeric purity of *(R)*-**2** was determined by the HPLC analysis of the corresponding 3,5-dinitrobenzoate of *(R)*-**2**[10]; (column: Chiralcel®-OJ [cellulose tris(*p*-methylbenzoate)], 25 cm × 4.6 mm; solvent: *n*-hexane/2-propanol (60:1); flow rate: 1.0 ml/min; detected at 254 nm); $R_t$ = 15.1 min [*(R)*-isomer, 97.9%], 22.2 min [*(S)*-isomer, 2.1%]. *(R)*-**2** was therefore of 95.8% e.e.

*(R)-2,4,4-Trimethy-2-cyclohexenyl tri-n-butylstannylmethyl ether* **5**. To a stirred and ice-cooled suspension of KH (20% dispersion in mineral oil, 14.9 g, 74 mmol) in dry THF (190 ml) and dry DMF (48 ml) was added dropwise a solution of *(R)*-**2** (8.0 g, 57 mmol, ~100% e.e.) in dry THF (57 ml) between 0 and 5°C under Ar. The mixture was stirred for 1 h at this temperature. Subsequently $(n\text{-Bu})_3SnCH_2I$ (32.7 g, 76 mmol) was added dropwise between 0 and 5°C. After stirring for 2 h at room temperature, the mixture was poured into ice-water and extracted with ether. The extract was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over $SiO_2$ (400 g). Elution with *n*-hexane–EtOAc (10:1~5:1) gave recovered *(R)*-**2** (1.4 g, 18% recovery) and **5** (19.5 g, 77%; 93% based on the consumed *(R)*-**2**). This was immediately used for the next step without further purification.

*(S)-2,6,6-Trimethyl-2-cyclohexenylmethanol [(S)-α-Cyclogeraniol]* **6**. A solution of **5** (19.5 g, 44 mmol) in dry THF (280 ml) was cooled to −70°C under Ar. To the solution was added dropwise a solution of *n*-BuLi in *n*-hexane (1.6 *M*, 36 ml, 58 mmol) below −70°C. The mixture was stirred for 1 h between −75 and −70°C, and the temperature was then allowed to rise to −20°C during 1 h. The mixture was poured into sat $NH_4Cl$ soln and extracted with ether. The extract was washed with sat $NaHCO_3$ soln and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over $SiO_2$ (130 g). Elution with *n*-hexane–ether (10:1~0:1) gave **6** (3.9 g, 57%) as a colorless oil; b.p. 62~63°C/3 Torr; $n_D^{22}$ 1.4838; $[\alpha]_D^{21}$ −116° (*c*= 1.23, EtOH) [ref.[17] $[\alpha]_D^{25}$ −109.2° (*c*= 1, EtOH), ref.[18] $[\alpha]_D^{25}$ −132.1° (EtOH)]; IR $\nu_{max}$ (film) 3370 (s), 3050 (w), 1650 (w), 1015 (s), 805 (s) $cm^{-1}$; $^1$H-NMR δ (90 MHz, $CDCl_3$) 0.88 (3H, s), 1.01 (3H, s), 1.05~1.30 (1H, m), 1.42~1.80 (2H, m), 1.73 (3H, d, *J*= 1.5 Hz), 1.83~2.15 (3H, m), 3.70 (2H, d, *J*= 3.5 Hz), 5.47~5.67 (1H, m).

*(S)-2,6,6-Trimethyl-2-cyclohexenecarbaldehyde [(S)-α-Cyclocitral]* **7**. A solution of dimethyl sulfoxide (1.0 ml, 14 mmol) in dry $CH_2Cl_2$ (2.3 ml) was added dropwise to a stirred and cooled solution of oxalyl chloride (0.85 ml, 9.7 mmol) in dry $CH_2Cl_2$ (23 ml) below −70°C under Ar. After stirring for 5 min at this temperature, a solution of **6** (1.0 g, 6.5 mmol) in dry $CH_2Cl_2$ (7 ml) was added dropwise below −70°C. After stirring for 15 min at this temperature, $Et_3N$ (4.1 ml, 29 mmol) was added to the mixture which was subsequently warmed to 0°C. Ice-water was added to the mixture and the mixture was extracted with ether. The extract was washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over $SiO_2$ (25 g). Elution with *n*-hexane–EtOAc (10:1) gave **7** (0.95 g, 96%) as a colorless oil; $^1$H-NMR δ (90 MHz, $CDCl_3$) 0.91 (3H, s), 0.99 (3H, s), 1.59 (3H, br. s), 1.12~1.88 (2H, m), 2.00~2.32 (2H, m), 2.35 (1H, d, *J*= 4.8 Hz), 5.62~5.85 (1H, m), 9.47 (1H, d, *J*= 4.8 Hz). This was immediately used for the next step without further purification.

*(1'S)-1-(2',6',6'-Trimethyl-2'-cyclohexenyl)-2-butyn-1-ol [(S)-Dehydro-α-damascol]* **8** (route A). A THF solution of propynylmagnesium bromide (0.50 *M*, 42 ml, 21 mmol) prepared from propyne and ethylmagnesium bromide was added dropwise to a stirred solution of **7** (0.65 g, 4.3 mmol) in dry THF (7 ml) between 15 and 20°C under Ar. After stirring for 1 h at room temperature, the reaction mixture was poured into sat $NH_4Cl$ soln and extracted with ether. The extract was washed with sat $NaHCO_3$ soln and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over $SiO_2$ (30 g). Elution with *n*-hexane–EtOAc (20:1~10:1) gave a colorless oil **8** (0.65 g, 79%) as a mixture of two diastereomers at C-1; $n_D^{21}$ 1.5008; $[\alpha]_D^{21}$ −208° (*c*= 2.75, EtOH); IR $\nu_{max}$ (film) 3470 (s), 3040 (m), 2230 (w), 1660 (w), 1055 (s), 1025 (s), 820 (m) $cm^{-1}$; $^1$H-NMR δ (90 MHz, $CDCl_3$) 0.87 and 0.92 (3H, s), 1.03 (3H, s), 1.08~1.27 (1H, m), 1.82 (3H, d, *J*= 2.4 Hz), 1.96 (3H, br. s), 1.47~2.17 (5H, m), 4.51~4.78 (1H, m), 5.44~5.58 and 5.62~5.83 (1H, m); Found: C, 81.05; H, 10.45; Calc for $C_{13}H_{20}O$: C, 81.20; H, 10.48. The ratio of the two diastereomers of **8** was determined to be 87:13 by GC analysis; (column: PEG-20M, 50 m × 0.25 mm at 70~220°C, +3.0°C/min; carrier gas: $N_2$, 1.5 ml/min); $R_t$= 19.8 min (major isomer, 87%), 21.3 min (minor isomer, 13%).

*(1'S,2E)-1-(2',6',6'-Trimethyl-2'-cyclohexenyl)-2-buten-1-ol [(S)-α-Damascol]* **9** (route A). To a stirred and cooled suspension of $LiAlH_4$ (0.63 g, 17 mmol) and NaOMe (0.45 g, 8.3 mmol) in dry THF (20 ml) was added dropwise a solution of **8** (0.80 g, 4.2 mmol) in dry THF (10 ml) between 0 and 5°C under Ar. After stirring for 15 h at room temperature, the reaction mixture was poured into water, neutralized with dil $H_2SO_4$ soln and extracted with ether. The extract was washed with sat $NaHCO_3$ soln and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over $SiO_2$ (25 g). Elution with *n*-hexane–ether (9:1) gave a colorless oil **9** (0.77 g, 96%) as a mixture of two diastereomers at C-1; $n_D^{21}$ 1.4908; $[\alpha]_D^{21}$ −162° (*c*= 3.51, EtOH); IR $\nu_{max}$ (film) 3480 (s), 3040 (m), 1665 (m), 1085 (m), 970 (s), 835 (m) $cm^{-1}$; $^1$H-NMR δ (90 MHz, $CDCl_3$) 0.87 (3H, s), 0.99 and 1.02 (3H, s), 1.10~1.31 (1H, m), 1.33~2.25 (11H, m), 4.25~4.51 (1H, m), 5.34~5.87 (3H, m); Found: C, 80.49; H, 11.22; Calc for $C_{13}H_{22}O$: C, 80.35; H, 11.41. The ratio of the two diastereomers of **9** was determined to be 91:9 by GC analysis; (under the same conditions as described for **8**); $R_t$= 13.8 min (major isomer, 91%), 15.6 min (minor isomer, 9%).

*(1'S,2E)-1-(2',6',6'-Trimethyl-2'-cyclohexenyl)-2-buten-1-one [(S)-α-Damascone]* (*S*)-**1** (route A). A mixture of **9** (0.41 g, 2.1 mmol) and activated $MnO_2$ (8.2 g, 95 mmol) in acetone (40 ml) was stirred for 90 h at room temperature. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by Lobar® column chromatography [Merck LiChroprep® Si 60 (40–63 μm); *n*-hexane–ether (200:1~10:1)] to give recovered **9** (56 mg, 13% recovery) and crude (*S*)-**1** (0.31 g) as a colorless oil. The enantiomeric purity of crude (*S*)-**1** was determined to be ca. 100% e.e. by GC analysis; (column: PMBCD-TH {heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin-coated capillary column], 50 m × 0.25 mm at 70~150 °C, +1.0 °C/min; carrier gas: $H_2$, 0.8 kg/$cm^2$); $R_t$= 74.3 min [(*S*)-isomer,~100%], (*R*)-isomer was not detected. The crude (*S*)-**1** was recrystallized from *n*-pentane to give (*S*)-**1** (0.28 g, 68%; 79% based on the consumed **9**) as colorless needles; m.p. 22~23 °C; $[\alpha]_D^{23}$ −514° (*c*= 4.03, $CHCl_3$) [ref.[7] m.p. 27.5~28 °C; $[\alpha]_D^{20}$ −488° (*c*= 4.0, $CHCl_3$)]; IR $\nu_{max}$ (film) 3060 (m), 1690 (s), 1665 (s), 1630 (s), 975 (s), 830 (m) $cm^{-1}$; $^1$H-NMR δ (300 MHz, $CDCl_3$) 0.86 (3H, s), 0.95 (3H, s), 1.17 (1H, ddd, *J*= 2.8, 5.8, 13 Hz), 1.57 (3H, d, *J*= 1.7 Hz), 1.70 (1H, ddd, *J*= 6.7, 10, 13 Hz), 1.90 (3H, dd, *J*= 1.6, 7.0 Hz), 1.96~2.23 (2H, m), 2.89 (1H,

s), 5.59~5.65 (1H, m), 6.31 (1H, dq, *J*= 15, 1.6 Hz), 6.88 (1H, dq, *J*= 15, 7.0 Hz); $^{13}$C-NMR δ (22.5 MHz, $CDCl_3$) 18.1, 22.6, 23.2, 27.7, 27.9, 31.3, 32.3, 61.2, 123.4, 130.5, 132.1, 142.0, 202.0; Found: C, 81.16, H, 10.48, Calc for $C_{13}H_{20}O$: C, 81.20, H, 10.48. The enantiomeric purity was determined by GLC analysis; (under the same conditions as described above); $R_t$= 72.3 min [(*S*)-isomer, single peak]. (*S*)-**1** was therefore of ca. 100% e.e. The spectral data were identical with those previously reported[1,7].

*(R)-2,4,4-Trimethyl-2-cyclohexenyl 2-butynyl ether* **10**. To a mixture of (*R*)-**2** (0.28 g, 2.0 mmol, 95.3% e.e.), NaOH (0.32 g, 8.0 mmol), tetra(*n*-butyl)ammonium iodide (37 mg, 0.10 mmol) and water (0.11g) was added dropwise 1-bromo-2-butyne (0.40 g, 3.0 mmol) at room temperature. After stirring for 17 h at room temperature, the reaction mixture was poured into water and extracted with ether. The extract was washed with sat $NH_4Cl$ soln and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over $SiO_2$ (25 g). Elution with *n*-hexane–EtOAc (29:1) gave **10** (0.38 g, 96%) as a colorless oil; $n_D^{20}$ 1.4800; $[\alpha]_D^{21}$ +21.2° (*c*= 3.03, EtOH); IR $\nu_{max}$ (film) 2300 (w), 2240 (w), 1135 (s), 1075 (s), 1055 (s) $cm^{-1}$; $^1$H-NMR δ (90 MHz, $CDCl_3$) 0.92 (3H, s), 0.98 (3H, s), 1.73 (3H, br. s), 1.84 (3H, t, *J*= 2.4 Hz), 1.15~1.83 (4H, m), 3.77 (1H, br. t, *J*= 4.7 Hz), 4.14 (2H, dq, *J*= 1.5, 2.4 Hz), 5.27 (1H, br. s); Found: C, 81.23, H, 10.59; Calc for $C_{13}H_{20}O$: C, 81.20, H, 10.48.

*(1'S)-1-(2',6',6'-Trimethyl-2'-cyclohexenyl)-2-butyn-1-ol [(S)-Dehydro-α-damascol]* **8** (route B). A solution of **10** (0.35 g, 1.8 mmol) and tetramethylethylenediamine (TMEDA) (0.27 ml, 1.8 mmol) in dry ether (2 ml) was cooled to −85°C in a liq. $N_2$–dry ice–acetone bath under Ar. To the solution was added dropwise a solution of *n*-BuLi in *n*-hexane (1.6 *M*, 3.4 ml, 5.4 mmol) between −85 and −80°C. The mixture was stirred for 2 h at this temperature, and the temperature was then allowed to rise to −40°C. After stirring for 1.5 h between −40 and −30°C, the reaction mixture was poured into sat $NH_4Cl$ soln and extracted with ether. The extract was washed brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed over $SiO_2$ (20 g). Elution with *n*-hexane–EtOAc (19:1) gave crude **8** (0.19 g, 54%) as a mixture with inseparable unidentified by-product(s). The GC analysis (under the same conditions as described for **8** in route A) of crude **8** revealed it to be a mixture of two diastereomers [$R_t$= 19.1 min (54%) and 20.9 min (31%)] and unidentified impurities (15%). IR $\nu_{max}$ (film) 3450 (s), 3040 (m), 2240 (w), 1955 (w), 1665 (w), 1055 (s), 1025 (s), 825 (m) $cm^{-1}$; $^1$H-NMR δ (90 MHz, $CDCl_3$) 0.87, 0.92, 0.96 and 1.03 (total 6H, s), 1.02~1.35 (1H, m), 1.82 (d, *J*= 2.4 Hz), 1.96 (br. s) and 1.43~2.27 (m) (total 11H), 4.48~4.96 (1H, m), 5.36, 5.52 and 5.72 (total 1H, m). Small peaks at $\nu_{max}$= 1955 (allene?) and δ= 0.96, 1.87 and 5.36 indicated the presence of unidentified impurities.

*(1'S,2E)-1-(2',6',6'-Trimethyl-2'-cyclohexenyl)-2-buten-1-ol [(S)-α-Damascol]* **9** (route B). In the same manner as described for the preparation of **9** in route A, crude **8** (0.34 g, 1.8 mmol) was reduced to crude **9** (0.26 g, 75%) as a mixture with inseparable unidentified by-products. The GC analysis (under the same conditions as described for **8** in route A) of crude **9** revealed it to be a mixture of two diastereomers [$R_t$= 14.0 min (47%) and 16.0 min (19%)] and unidentified impurities (34%). IR $\nu_{max}$ (film) 3460 (s), 3040 (m), 1665 (m), 1085 (m), 970 (s), 835 (m) $cm^{-1}$; $^1$H-NMR δ (90 MHz, $CDCl_3$) 0.87, 0.95, 0.99 and 1.02 (total 6H, s), 1.03~1.34 (1H, m), 1.35~2.28 (11H, m), 4.24~4.52 (1H, m), 5.32~5.89 (3H, m). Small peaks at δ= 0.95, 1.42, 1.45 and 1.53 indicated the presence of unidentified impurities.

*(1'S,2E)-1-(2',6',6'-Trimethyl-2'-cyclohexenyl)-2-buten-1-one [(S)-α-Damascone]* (*S*)-**1** (route B). In the same manner as described for the preparation of (*S*)-**1** in route A, crude **9** (0.25 g, 1.3 mmol) was oxidized to crude (*S*)-**1** (0.14 g) as a colorless oil. The enantiomeric purity of crude (*S*)-**1** was determined to be 95.2% e.e. by GC analysis; (under the same conditions as described for (*S*)-**1** in route A); $R_t$= 74.0 min [(*S*)-isomer, 97.6%], 74.9 min [(*R*)-isomer, 2.4%]. The crude (*S*)-**1** was recrystallized from *n*-pentane to give (*S*)-**1** (0.10 g, 41%, 17% based on **10**) as colorless crystals; m.p. 20~21°C; $[\alpha]_D^{24}$ −510° (*c*= 1.92, $CHCl_3$); IR $\nu_{max}$ (film) 3050 (m), 1690 (s), 1665 (s), 1630(s), 975 (s), 830 (m) $cm^{-1}$; $^1$H-NMR δ (300 MHz, $CDCl_3$) 0.86 (3H, s), 0.95 (3H, s), 1.17 (1H, ddd, *J*= 2.9, 5.8, 13 Hz), 1.57 (3H, d, *J*= 1.7 Hz), 1.70 (1H, ddd, *J*= 6.8, 9.9, 13 Hz), 1.90 (3H, dd, *J*= 1.7, 7.0 Hz), 1.97~2.22 (2H, m), 2 89 (1H, s), 5.58~5.65 (1H, m), 6.31 (1H, dq, *J*=15, 1.7 Hz), 6.88 (1H, dq, *J*= 15, 7.0 Hz); $^{13}$C-NMR δ (22.5 MHz, $CDCl_3$) 18.1, 22.6, 23.2, 27.7, 28.0, 31.4, 32.4, 61.4, 123.5, 130.6, 132.2, 142.0, 202.0. The spectral data were identical with those of (*S*)-**1** prepared by route A. Found: C, 80.91, H, 10.47; Calc for $C_{13}H_{20}O$: C, 81.20, H, 10.48. The enantiomeric purity was determined by GLC analysis; (under the same conditions as described for (*S*)-**1** in route A); $R_t$= 72.6 min [(*S*)-isomer, single peak]. (*S*)-**1** was therefore of ca. 100% e.e.

**Acknowledgment**: Our thanks are due to T. Hasegawa Co., Ltd. for financial support.

## REFERENCES AND NOTE

1. Ohloff, G.; Uhde, G. *Helv. Chim. Acta* **1970**, *53*, 531–541.
2. Demole, E.; Enggist, P.; Säuberli, U.; Stoll, M.; sz. Kováts, E. *Helv. Chim. Acta* **1970**, *53*, 541–551.
3. König, W. A.; Evers, P.; Krebber, R.; Schulz, S.; Fehr, Ch.; Ohloff, G. *Tetrahedron* **1989**, *45*, 7003–7006.
4. Pickenhagen, W. 'Enantioselectivity in Odor Perception' in *Flavor Chemistry, Trends and Developments*; Teranishi, R.; Buttery, G. R.; Shahidi, F. Eds.; *ACS Symposium Series* **1989**, *388*, 151.
5. Yamada, S.; Shibasaki, M.; Terashima, S. *Tetrahedron Lett.* **1973**, 381–384.
6. Shibasaki, M.; Terashima, S.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 279–284.
7. Fehr, Ch.; Galindo, J. *J. Am. Chem. Soc.* **1988**, *110*, 6909–6911.
8. Mori, K.; Puapoomchareon, P. *Liebigs Ann Chem.* **1991**, 1053–1056.
9. Mori, K. *Bull. Soc. Chim. Belg.* **1992**, *101*, 393–405.
10. Mori, K.; Aki, S. *Acta Chem. Scand.* **1992**, *46*, 625–629.
11. Mori, K.; Aki, S. *Liebigs Ann. Chem.* **1993**, in press.
12. Mori, K.; Khlebnikov, V. *Liebigs Ann. Chem.* **1993**, in press.
13. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem Soc.* **1987**, *109*, 5551–5553.
14. Corey, E. J. *Pure Appl. Chem.* **1990**, *62*, 1209–1216 and refs. therein.
15. Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107–124.
16. Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927–1928.
17. Mayer, H.; Rüttimann, A. *Helv. Chim. Acta* **1980**, *63*, 1451–1455.
18. Buchecker, R.; Egli, R.; Regel-Wild, H.; Tscharner, C.; Eugster, C.; Uhde, G.; Ohloff, G. *Helv. Chim. Acta* **1973**, *56*, 2548–2563.
19. Schulte-Elte, K. H.; Rautenstrauch, V.; Ohloff, G. *Helv. Chim. Acta* **1971**, *54*, 1805–1812.
20. Mori, K. 'Bioorganic Methods in Terpene Synthesis' in *Third Haarmann & Reimer International Symposium*, Kyoto, Japan, April 12–15, 1992, Lecture No.5.
21. Werkhoff, P.; Bretschneider, W.; Güntert, M.; Hopp, R.; Surburg, H. *Z. Lebensm. Unters. Forsch.* **1991**, *192*, 111–115. They noted qualitative difference between the oder of (*R*)-**1** (fruity) and (*S*)-**1** (woody, minty), but the quantitative difference was small (detection threshold = 1 ppb for both the enantiomers).
22. Mori, K.; Mori, H. *Tetrahedron* **1985**, *41*, 5487–5493.
23. Mori, K.; Tamura, H. *Tetrahedron* **1986**, *42*, 2643–2646.
24. Mori, K.; Nakazono, Y. *Tetrahedron* **1986**, *42*, 6459–6464.