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Synthesis and odor of optically active *trans*-2,2,6-trimethylcyclohexyl methyl ketones and their related compounds

Takeshi Yamamoto,* Hideo Ujihara, Shinya Watanabe, Makoto Harada, Hiroyuki Matsuda and Toshimitsu Hagiwara

Central Research Laboratory, Takasago International Corporation, Nishi-Yawata 1-4-11, Hiratsuka, Kanagawa 254-0073, Japan

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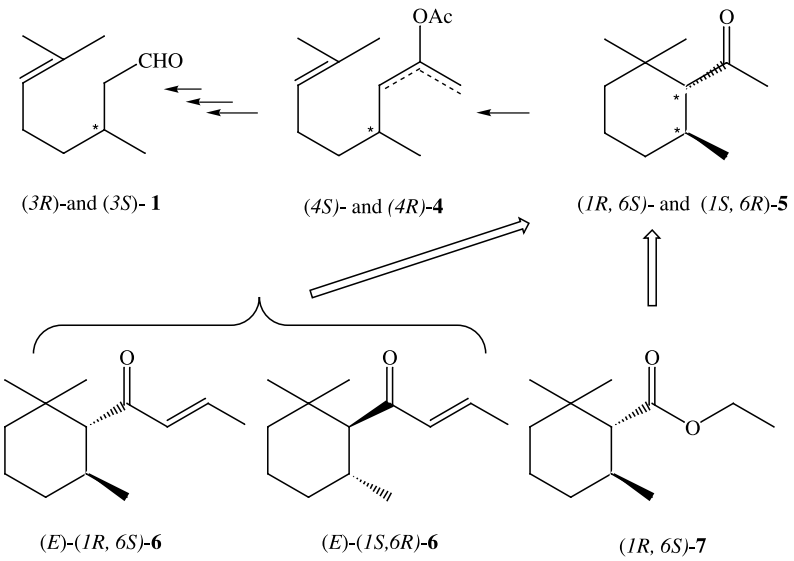
Abstract—The synthesis characterized by cationic olefin cyclizations accomplished using ketone enol esters and odor of novel (1*R*,6*S*)- and (1*S*,6*R*)-2,2,6-trimethylcyclohexyl methyl ketones (**5**) are described. The stereoselective syntheses of (*E*)-(1*R*,6*S*)- and (*E*)-(1*S*,6*R*)-1-(2,2,6-trimethylcyclohexyl)-2-buten-1-one (**6**) and (1*R*,6*S*)-ethyl 2,2,6-trimethylcyclohexylcarboxylate (**7**), useful raw materials for flavor and fragrance, starting from the (1*R*,6*S*)- and (1*S*,6*R*)-**5** are also described. © 2003 Published by Elsevier Science Ltd.

1. Introduction

Many 2,2,6-trimethylcyclohexyl derivatives, such as α-ionone, α-damascone and Timberol® {1-(2,2,6-trimethylcyclohexyl) hexan-3-ol}, etc. are used as important raw materials for flavor and fragrance, and the sensory properties of the optically active isomers[1] have recently been studied revealing fairly large differences in odor qualities between the diastereomeric pairs. In the previous study[2] on α-damascone-related compounds **6** and **7**, we had similarly recognized fairly large differences in odor qualities between the diastereomeric pairs, namely the both (*E*)-*trans*-diastereomers {(*E*)-(1*S*,6*R*)- and (*E*)-(1*R*,6*S*)-**6**}[3] were sensory active and showed more characteristic fruity-floral odors than the racemic (*E*)-*trans*-**6**. In contrast, the (1*R*,6*S*)-**7**[4] was sensory active and showed a more characteristic



Scheme 1.

Keywords: odor, (3*S*)- and (3*R*)-citronellal; (1*R*,6*S*)- and (1*S*,6*R*)-2,2,6-trimethylcyclohexyl methyl ketone; cyclization; (4*S*)- and (4*R*)-4,8-dimethyl-2,7 (and 1,7)-nonen-2-yl acetate; (2*RS*,4*S*)- and (2*RS*,4*R*)-4,8-dimethyl-7-nonen-2-ol; (4*S*)- and (4*R*)-4,8-dimethyl-7-nonen-2-one; (1*R*,6*S*)- and (1*S*,6*R*)-1-(2,2,6-trimethylcyclohexyl)-2-buten-1-one; (1*R*,6*S*)-ethyl 2,2,6-trimethylcyclohexylcarboxylate.

* Corresponding author. Tel.: +81-463-25-2218; fax: +81-463-25-2081; e-mail: takeshi_yamamoto@takasago.com

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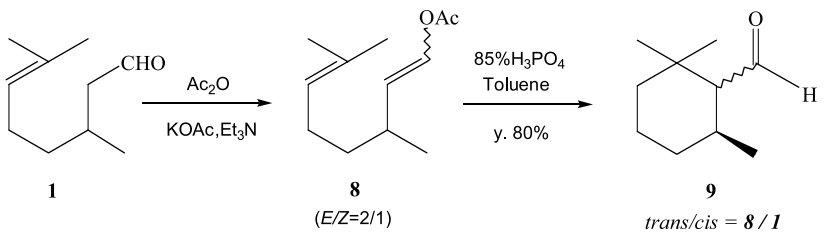


Scheme 2.

fruity-floral odor than the (1*S*,6*R*)-**7** and the racemic *trans*-**7**. However, the *trans*-selectivities of the diastereomers **6** and **7** in these synthetic methods were about 90% and consequently, the improvement of the *trans*-selectivities in these processes is an important problem from the point of improving better odor qualities. Because it has been found that the *trans*-**6** and **7** are geometrically more sensory active than the *cis*-**6** and **7**, and that the potential of mixtures of the *trans*-form {(1*R*,6*S*) and /or (1*S*,6*R*)} and the *cis*-form {(1*R*,6*R*) and/or (1*S*,6*S*)} as raw materials for flavor and fragrance is directly proportional to the ratio of the *trans*-form in the diastereomers, respectively.[5]

In regard to the synthesis of 2,2,6-trimethylcyclohexyl methyl ketone (**5**), optically active *trans*-**5** has not been reported yet, though a few reports[6] for the racemic **5** and only one synthetic study[7] for the optically active *cis*-**5** have been reported. During retro-synthesis of these *trans*-diastereomers **6** and **7**, optically active *trans*-**5**, namely (1*R*,6*S*)- and (1*S*,6*R*)-**5**, seemed to be useful starting materials as shown in Scheme 1.

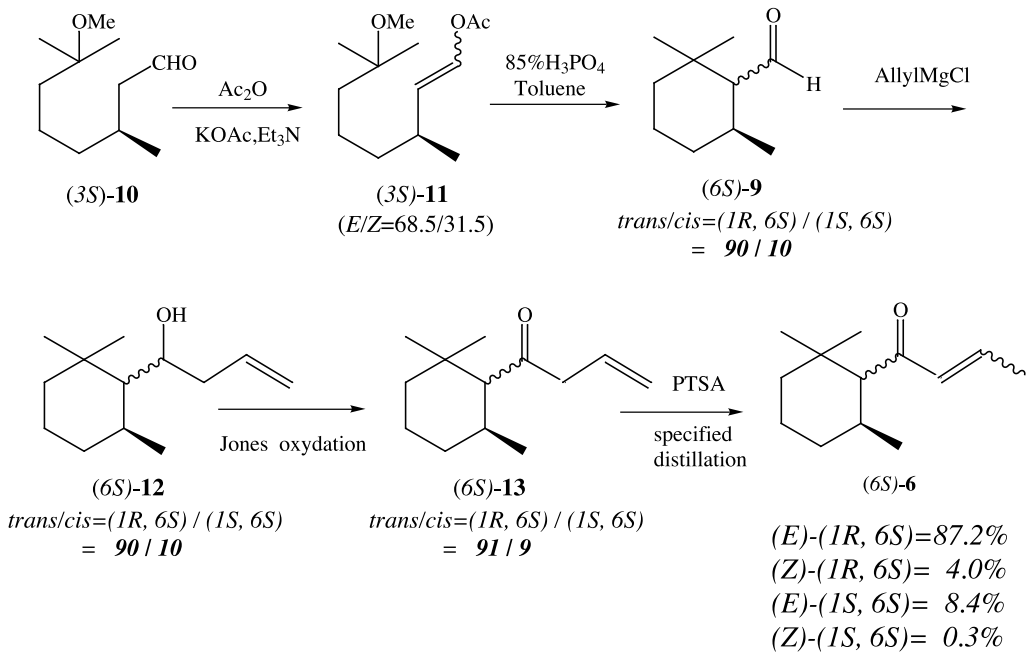
We now wish to report the syntheses and odor of the novel (1*R*,6*S*)- and (1*S*,6*R*)-**5** derived from the (3*S*)- and (3*R*)-aldehydes **1** (98%ee) in four steps, and also the syntheses of the both *trans*-diastereomers {(1*R*,6*S*)- and (1*S*,6*R*)-**6**} and the (1*R*,6*S*)-**7** starting from the both *trans*-diastereomers {(1*R*,6*S*)- and (1*S*,6*R*)-**5**}.

2. Results and discussion

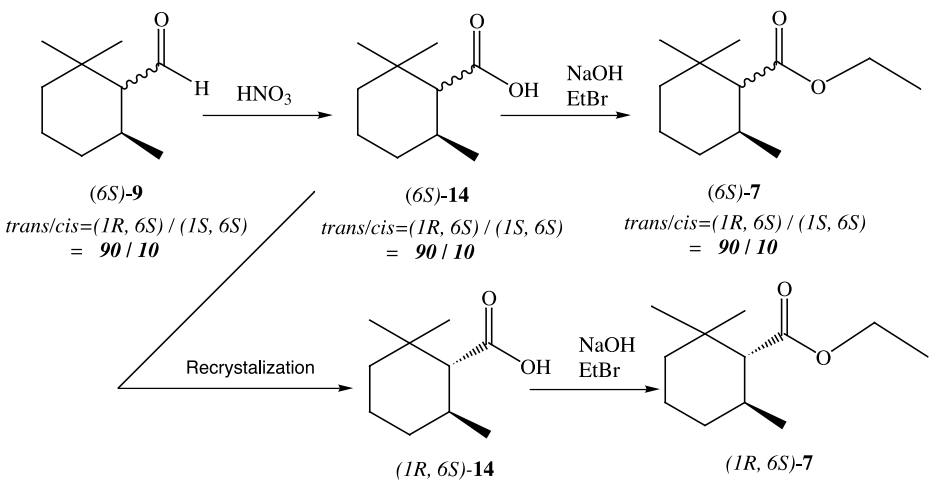
Cationic cyclizations have been widely utilized for the synthesis of terpenes and other naturally occurring cyclic systems. Cyclization initiated by protonation of trisubstituted double bonds has been accomplished using many functional groups.[8] As an example of the cationic olefin cyclizations accomplished using aldehyde enol esters, it is reported that racemic 3,7-dimethyl-1,6-octadienyl acetate (**8**) (*E*/*Z*=2/1) was cyclized by a catalytic amount of 85% H_3PO_4 to yield racemic 2,2,6-trimethylcyclohexylcarbaldehyde (**9**)[9] (*trans*/*cis*=8/1) in 80% yield as shown in Scheme 2, and also the optically active **9** from the chiral enol acetate **8**.[10]

In previous studies,[3,4] we synthesized the optically active aldehyde **9** starting from the optically active 7-methoxycitronellal (**10**) in a similar cyclization method via the enol acetate **11**, and used the aldehyde **9** (*trans*/*cis*=(1*R*,6*S*)/(1*S*,6*R*)=90/10) as the starting materials for the syntheses of the optically active **6** and **7**, of which geometrical ratios of *trans*/*cis* are equal to about (90–91)/(10–9) resulting from the diastereomeric composition of the starting material **9** (for **6**; Scheme 3, for **7**; Scheme 4).

In these synthetic methods, the pure *trans*-diastereomer **6** and **7** are practically obtainable by repeating highly specific distillation of the product **6** and **7** {*trans*/*cis*=(90–91)/



Scheme 3.



Scheme 4.

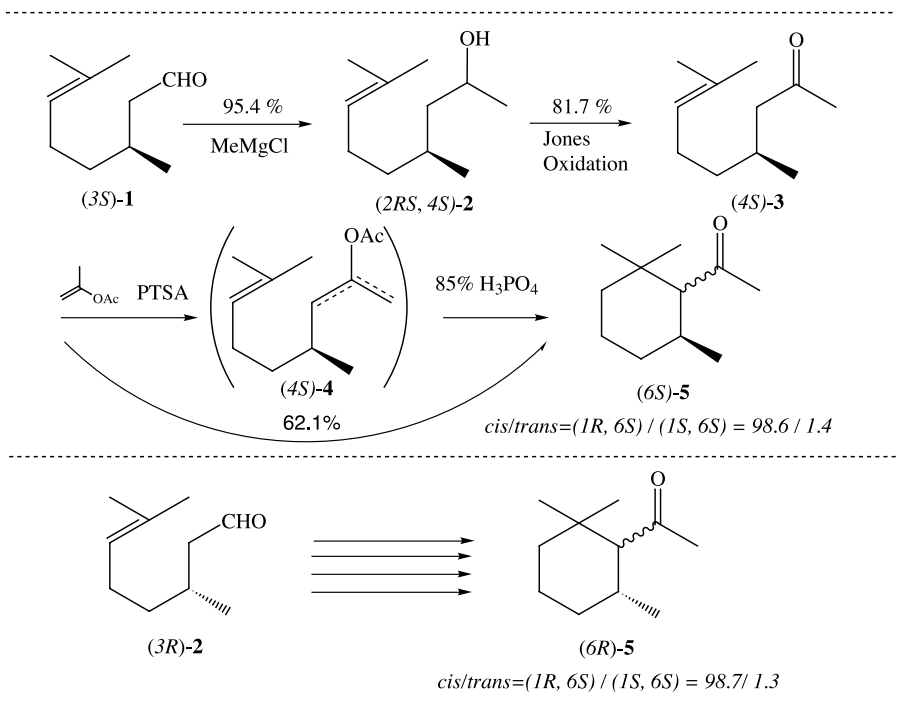
(10–9)} or by recrystallization of the intermediate (6*S*)-**14** for the (1*R*,6*S*)-**7**. However, these purification methods are troublesome from a viewpoint of total expense for the production.

Therefore, a process improvement to raise the ratio of the *trans*-isomer, which may be to improved by changing the aldehyde enol acetate to another functional group, was strongly desired. With that objective, cationic olefin cyclization was accomplished using a ketone enol acetate.

The synthetic route, characterized by cationic olefin cyclization terminated by the ketone enol acetate formation, to the novel optically active *trans*-ketones **5** in four steps starting from the (3*S*)- and (3*R*)-**1** is shown in Scheme 5.

Two key steps, the ketone enol acetylation and the subsequent cyclization reaction, were successfully accomplished by applying the enol ester-exchange method.[11] Namely, the reaction of the ketone (4*S*)-**3** with isopropenyl acetate in the presence of Brønsted acids such as *p*-toluenesulfonic acid monohydrate (PTSA), methanesulfonic acid, camphorsulfonic acid and sulfuric acid, resulted in a mixture of the enol acetates (4*S*)-**4** in 83–87% yields. Subsequently, the enol acetates (4*S*)-**4** were stereoselectively cyclized to afford the (1*R*,6*S*)-**5** using a catalytic amount of Lewis or Brønsted acids. The best result was obtained by phosphoric acid. The stereoselectivity of the *trans*-**5** has reached more than 98% depending on the reaction conditions. However, the *trans*-**5** isomer was isomerized to the *cis*-**5** isomer to yield a few % lower *trans*-selectivity when the temperature is higher than about 125°C for this reaction system.

The optimized geometries of ketone **5** and aldehyde **9**



Scheme 5. Synthesis of (1*R*,6*S*)- and (1*S*,6*R*)-**5**.

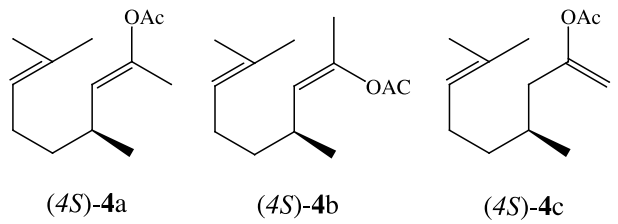


Figure 1.

were calculated by use of CAChe 5.02 in MOPAC using PM3 parameters resulting in the heats of formation (kcal/mol) of *trans*-**5**: −82.25, *cis*-**5**: −79.47, *trans*-**9**: −75.38 and *cis*-**9**: −74.25. The energy difference of the heats of formation between *trans*-**5** and *cis*-**5** isomers is larger than that between the *trans*-**9** and *cis*-**9** isomers and may be one of the reasons yielding the higher *trans*-selectivity by the cyclization terminated by the ketone enol acetate formation.

Typical procedure is as follows; Grignard reaction of the (3*S*)-aldehyde **1** (98%ee) with methylmagnesium chloride (1.2 equiv.) in THF and toluene at −5°C afforded the (2*RS*,4*S*)-alcohol **2** in 95.4% yield. Jones oxidation of the (2*RS*,4*S*)-alcohol **2** at −5 to 0°C gave the (4*S*)-ketone **3** in 81.7% yield. Subsequent treatment of the (4*S*)-ketone **3** with isopropenyl acetate (2.2 equiv.) in the presence of PTSA, with slow removal of the generated acetone by distillation for 18 h, gave a mixture of the enol acetates (4*S*)-**4** which is composed of three stereoisomers supposed to be (4*S*)-**4a** (67.8%), (4*S*)-**4b** (26.0%) and (4*S*)-**4c** (6.2%) along with a very small amount of *exo*-olefin isomers at the C_8 position (Fig. 1).

Without quenching with water, the reaction solution was dropped into a mixture of 85% H_3PO_4, and toluene at 95–110°C with stirring for 24 h to give the (1*R*,6*S*)-ketone **5** (*trans*/*cis*=(1*R*,6*S*)/(1*S*,6*R*)=98.6/1.4) stereoselectively in 62.1% yield from the (4*S*)-ketone **3**.

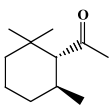
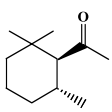
On the other hand, the antipode {(1*S*,6*R*)-ketone **5**} was synthesized from the (3*R*)-aldehyde **1** in a similar manner.

After purification by column chromatography (silica gel, hexane/EtOAc=95/5), the diastereomeric pair of the pure *trans*-ketones **5** was evaluated and it was found that the (1*R*,6*S*)-(−)-**5** has a more characteristic odor and olfactory superior to the (1*S*,6*R*)-(+)-**1**, although the (1*S*,6*R*)-(+)-**5** has a stronger odor than the (1*R*,6*S*)-(−)-**5** as shown in Table 1.

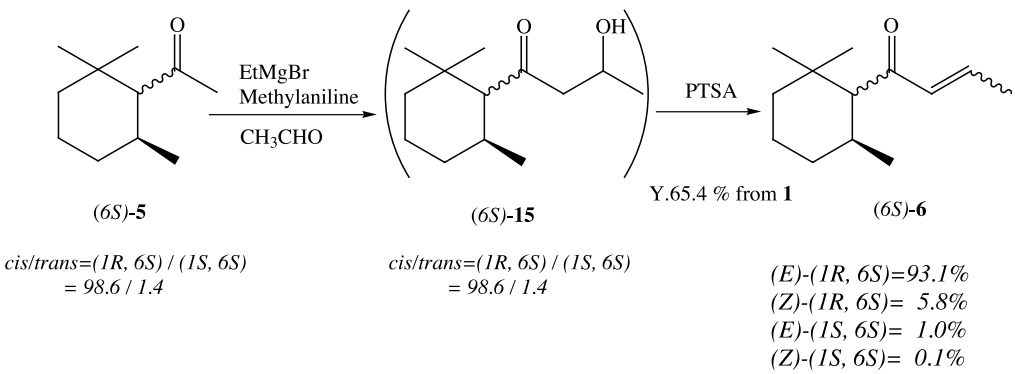
Using the chiral *trans*-ketone **5** as the starting material, a new practical synthetic route to the chiral *trans*-**6** and **7** have been achieved in two steps, respectively. Specifically, the *trans*-(6*S*)-**6** was synthesized by aldol reaction of the (6*S*)-**5** (*trans*/*cis*=98.6/1.4) with acetaldehyde (1.5 equiv.) using *N*-methylanilinomagnesium bromide (1.0 equiv.) as the base and subsequent dehydration of the aldol products {(6*S*)-4-(2,2,6-trimethylcyclohexyl)-4-oxo-butan-2-ol (**15**) with a catalytic amount of PTSA under toluene-reflux, followed by the synthetic method of racemic **6**.[12] As a result, the *trans*-(6*S*)-enone **6**, of which four diastereomers are composed of (*E*)-(1*R*,6*S*)-**6**; 93.1%, (*Z*)-(1*R*,6*S*)-**6**; 5.8%, (*E*)-(1*S*,6*S*)-**6**; 1.0%, and (*Z*)-(1*S*,6*S*)-**6**; 0.1%, was obtained in 65.4% yield from the (6*S*)-ketone **5** (Scheme 6).

In these reaction conditions, the epimerizations of the C1-position at the rings caused by the enol formation of the carbonyl groups have not been well recognized, that is the diastereomer's ratio {(1*R*,6*S*)/(1*S*,6*S*)=98.9/1.1} of the

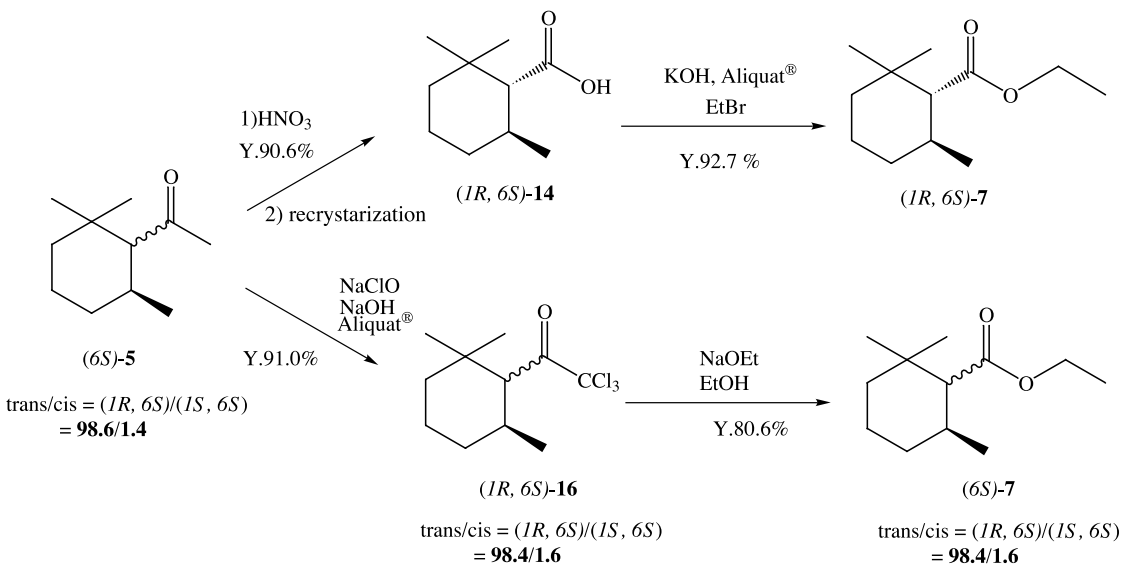
Table 1. Odor property of the diasteromeric *trans*-**5**

trans-**5**	Configuration	%ee	Odor character[a]
	(1*R*,6*S*)	98	Diffusive minty, green, camphoraceous stronger than the (1*S*,6*R*)-**5**
	(1*S*,6*R*)	98	Minty, green, camphoraceous, white-floral, fruity, earthy, marine, ozonic

[a] Odor was evaluated on blotters by three perfumers 30 min after neat samples were taken on blotters.



Scheme 6.



Scheme 7.

product **6** was almost the same as the ratio {(1*R*,6*S*)/(1*S*,6*S*)=98.6/1.4} of the raw material **5**. On the stereochemistry of the side chain in this dehydration condition, the ratio of the (*E*)-**6**/the (*Z*)-**6** was 94.1/5.9.

In comparison with the odor properties, the *trans*-(6*S*)-enone **6** {(1*R*,6*S*)/(1*S*,6*S*)=98.9/1.1} in the present work was found to be better than the (6*S*)-enone **6** {(1*R*,6*S*)/(1*S*,6*S*)=91.2/8.8} synthesized by a previous process.[3]

In contrast, the (6*R*)-enone **6** {(1*S*,6*R*)/(1*R*,6*R*)=98.9/1.1} was synthesized from the (6*R*)-**5** {(1*S*,6*R*)/(1*R*,6*R*)=98.6/1.4} in a similar manner.

On the other hand, a new route to optically active *trans*-**7** {(1*R*,6*S*)-**7**} via (1*R*,6*S*)-2,2,6-trimethylcyclohexylcarboxylic acid (**14**) synthesized by the oxidation of (1*R*,6*S*)-**5** was successfully accomplished. The (6*S*)-ketone **5** (*trans*/*cis*=98.6/1.4) was oxidized by a 90% aqueous-HNO_3 at 90°C to afford the (6*S*)-acid **14** (*trans*/*cis*=98.3/1.7) in 91% yield. Subsequent purification of the (6*S*)-acid **14** by recrystallization from CH_2Cl_2 gave the geometrically pure (1*R*,6*S*)-**14**. Esterification of the potassium salt of the (1*R*,6*S*)-**14** with ethyl bromide afforded the (1*R*,6*S*)-**7** in 92.7% yield. Another conventional synthetic route to the (6*S*)-ester **7** {*trans*/*cis*=98.4/1.6} was also achieved by the following method. The (6*S*)-ketone **5** (*trans*/*cis*=98.6/1.4) was reacted with a solution of 13% aqueous sodium hypochloride (3 equiv.), sodium hydroxide (3 equiv.) and a catalytic amount of Aliquat 336® at 65°C for 8 h to give (6*S*)-trichloromethyl 2,2,6-trimethylcyclohexyl ketone (**16**) (*trans*/*cis*=98.4/1.6) in 91% yield, which was reacted with an ethanol solution of sodium ethoxide (4.5 equiv.) at 78°C to afford the (6*S*)-ester **7** (*trans*/*cis*=98.4/1.6) in 80% yield (Scheme 7).

Similarly as the result of the ketone **6**, the epimerizations of the C1-position at the rings caused by the enol formation of the carbonyl groups have not been well recognized in these reaction conditions.

Thus, the present work has provided a practical new way to synthesize the optically active *trans*-**6** and **7**, namely (1*R*,6*S*)- and (1*S*,6*R*)-**6** and (1*R*,6*S*)-**7**.

3. Experimental

3.1. General

Apparatus. ^{1}H NMR (CD)($CDCl_3$); Bruker DRX 500, GC–MS; Hewlett–Packard HP6890-5973MSD Column HP-1MS (60 m×0.25 mm ID), GC; Hewlett–Packard 5890-11 Column NEUTRABOND-1 (30 m×0.25 mm ID) and Chiraldex G-TA (0.25 mm ID×30 m), IR; Nicolet AVATAR FT-IR, Optical rotation; JASCO DIP-360.

Materials. (3*R*)- and (3*S*)-**1**; Commercial products (Takasago International Corporation) produced by asymmetric isomerization of geranyldiethylamine catalyzed by Rh–BINAP complexes.[13,14] (3*S*)-**1**: GC; 99.9%, 98%ee, $[\alpha]_D^{24}=-16.2°$ (*c* 1.00, $CHCl_3$), (3*R*)-**1**: chemical purity; 99.9%, Optical purity; 98%ee, $[\alpha]_D^{24}=+16.2°$ (*c* 1.00, $CHCl_3$).

3.2. (1*R*,6*S*)- and (1*S*,6*R*)-2,2,6-Trimethylcyclohexyl methyl ketone {(1*R*,6*S*)- and (1*S*,6*R*)-5}

3.2.1. (2*RS*,4*S*)-4,8-Dimethyl-7-nonen-2-ol {(2*RS*,4*S*)-2}. Under a nitrogen atmosphere, the (3*S*)-aldehyde **1** (462.8 g, 3.0 mol) was added dropwise during 1.5 h at −5°C to the stirred solution of methylmagnesium chloride (3.6 mol) which was prepared by reacting Mg (87.1 g, 3.6 mol) in THF (442 g) and toluene (927 g) with slow stream of methyl chloride gas (218 g, 4.3 mol) at 40–45°C for 5 h. After stirring for another 2 h at the same temperature, the mixture was quenched with a saturated aqueous NH_4Cl at 0–5°C and worked up as usual, followed by distillation to give the (2*RS*,4*S*)-alcohol **2**; {486 g, 95.4%; bp 70–71°C/0.1 Torr, $[\alpha]_D^{24}=+1.9°$ (*c* 1.03, EtOH), GC; 99.9%}. The (2*RS*,4*S*)-alcohol **2** was assured to be an equivalent mixture of the diastereomers {(2*S*,4*S*)-**2**/(2*R*,4*S*)-**2**=50/50} by NMR

analysis {δ 1.19 (d, 3H, J=6.2 Hz)⇒(a) 1.185 (d, 3H, J=6.2 Hz)+(b) 1.189 (d, 3H, J=6.2 Hz), δ 0.91 (d, 3H, J=6.6 Hz)⇒(a) 0.908 (d, 3H, J=6.6 Hz)+(b) 0.912 (d, 3H, J=6.6 Hz)}. ^{1}H NMR ($CDCl_3$); δ 5.10 (t, 1H, J=7.1 Hz), 3.89 (dq, 1H, J=12.8, 6.2 Hz), 2.0 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.55 (m, 1H), 1.5 (m, 1H), 1.4 (m, 2H), 1.19 (d, 3H, J=6.2 Hz), 1.1 (m, 1H), 0.91 (d, 3H, J=6.6 Hz). MS (*m/e*); 170 (M^+, 10%), 152 (2), 137 (8), 109 (70), 95 (65), 82 (100), 69 (80), 55 (50), 43 (76). IR (NaCl); 3343 cm^{-1} (br). HRMS calcd for $C_{11}H_{22}O$; 170.1671, found 170.1702.

3.2.2. (4*S*)-4,8-Dimethyl-7-nonen-2-one {(4*S*)-3}. Jones reagent, prepared by mixing water (260 g), conc. H_2SO_4 (83 g, 0.83 mol) and CrO_3 (56 g, 0.56 mol), was added dropwise into an acetone (1 L) solution of the (4*S*)-alcohol **2** (120 g, 0.71 mol) with stirring at 0–5°C for 4 h. After stirring for further 2 h at the same temperature, $NaHSO_3$ was gradually added until the orange color of the chromium (VI) disappeared. The mixture was worked up as usual, and subsequent distillation to give the (4*S*)-ketone **3** {97 g, 0.58 mol, 81.7%; bp 63°C/1.0 Torr, $[\alpha]_D^{24}=-10.7°$ (c 1.00, EtOH), GC; 99.5%}. MS (*m/e*); 168 (M^+, 19%), 150 (8), 135 (25), 110 (58), 95 (100), 85 (42), 69 (47), 43 (64). IR (NaCl); 1716 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 5.09 (t, 1H, J=7.1 Hz), 2.42 (dd, 1H, J=5.6, 15.7 Hz), 2.22 (dd, 1H, J=8.2, 15.7 Hz), 2.0 (m, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.3 (m, 1H), 1.2 (m, 1H), 0.91 (d, 3H, J=6.6 Hz). HRMS calcd for $C_{11}H_{20}O$; 168.1514, found 168.1526.

3.2.3. (4*S*)-4, 8-Dimethyl-2,7 (and 1,7)-nonadien-2-yl acetate {(4*S*)-4}. A mixture of PTSA (19 g, 0.1 mol) and toluene (40 ml) was refluxed to remove any water for 1 h, and then cooled to room temperature. The mixture of the (4*S*)-ketone **3** (168 g, 1.0 mol) and isopropenyl acetate (220.3 g, 2.2 mol) was then added to the solution and the mixture was heated to 90–118°C for 18 h with slow removal of the generated acetone by distillation. The mixture was subjected to the next step without any handling. Sampling analysis of the reaction mixture by GC showed presence of three isomers of the enol acetates (4*S*)-**4** with the composition of (4*S*)-**4a** (67.8%), (4*S*)-**4b** (26.0%) and (4*S*)-**4c** (6.2%). GC/MS: (4*S*)-**5a**; 210 (M^+, 1%), 168 (17), 150 (68), 135 (38), 109 (77), 95 (57), 85 (100), 69 (47), 43 (100), (4*S*)-**5b**; 210 (M^+, 1%), 168 (10), 150 (57), 135 (30), 109 (68), 95 (43), 85 (98), 69 (36), 43 (100), (4*S*)-**5c**; 210 (M^+, 1%), 167 (8), 150 (64), 135 (38), 109 (100), 95 (75), 85 (30), 69 (62), 43 (94).

3.2.4. (1*R*,6*S*)-2,2,6-Trimethylcyclohexyl methyl ketone {(1*R*,6*S*)-5}. To the reaction solution containing a mixture of enol acetates (4*S*)-**4**, 85% H_3PO_4 (25 g) and toluene (750 ml) were added dropwise with stirring at 95–110°C and then the mixture was stirred for an additional 24 h to complete the cyclization reaction. The mixture was worked up as usual, followed by distillation, gave the (6*S*)-ketone **5** {(1*R*,6*S*)/(1*S*,6*S*)=98.6/1.4; 104.3 g, 62.1% yield from the (4*S*)-**3**; bp 78°C/9 Torr, $[\alpha]_D^{24}=-23.78°$ (c 1.03, EtOH)}. Further purification by column chromatography (hexane/EtOAc=95/5) gave the geometrically pure *trans*-ketone (1*R*,6*S*)-**5** {$[\alpha]_D^{24}=-23.92°$ (c 1.03, EtOH)} for the odor evaluation.

The optical purity of the (1*R*,6*S*)-**5** was confirmed to be 98%ee by gas chromatographic analysis using a chiral stationary phase. MS (*m/e*); 168 (M^+, 42%), 153 (14), 135 (21), 125 (47), 110 (64), 95 (53), 83 (60), 69 (100), 43 (66). IR (NaCl); 1708 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 2.16 (s, 3H), 2.07 (d, 1H, J=11.2 Hz), 1.8 (m, 1H), 1.7 (m, 1H), 1.5 (m, 2H), 1.4 (ddd, 1H, J=1.4, 3.3, 13.1 Hz), 1.2 (m, 1H), 0.96 (s, 3H), 0.93 (s, 3H), 0.9 (m, 1H), 0.8 1 (d, 3H, J=6.3 Hz). HRMS calcd for $C_{11}H_{20}O$; 168.1514, found 168.1518.

(1*S*,6*S*)-**5**; GC/MS (*m/e*); 168 (M^+, 34%), 153 (10), 135 (17), 125 (20), 110 (62), 99 (100), 85 (45), 69 (89), 43 (62).

3.2.5. (1*S*,6*R*)-2,2,6-Trimethylcyclohexyl methyl ketone {(1*S*,6*R*)-5}. The (6*R*)-ketone **5** {(1*S*,6*R*)/(1*R*,6*R*)=98.7/1.3; bp 78°C/9 Torr, $[\alpha]_D^{24}=+23.79°$ (c 1.07, EtOH)} was synthesized starting from the (3*R*)-aldehyde **1** in the same manner as the synthesis of the (1*R*,6*S*)-**5**. Further purification by column chromatography (hexane/EtOAc=95/5) gave the geometrically pure *trans*-ketone (1*S*,6*R*)-**5** {$[\alpha]_D^{24}=+23.92°$ (c 1.03, EtOH)} for the odor evaluation.

3.3. (*E*)-(1*R*,6*S*)- and (1*S*,6*R*)-1-(2,2,6-Trimethylcyclohexyl)-2-buten-1-one {(*E*)-(1*R*,6*S*)- and (*E*)-(1*S*,6*R*)-6}

3.3.1. (6*S*)-1-(2,2,6-Trimethylcyclohexyl)-2-buten-1-one {(1*R*,6*S*)/(1*S*,6*S*)=98.9/1.1} {(6*S*)-6}. Under a nitrogen atmosphere, *N*-methylaniline (48.2 g, 0.45 mol) in toluene (70 ml) was added dropwise to the THF solution (160 ml) of ethylmagnesium bromide (0.45 mol) with stirring at 0–5°C for 1 h. The (6*S*)-ketone **5** (*trans*/*cis*=98.6/1.4; 75.6 g, 0.45 mol) in toluene (80 ml) was added dropwise to the *N*-methylanilinomagnesium bromide solution with stirring at 0°C for 0.5 h, followed by stirring at 0°C for 0.5 h to complete the reaction. Acetaldehyde (29.7 g, 0.68 mol) in toluene (50 ml) was then added dropwise to the mixture with stirring at 0°C for 0.5 h and for an additional 1.5 h at 0°C. The mixture was decomposed with 3N HCl (150 ml) and the organic layer was washed three times with 3N HCl (100 ml). The organic layer was refluxed in the presence of PTSA (0.5 g) to remove the water produced by dehydration of the aldol adducts (6*S*)-4-(2,2,6-trimethylcyclohexyl)-4-oxo-butan-2-ol (**15**). The cooled mixture was worked up as usual, followed by distillation to give the (6*S*)-enone **6** {(1*R*,6*S*)/(1*S*,6*S*)=98.9/1.1; 28 g, 65.4% from the (6*S*)-ketone **5**; bp 73–75°C/0.15 Torr, $[\alpha]_D^{24}=-16.10°$ (c 1.03, EtOH)}. Compositions of the four diastereomers of the (6*S*)-enone **6** by GC were (*E*)-(1*R*,6*S*)-**6**; 93.1%, (*Z*)-(1*R*,6*S*)-**6**; 5.8%, (*E*)-(1*S*,6*S*)-**6**; 1.0%, (*Z*)-(1*S*,6*S*)-**6**; 0.1%.

GC/MS: (*E*)-(1*R*,6*S*)-**6**; 194 (M^+, 30%), 179 (43), 151 (57), 125 (28), 111 (55), 95 (19), 83 (33), 69 (100). (*Z*)-(1*R*,6*S*)-**6**; 194 (M^+, 15%) 17 9 (15), 151 (23), 125 (15), 109 (23), 95 (11), 83 (21), 69 (100). (*E*)-(1*S*,6*S*)-**6**; 194 (M^+, 18%), 179 (45), 151 (38), 125 (73), 111 (43), 95 (23), 83 (17), 69 (100). (*Z*)-(1*S*,6*S*)-**6**; 194 (M^+, 1%), 179 (1), 153 (23), 125 (64), 109 (5), 95 (4), 83 (34), 69 (100).

The enone (6*S*)-**6** was purified by column chromatography (silica gel impregnated with $AgNO_3$, hexane/AcOEt=97/3) to give the geometrically pure (*E*)-(1*R*,6*S*)-**6**: GC; 99.9%, 98%ee, $[\alpha]_D^{25}=-18.74°$ (c 1.02, $CDCl_3$). ^{1}H NMR: δ 0.73 (d, 3H, J=6.4 Hz), 0.89 (s, 3H), 0.91 (m, 2H), 0.92 (s, 3H), 1.37 (m, 1H), 1.51 (m, 2H), 1.72 (m, 1 h), 1.88 (dd, 3H, J=

6.8, 1.66 Hz), 2.22 (m, 1H), 6.19 (dd, 1H, J=15.5, 1.66 Hz), 6.8 (qd, 1H, J=15.5, 6.8 Hz). IR (NaCl); 2930, 1690, 1660, 1630, 970 cm^{-1}. HRMS calcd for $C_{13}H_{22}O$; 194.1671, found 194.1669.

3.3.2. (6*R*)-1-(2,2,6-Trimethylcyclohexyl)-2-buten-1-one {(1*S*,6*R*)/(1*R*,6*R*)=98.9/1.1} {(6*R*)-6}. The (6*R*)-enone **6** {(1*S*,6*R*)/(1*R*,6*R*)=98.9/1.1; bp 73–75°C/0.15 Torr, $[\alpha]_D^{24}$=+16.10° (*c* 1.03, EtOH)} was synthesized from the (6*R*)-ketone **5** {(1*S*,6*R*)/(1*R*,6*R*)=98.7/1.3} in the same manner as the synthesis of (6*S*)-**6**. Compositions of four diastereomers of the (6*R*)-enone **6** by GC were as follows; (*E*)-(1*S*,6*R*)-**6**; 93.1%, (*Z*)-(1*S*,6*R*)-**6**; 5.8%, (*E*)-(1*R*,6*R*)-**6**; 1.0% and (*Z*)-(1*R*,6*R*)-**6**; 0.1%.

The enone (6*R*)-**6** was purified by column chromatography (silica gel impregnated with $AgNO_3$, hexane/AcOEt=97/3) to give the geometrically pure (*E*)-(1*S*,6*R*)-**6**: GC; 99.9%, 98%ee, $[\alpha]_D^{25}$=+18.8° (*c* 1.05, $CDCl_3$).

3.4. (1*R*,6*S*)-Ethy1 2,2,6-trimethylcyclohexylcarboxylate {(1*R*,6*S*)-7}

3.4.1. (1*R*,6*S*)-2,2,6-Trimethylcyclohexylcarboxylic acid {(1*R*,6*S*)-14}. The (6*S*)-ketone **5** {(1*R*,6*S*)/(1*S*,6*S*)=98.6/1.4; 100.0 g; 0.595 mol} was added dropwise to a 90% aqueous-nitric acid (800 ml) with stirring at 90°C for 5 min, followed by stirring for three more hours to complete the reaction. The mixture was worked up as usual to give the crude crystals of (6*S*)-**14** {93.7 g, 90.6%; mp 62–64°C, $[\alpha]_D^{25}$=+13.67° (*c* 1.03, EtOH), GC; 98%} which were purified by recrystallization from CH_2Cl_2 to give the pure (1*R*,6*S*)-**14** {84.2 g; mp 67.8–68.0°C, $[\alpha]_D^{25}$=+14.41° (*c* 1.01, $CHCl_3$)}.

MS (*m*/*e*); 170 (M^+, 7%), 152 (35), 137 (4), 127 (7), 119 (100), 100 (7), 87 (54), 69 (96), 56 (46), 41 (30). ^1H NMR ($CDCl_3$); δ 0.90 (d, 3H, J=6.9 Hz), 0.91 (m, 1H), 0.99 (s, 3H), 1.01 (s, 3H), 1.18 (m, 1H), 1.42 (m, 1H), 1.50 (m, 2H), 1.73 (m., 1H), 1.83 (m, 2H). IR (NaCl); 3400–2500, 2950, 2925, 1700. 950 cm^{-1}. HRMS calcd for $C_{10}H_{18}O_2$; 170.1307, found 170.1321.

3.4.2. (1*R*,6*S*)-Ethyl 2,2,6-trimethylcyclohexylcarboxylate {(1*R*,6*S*)-7}. The (1*R*,6*S*)-**14** (67.5 g, 0.40 mol) in toluene (120 ml) was added dropwise to a mixture of Aliquat 336® (5.3 g, 0.013 mol) and KOH powder (54.6 g, 0.98 mol) with stirring bellow 40°C for 0.5 h. After stirring for further 20 min, ethyl bromide (60 g, 0.7 mol) was added dropwise with stirring at 40–45°C for 1 h, followed by stirring for three more hours to complete the reaction. The mixture was worked up as usual to give a concentrated oil (79.8 g) which was purified by distillation to give the geometrically pure (1*R*,6*S*)-**7** {72.9 g, 92.7%; bp 98°C/10 mm Hg, $[\alpha]_D^{25}$=+14.17° (*c* 1.016, $CHCl_3$)}. ^1H NMR ($CDCl_3$): δ 0.82 (d, 3H, J=6.0 Hz), 0.90 (m, 1H), 0.94 (s, 3H), 0.97 (s, 3H), 1.15 (m, 1H), 1.26 (t, 3H, J=7.1 Hz), 1.39 (m, 1H), 1.50 (m, 2H), 1.69 (m, 1H), 1.79 (d, 1H, J=11.4 Hz), 1.85 (m 1H), 4.14 (q, 2H, J=7.1 Hz). MS (*m*/*e*); 198 (M^+, 8), 183 (4), 152 (27), 109 (86), 87 (53), 69 (100), 55 (62), 41 (95), 29 (96). IR (NaCl); 2925, 1250, 1195, 1040 cm^{-1}. HRMS calcd for $C_{12}H_{22}O_2$; 198.1620, found 198.1635.

3.4.3. (6*S*)-Trichloromethyl 2,2,6-trimethylcyclohexyl ketone {(1*R*,6*S*)/(1*S*,6*S*)=98.4/1.6} {(6*S*)-16}. The (6*S*)-ketone **5** {(1*R*,6*S*)/(1*S*,6*S*)=98.6/1.4; 16.8 g, 0.10 mol} was added dropwise during 30 min at 65°C to a vigorously stirred mixture of 13% aqueous sodium hypochloride (17.2 g, 3 equiv.), sodium hydroxide (12.5 g, 3 equiv.) and Aliquat 336® (840 mg), followed by stirring for eight more hours to complete the reaction. The mixture was worked up as usual to give the (6*S*)-ketone **16** {(1*R*,6*S*)/(1*S*,6*S*)=98.4/1.6; 24.7 g, 91.0%; bp 123°C/7 mm Hg, $[\alpha]_D^{25}$=−27.37° (neat)}.

MS (*m*/*e*); 152 (3%), 125 (41), 109 (16), 83 (27), 69 (100), 55 (26), 41 (17). IR (NaCl); 2957, 2930, 2889, 2848, 1740, 1729, 1460, 1392, 1346, 1051 cm^{-1}. ^1H NMR ($CDCl_3$); δ 0.91 (d, 3H, J=6.6 Hz), 0.99 (s, 3H),), 1.01 (m, 1H), 1.07 (s, 3H), 1.27 (m, 1H), 1.47 (m, 1H), 1.54–1.62 (m, 2H), 1.78 (m, 1H), 1.94 (m, 1H), 3.28 (d, 1H, J=10.8 Hz). HRMS calcd for $C_{11}H_{17}OCl_3$; 270.0345, found 270.0357.

3.4.4. (6*S*)-Ethyl 2,2,6-trimethylcyclohexylcarboxylate {(1*R*,6*S*)/(1*S*,6*S*)=98.4/1.6} {(6*S*)-7}. The (6*S*)-ketone **16** {(1*R*,6*S*)/(1*S*,6*S*)=98.6/1.4; 5 g; 18.4 mmol} was added dropwise to the ethanol (25 ml) solution of sodium ethoxide (5.63 g, 82.8 mmol) with stirring at 78°C for 30 min, followed by stirring for four more hours to complete the reaction. The mixture was worked up as usual and purified by column chromatography to give the (6*S*)-ester {(1*R*,6*S*)/(1*S*,6*S*)=98.4/1.6} **7** (2.91 g, 80.6%).

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