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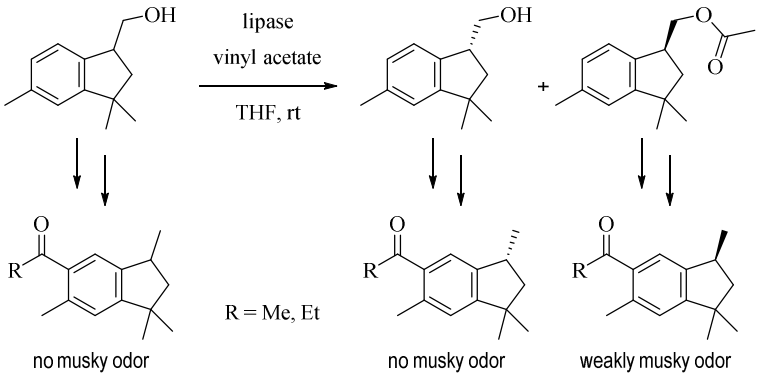

Synthesis and odor properties of Phantolide analogues

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Abstract

Phantolide analogues **1a**-**1d** were newly synthesized to evaluate their odor profiles. The enantiomers of **1a** and **1b** were also synthesized. Both (*S*) enantiomers of **1a** and **1b** had musk odor although weakly, and but neither of the (*R*) enantiomers **1a** and **1b** had musk odor. During the investigations, we encountered the undesirable racemization in Friedel-Crafts reaction of the intermediate (*S*)-**5**.

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Keywords: Asymmetric synthesis; Friedel-Crafts reaction; Lipase; Phantolide; Racemization

1. Introduction

Musk is secreted from the exocrine odor glands, called musk pods, of male musk deer.[1,2] Before 1979, when musk deer were protected from extinction by the Convention on International Trade in Endangered Species of Wild Fauna and Flora, musk tincture was used in the production of perfume.[1] The musk pods were dried and then opened to yield brownish grain from which the musk was extracted with ethanol.[1]

Musk odor, although difficult to describe, is often likened to warm, sweet, powdery, animal smells.[3] The most intense chemical component of musk, (*R*)-muscone (Fig. 1), was isolated in 1906, and the structure was elucidated in 1926.[2] Because the production of musk tincture from musk deer has been prohibited, and industrial synthetic routes to (*R*)-muscone have not been developed until recently, synthetic musk odor compounds have been used.[4] Five main classes of musk odorants are known at present: macrocyclic musks, nitro musks, polycyclic musks, linear musks and dienone musks (Fig. 1).[2,5] Compounds totally different from (*R*)-muscone in structure have the musk odor. Kraft *et al*. have been studying the odor-structure relationship of musk odorants to design new ones.[5-8] Among the musk odorants, polycyclic aromatic musks were inexpensively synthesized and consequently used in large quantities.[4] The ease with which the 1,1,2,3,3-pentamethylindane skeleton can be constructed

explains the attractive price of Galaxolide and Phantolide.[2]

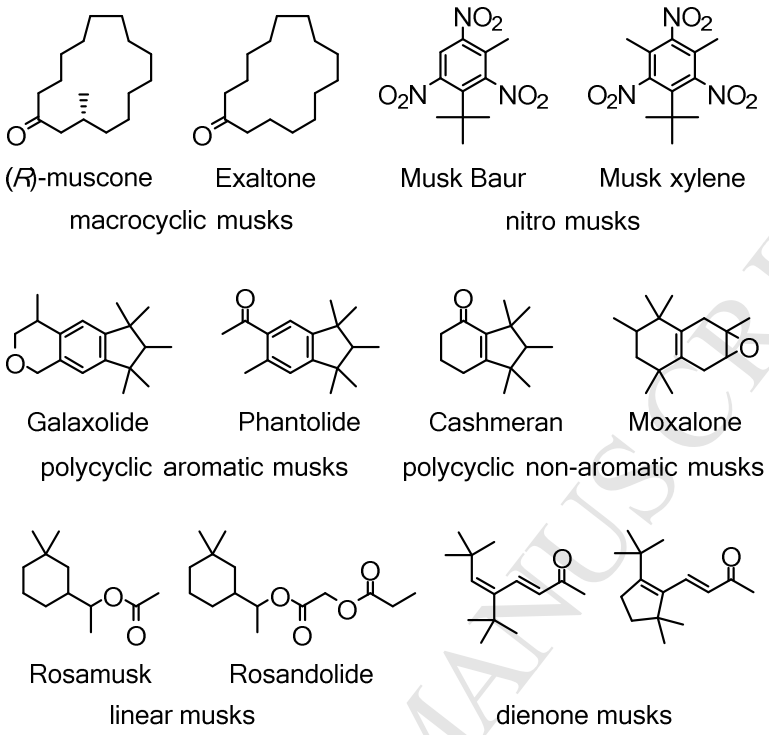


Figure 1. Musk odorants.

The enantiomers of many chemical compounds are perceived differently as odorants by the human nose; in plain terms, they smell differently.[9] Many natural flavors and fragrances occur in nature as specific enantiomers, and the aromas of such specific enantiomers can be distinctive and characteristic.[10] For example, (*R*)-carvone has a herbaceous odor reminiscent of spearmint, while (*S*)-carvone has a herbaceous odor reminiscent of caraway and dill seeds.[10,11] The synthesis of the enantiomers of fragrance ingredients in highly enantiomerically pure form and the evaluation of the difference in the odor properties of the enantiomers are accordingly of great interest.[8,12-14] We have also been interested in the differences in the olfactory properties of the enantiomers of fragrance ingredients and have reported the synthesis of the enantiomers of floral odorants and citrus odorants.[15-17] There are some reports on the evaluation of the odors of the enantiomers of musk odorants. (*R*)- and

(*S*)-muscone show distinct differences in their odor. (*R*)-muscone, naturally occurring, is described as "a very nice musky note, rich and powerful", whereas (*S*)-muscone is "poor and less strong".[18] Felker *et al*. recently reported the differences in the olfactory properties between the enantiomers of some Cashmeran odorants.[8] Fráter *et al*. reported the differences in the olfactory properties of the four diastereomers of Galaxolide.[19] We, therefore, have become interested in the differences in the olfactory properties of the enantiomers of musk odorants.

We herein report the synthesis of racemic and optically active Phantolide analogues **1a-1d**, which have never been synthesized before, and the evaluation of their odor profiles (Fig. 2). We also report the racemization which we encountered in the course of the asymmetric synthesis of the Phantolide analogues **1a** and **1b** in Friedel-Crafts reactions.

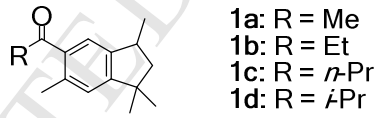


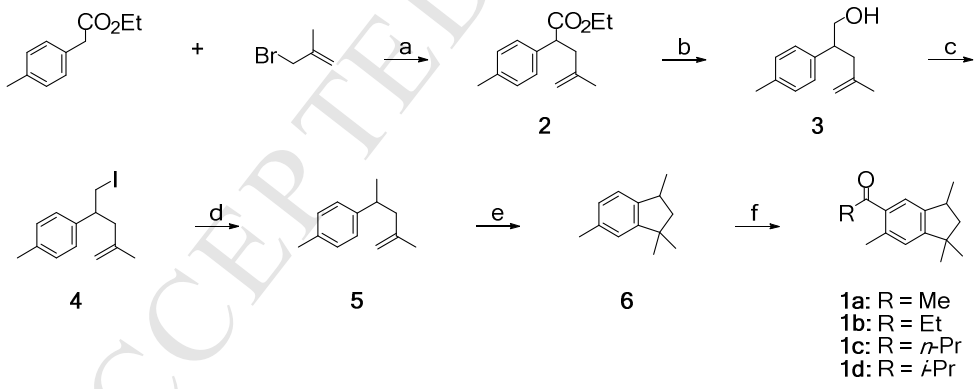
Figure 2. Phantolide analogues 1a-1d.

2. Results and Discussion

2.1. Synthesis and odor profiles of racemic Phantolide analogues 1a-1d

The syntheses of racemic Phantolide analogues **1a-1d** are shown in Scheme 1. The enolate that was generated in situ from ethyl (4-methylphenyl)acetate and LDA was treated with 1-bromo-3-methyl-2-butene to give the desired ester **2** in 90% yield.

Reduction of **2** with $LiAlH_4$ provided the primary alcohol **3** in 83% yield, which was converted to the corresponding iodide **4** using the Appel reaction in 83% yield. The iodide **4** was then treated with $LiAlH_4$ to give the desired aromatic hydrocarbon **5** in 84% yield. Intramolecular Friedel-Crafts alkylation with $AlCl_3$ as the catalyst in benzene smoothly proceeded and gave the desired indane **6** in 62% yield. No reaction took place in CH_2Cl_2 instead of benzene as the solvent or with $BF_3 \cdot OEt_2$, $ZnCl_2$, $SnCl_2$ in benzene, respectively. The syntheses of the racemic Phantolide analogs **1a-1d** were accomplished by Friedel-Crafts acylation of **6** with acyl chlorides in the presence of $AlCl_3$, and **1a-1d** were obtained in 57-75% yield as a single regioisomer. The regioselectivity of the acylation was determined by the NOESY experiment of **1a** (Fig. 3), and those of the other derivatives **1b-1d** were determined by the analogy of their ^1H NMR spectra to **1a**.



Scheme 1. Synthesis of racemic Phantolide analogues **1a-1d.** Reagents and conditions: (a) LDA, HMPA, THF, -78 °C to 0 °C, 90%; (b) $LiAlH_4$, THF, 0 °C to rt, 83%; (c) I_2, PPh_3, imidazole, THF, 0 °C to rt, 83%; (d) $LiAlH_4$, THF, 0 °C to rt, 84%; (e) $AlCl_3$, benzene, 0 °C to rt, 62%; (f) acyl chloride, $AlCl_3$, CH_2Cl_2, 0 °C to rt, **1a:** 61%; **1b:** 57%; **1c:** 75%; **1d:** 72%.

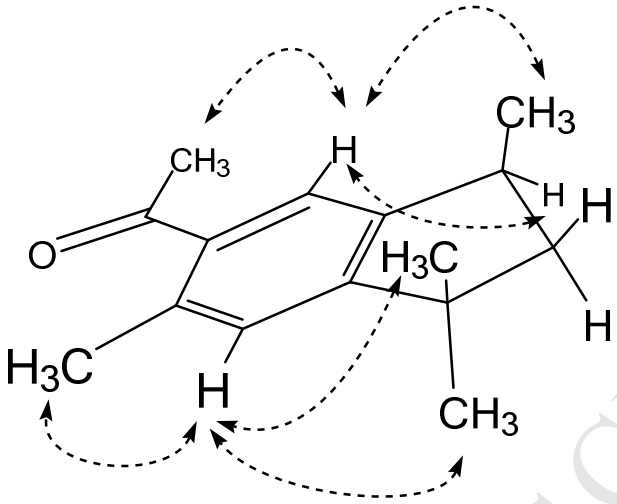


Figure 3. NOESY correlations for **1a**.

The odor profiles of the racemic Phantolide analogues **1a**-**1d** were evaluated by two skilled perfumers and two skilled flavorists (TAIYO CORPORATION). The following descriptions were obtained (Table 1).

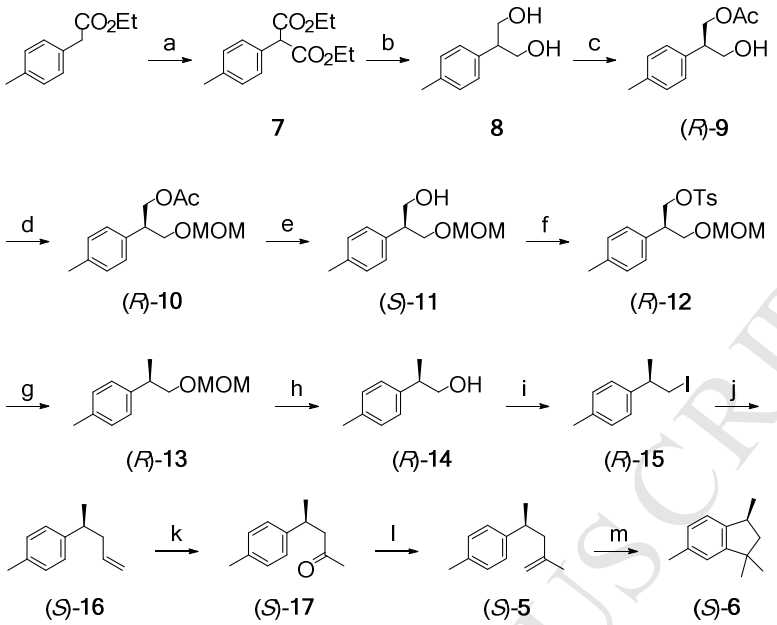
Table 1. Odor profiles of racemic Phantolide analogues **1a**-**1d**.

Compound	Odor profiles
1a	ambergris, dusty, tomato fiber, mixture of citrus and sandalwood
1b	soap, ionone, sandalwood, plain
1c	odor like unclear **1b**, citrus, odor like **1b** with unpleasant feeling
1d	peach, *p*-*t*-butylcyclohexyl acetate-like, powdery, heavy, organic solvent-like, odor like **1b** with unpleasant feeling

Although none of the Phantolide analogues **1a**-**1d** had a musk odor, analogues **1a** and **1b** received good evaluations like ambergris and ionone, respectively. We, therefore, decided to synthesize the enantiomers of **1a** and **1b** and evaluate their odor.

2.2. Synthesis and odor profiles of optically active Phantolide analogues 1a, 1b

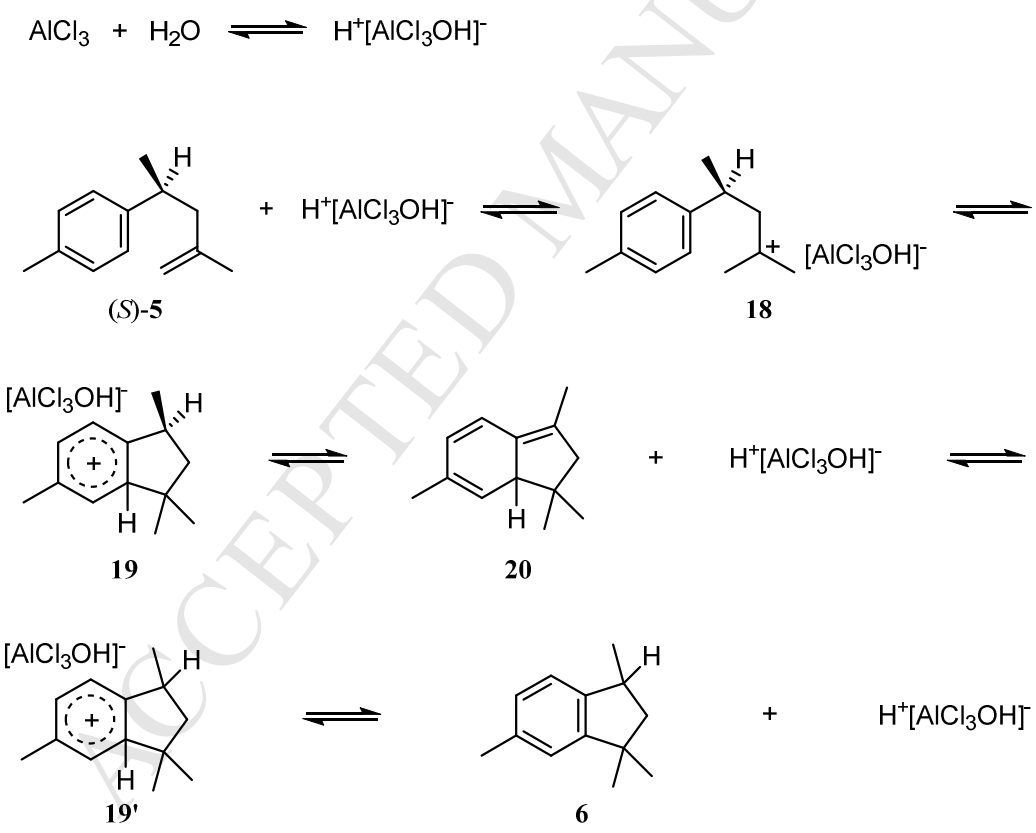
We first tried to synthesize optically active intermediate (*S*)-**6** for the enantiodivergent synthesis of (*S*)-**1a** and (*S*)-**1b** according to Scheme 2. The first step in the sequence leading to (*S*)-**6** is the ethoxycarbonylation of ethyl (4-methylphenyl)acetate with LiHMDS and ethyl cyanoformate to give the diester **7** in 96% yield, and then the diester was reduced with $LiAlH_4$ to the corresponding diol **8** in 79% yield. We followed the preparation, porcine pancreatic lipase (PPL)-catalyzed enantioselective acetylation of **8** with vinyl acetate, reported by Shishido *et al*.[20] and obtained (*R*)-**9** in 90% yield and 99% enantiomeric excess (ee). The monoester (*R*)-**9** on treatment with MOMCl and DIPEA afforded the ester (*R*)-**10** in 96% yield. Hydrolysis of the ester moiety of (*R*)-**10** with K_2CO_3 quantitatively gave the alcohol (*S*)-**11**. Treatment of (*S*)-**11** with TsCl and Et_3N quantitatively afforded the corresponding tosylate (*R*)-**12**. Reduction of (*R*)-**12** with $NaBH_4$ in DMSO afforded the protected alcohol (*R*)-**13** in 85% yield. Deprotection of (*R*)-**13** with HCl allowed the formation of the primary alcohol (*R*)-**14**[21] with 99% ee in 95% yield. The ee of (*R*)-**14** was the same as that of the intermediate (*R*)-**9**, and this means that no racemization occurred during the transformation from (*R*)-**9** into (*R*)-**14**. Iodination of (*R*)-**14** afforded the corresponding iodide (*R*)-**15** in 83% yield. The cross-coupling reaction of (*R*)-**15** gave the desired olefin (*S*)-**16** in 71% yield. Wacker oxidation of (*S*)-**16** (59%) and subsequent Wittig reaction of the resulting ketone (*S*)-**17** (70%) gave the desired olefin (*S*)-**5**[24] with 99% ee.



Scheme 2. Synthesis of the optically active intermediate (*S*)-**6**. Reagents and conditions: (a) LiHMDS, ethyl cyanoformate, THF, -78 °C to 0 °C, 96%; (b) $LiAlH_4$, THF, 0 °C to rt, 79%; (c) vinyl acetate, PPL, rt, 90%, 99% ee; (d) MOMCl, DIPEA, CH_2Cl_2, 0 °C to rt, 96%; (e) K_2CO_3, MeOH, rt, quant.; (f) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, quant.; (g) $NaBH_4$, DMSO, 60 °C, 85%; (h) conc. HCl, MeOH, reflux, 95%, 99% ee; (i) I_2, imidazole, PPh_3, CH_2Cl_2, 0 °C to rt, 83%; (j) $(CH=CH)_2CuLi$, Et_2O, -78 °C to 0 °C, 71%; (k) CuCl, $PdCl_2$, O_2, DMF, H_2O, rt, 59%; (l) $CH_2=PPh_3$, THF, rt, 70%, 99% ee; (m) $AlCl_3$, C_6H_6, 0 °C to rt.

With the intermediate, olefin (*S*)-**5**, in hand, next we tried intramolecular Friedel-Crafts alkylation of (*S*)-**5** according to the same procedure as that for the synthesis of racemic **6** and observed partial racemization in the cyclization with the ees of the product (*S*)-**6** (93% ee at the 1st run and 86% ee at the 2nd run) lower than that of (*S*)-**5** (99% ee). We mixed (*S*)-**6** (99% ee) with $AlCl_3$ under the same conditions to confirm whether (*S*)-**6** itself racemizes and found that the ee of recovered (*S*)-**6** (98% ee) decreased a little. This suggests that the decrease of the ee of (*S*)-**6** occurs mainly during the cyclization of (*S*)-**5**. A plausible mechanism of the racemization is proposed in Scheme 3. The mechanism assumes that the initial step is the attack by the hydrated form of $AlCl_3$, $H^+[AlCl_3OH]^-$, which was produced by the interaction of $AlCl_3$ with the trace of moisture, on the olefin moiety of (*S*)-**5** with the formation of the

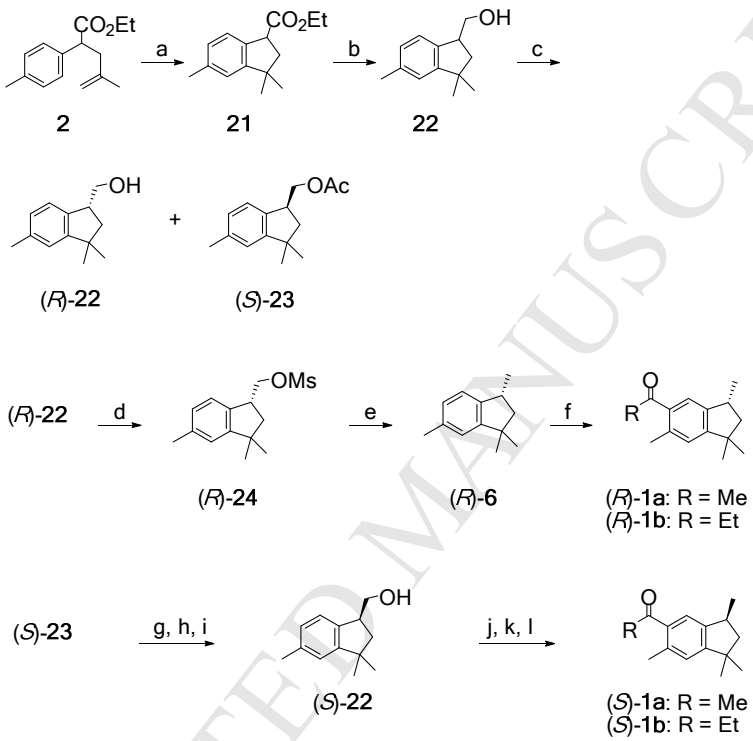
intermediate complex **18**.[25] The next step would be the intramolecular attack of the cation moiety of **18** on the aromatic ring to form the complex **19**, and then the hydrogen of the benzyl position, which was a chiral center eliminated to form a double bond **20** with the regeneration of $H^+[AlCl_3OH]^-$. The last step would be attack by the $H^+[AlCl_3OH]^-$ on the olefin moiety of the cyclopentene ring of **20** with the formation of the partially racemized intermediate complex **19'**, which forms **6** with the regeneration of $H^+[AlCl_3OH]^-$. To the best of our knowledge, there are no reports of racemization on the benzyl position during intramolecular Friedel-Crafts alkylation.



Scheme 3. Plausible mechanism of racemization.

As mentioned above, we encountered partial racemization in the intramolecular Friedel-Crafts alkylation of (*S*)-**5**, so we examined an alternative route to obtain

optically pure **1a** and **1b** (Scheme 4). We planned to construct the indane skeleton **21** first and obtain the chiral intermediates (*R*)-**22** and (*S*)-**23** by resolution, after which they would be transformed to optically pure final products, respectively.



Scheme 4. Synthesis of optically active Phantolid analogues **1a**, **1b**. Reagents and conditions: (a) $AlCl_3$, benzene, 0 °C to rt, 87%; (b) $LiAlH_4$, THF, 0 °C to rt, 95%; (c) PPL, vinyl acetate, THF, rt, (*R*)-**22**: 44%, >99% ee; (*S*)-**23**: 56%, 76% ee; (d) MsCl, pyridine, CH_2Cl_2, 0 °C to rt, 89%; (e) $LiAlH_4$, Et_2O, 0 °C to rt, 91%, >99% ee; (f) acyl chloride, CH_2Cl_2, 0 °C to rt, (*R*)-**1a**: 91%, >99% ee; (*R*)-**1b**: 89%, 99% ee; (g) 6 *M* NaOH, EtOH, rt, 98%, 76% ee; (h) PPL, vinyl acetate, THF, rt, 54%, 99% ee; (i) 6 *M* NaOH, EtOH, rt, 98%, 99% ee; (j) MsCl, pyridine, CH_2Cl_2, 0 °C to rt, 96%; (k) $LiAlH_4$, Et_2O, 0 °C to rt, 96%, 99% ee; (l) acyl chloride, $AlCl_3$, CH_2Cl_2, 0 °C to rt, (*S*)-**1a**: 71%, 98% ee; (*S*)-**1b**: 86%, 99% ee.

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Ester **2** was first subjected to intramolecular Friedel-Crafts alkylation to give rise to the cyclized product **21** in 87% yield, which was converted to the corresponding alcohol **22** in 95% yield.

The most important point of the present synthesis is to prepare (*R*)- and (*S*)-**22** in

highly optically active forms. We achieved this by the optical resolution of **22** through the porcine pancreatic lipase (PPL)-catalyzed enantioselective acetylation of **22** with vinyl acetate. We initially investigated the effects of the reaction solvents on the enantioselectivity of the PPL-catalyzed resolution (Table 2), because the enantioselectivity of lipases was found to depend on the nature of reaction solvents.[26] As a result of the screening of the solvent, we found that THF was the most suitable solvent for this resolution (E^{22} = 49).

Table 2. PPL-catalyzed transesterification of **22**.

Solvent	Time (h)	Conversion[a] (%)	ee of (*R*)-**22** (%)	ee of (*S*)-**23** (%)	E^a
hexane	0.2	88[b]	-	-	-
cyclohexane	20.5	48	80	85	30
toluene	5.5	48	80	87	35
CH_2Cl_2	19.5	3[b]	-	-	-
diethyl ether	2.3	49	86	89	48
ethyl acetate	3.5	49	86	88	43
THF	6.3	49	87	89	49
acetone	3.5	48	83	89	45
acetonitrile	4.0	48	81	89	43
1,4-dioxane	4.3	48	79	86	32

Conditions: PPL (100 mg mL^{-1}), **22** (45 m*M*), vinyl acetate (1 *M*), room temperature.
[a]Calculated from ees of (*R*)-**22** and (*S*)-**23**.[22] [b]Determined by GC analysis.

On the basis of these results, we conducted a large-scale resolution of **22** in THF to obtain (*R*)-**22** with >99% ee in 44% yield and (*S*)-**23** with 76% ee in 56% yield, respectively. Treatment of (*R*)-**22** with MsCl afforded the corresponding mesylate

(*R*)-**24** in 89% yield. The mesylate (*R*)-**24** was then treated with $LiAlH_4$ to give the desired aromatic hydrocarbon (*R*)-**6** with >99% ee in 91% yield. The synthesis of (*R*)-**1a** and (*R*)-**1b** was accomplished by Friedel-Crafts acylation of (*R*)-**6** with acyl chlorides in the presence of $AlCl_3$ in 91 and 89% yield, respectively.

The acetate (*S*)-**23** did not have a sufficiently high ee for use in the initial resolution, and we examined the preparation of (*S*)-**23** with higher ee. The initial acetate (*S*)-**23** was hydrolyzed to the corresponding alcohol (*S*)-**22**, which was subjected to the PPL-catalyzed transesterification again to obtain (*S*)-**23** with 99% ee. The acetate (*S*)-**23** with high ee obtained above was converted to (*S*)-**1a** and (*S*)-**1b** in the same manner as for (*R*)-**1a** and (*R*)-**1b** as shown in Scheme 3.

The odor profiles of the obtained optically pure Phantolide analogues (*R*)- and (*S*)-**1a** and **1b** were evaluated by two skilled perfumers and two skilled flavorists (TAIYO CORPORATION). The following descriptions were obtained (Table 3).

Table 3. Odor profiles of optically active Phantolide analogues **1a**, **1b**.

Compound	Odor profiles
(*R*)-**1a**	powdery, chemical, weakly woody, the smell of burnt plastic, artificial
(*S*)-**1a**	powdery, weakly musky, woody, musk with a light floral note and a metallic tone, mild sandalwood
(*R*)-**1b**	very weakly woody, sweet like vanilla, odorless
(*S*)-**1b**	weakly woody, (weakly) musky, powdery with chemical substance note

It is very interesting that both the (*S*) enantiomers of **1a** and **1b** showed musk odor although weakly, but neither of the (*R*) enantiomers showed musk odor. As

previously mentioned, neither racemic **1a** nor **1b** had a musk odor. Therefore, it is supposed that the musky odors of (*S*) enantiomers would be masked by (*R*) enantiomers. In these substrates, the absolute configuration played a very important role in their odor profiles.

3. Conclusions

We newly synthesized four racemic Phantolide analogues **1a**-**1d** and evaluated their odor profiles. Although none of them had a musk odor, **1a** and **1b** had a good odor like ambergris and ionone, respectively. Both (*S*) enantiomers of **1a** and **1b** had a musk odor although weakly, but neither of the (*R*) enantiomers **1a** and **1b** had a musk odor. The absolute configuration in these substrates was very important for their odor profiles.

During these investigations, we encountered the racemization in the Friedel-Crafts reaction of (*S*)-**5**. To the best of our knowledge, there are no reports of racemization on the benzyl position during intramolecular Friedel-Crafts alkylation.

4. Experimental Section

4.1. General

All commercially available reagent chemicals were obtained from Aldrich, Kanto Kagaku, Nacalai Tesque, Tokyo Kasei, and Wako Chemicals and generally used without further purification, unless otherwise indicated. Porcine pancreatic lipase was

purchased from Sigma-Aldrich and dried over P_2O_5 for three days at room temperature. NMR spectra were recorded on either a Bruker Advance II 400 spectrometer (^{1}H 400 MHz, and ^{13}C 100 MHz) or a Varian UNITY plus 500 spectrometer (^{1}H 500 MHz, and ^{13}C 125 MHz). Chemical shifts (δ) are reported in parts per million (ppm) and referenced to TMS (δ = 0.00 ppm). IR spectra were recorded on a Jasco FT/IR-410 spectrometer. HRMS was performed on a Jeol MStation JMS-700 instrument. Optical rotations were recorded on a Jasco P-1300 polarimeter. The melting point was measured by a Yanaco MP-S3 micro-melting point apparatus. Gas chromatography (GC) analyses were performed on a Shimadzu GC-2014 gas chromatograph equipped with a CP-Cyclodextrin-β-2,3,6-M-19 capillary column (Agilent Technologies, 0.25 mm ϕ × 25 m) or InertCap 1 capillary column (GL Sciences, 0.25 mm ϕ × 30 m). High performance liquid chromatography (HPLC) analyses were performed on a Shimadzu LC-20AD intelligent pump with a Shimadzu SPD-20A UV detector, using CHIRALCEL OB-H, CHIRALCEL OD-H, CHIRALCEL OJ-H, or CHIRALPACK AS-H (all the columns from Dicel, 4.6 mm ϕ × 25 cm).

4.2. Ethyl 4-methyl-2-(4-methylphenyl)-4-pentenoate ***2***

LDA was prepared by the treatment of diisopropylamine (3.455 g, 34.14 mmol) with *n*-BuLi (1.6 *M* solution in hexane, 21 mL, 34 mmol) in dry THF (50 mL) at 0 ºC for 30 min. To a solution of ethyl *p*-tolylacetate (5.043 g, 28.30 mmol) in dry THF (50 ml), HMPA (7.612 g, 42.48 mmol) and the LDA were added at -78 ºC, and the mixture was stirred at -78 ºC for 30 min. To the mixture was added 3-bromo-2-methyl-1-propene (4.538 g, 33.62 mmol) at -78 ºC. The mixture was allowed to warm to 0 ºC for 20 min. Aqueous saturated NH_4Cl was added at 0 ºC, and the aqueous mixture was

extracted three times with EtOAc. The combined organic extracts were washed with brine and then dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography using silica gel (hexane/EtOAc = 50/1 to 30/1) to afford **2** as a colorless oil (5.913 g, 90%). IR (neat) 1733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (3H, t, J = 7.0 Hz), 1.72 (3H, s), 2.32 (3H, s), 2.41 (1H, dd, J = 6.5, 15.0 Hz), 2.82 (1H, dd, J = 9.3, 15.0), 3.76 (1H, dd, J = 6.5, 9.3 Hz), 4.03-4.17 (2H, m), 4.70 (1H, s), 4.75 (1H, s), 7.12 (2H, d, J = 7.8 Hz), 7.22 (2H, d, J = 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.01, 20.92, 22.51, 41.30, 49.56, 60.52, 111.90, 127.60, 129.14, 135.87, 136.68, 142.65, 173.58; HRMS (FAB) m/z calcd for $C_{15}H_{21}O_2$ $(M+H)^+$ 233.1542, found 233.1553.

*4.3. 4-Methyl-2-(4-methylphenyl)-4-penten-1-ol **3***

To a suspension of $LiAlH_4$ (1.704 g, 44.90 mmol) in dry THF (30 mL) was slowly added a solution of ester **2** (5.210 g, 22.43 mmol) in dry THF (20 mL) at 0 ºC. The mixture was stirred at room temperature overnight. Water was added to the mixture at 0 ºC, and then 6 *M* HCl was added to the mixture. The resulting mixture was extracted three times with Et_2O, and the combined organic extracts were washed with brine and then dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography using silica gel (hexane/acetone = 10/1) to afford **3** as a colorless oil (3.549 g, 83%). IR (neat) 3337, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.71 (3H, s), 2.32 (1H, dd, J = 8.0, 13.8 Hz), 2.33 (3H, s), 2.44 (1H, dd, J = 7.2, 13.8 Hz) 2.97-3.04 (1H, m), 3.66-3.71 (1H, m), 3.74-3.80 (1H, m), 4.67 (1H, s), 4.71 (1H, s), 7.12 (2H, d, J = 8.4 Hz), 7.14 (2H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.91, 22.25, 40.57, 45.67, 67.19, 112.16, 127.72, 129.15, 136.06,

138.91,143.37; HRMS (FAB) *m/z* calcd for $C_{13}H_{19}O$ $(M+H)^+$ 191.1436, found 191.1433.

*4.4. 5-Iodo-2-methyl-4-(4-methylphenyl)-1-pentene **4***

To a solution of the alcohol **3** (0.443 g, 2.33 mmol) in dry CH_2Cl_2 (7 ml) were added imidazole (0.238 g, 3.50 mmol), triphenylphosphine (0.734 g, 2.80 mmol), and iodine (0.888 g, 3.50 mmol) at 0 ºC. After the mixture was stirred at room temperature for 1 h, aqueous saturated $Na_2S_2O_3$ was added. The mixture was extracted with CH_2Cl_2, and the organic layers were dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography using silica gel (hexane/EtOAc = 50/1 to 30/1) to afford **4** as a colorless oil (0.579 g, 83%). IR (neat) 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.67 (3H, s), 2.33 (3H, s), 2.35 (1H, dd, *J* = 8.5, 13.8 Hz), 2.56 (1H, dd, *J* = 7.0, 13.8 Hz), 2.98-3.04 (1H, m), 3.33 (1H, dd, *J* = 7.5, 10.0 Hz), 3.42 (1H, dd, *J* = 6.0, 10.0 Hz), 4.66 (1H, s), 4.73 (1H, s), 7.06 (2H, d, *J* = 7.8 Hz), 7.13 (2H, d, *J* = 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.97, 21.06, 22.20, 43.91, 45.33, 112.89, 127.14, 129.08, 136. 38, 139.62, 142.62; HRMS (FAB) $(M+H)^+$ *m/z* calcd for $C_{13}H_{18}I$ 301.0453, found 301.0462.

*4.5. 2-Methyl-4-(4-methylphenyl)-1-pentene **5***

To a solution of **4** (2.000 g, 6.66 mmol) in dry THF (50 ml) was added $LiAlH_4$ (0.763 g, 20.10 mmol) at 0 ºC. The mixture was stirred at room temperature for 3.5 h, and 10% NaOH was added to the mixture at 0 ºC. The mixture was filtered off with suction, and the resulting solution was dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography using silica gel (hexane) to

afford **5** as a colorless oil (0.978 g, 84%). ^{1}H NMR spectra data were identical to those reported in the literature.[27]

*4.6. 1,3,3,5-Tetramethylindane **6***

To a solution of **5** (0.300 g, 1.72 mmol) in dry benzene (6 ml) was added $AlCl_3$ (0.045 g, 0.34 mmol) at 0 ºC. The solution was stirred at room temperature for 2 h. Aqueous saturated $NaHCO_3$ was added at 0 ºC, and the resulting mixture was extracted twice with EtOAc. The combined organic layers were washed with water, and brine in this order and then dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography using silica gel (hexane) to give **6** as a colorless oil (0.186 g, 62%). IR (neat) 3003, 812 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (3H, s), 1.28 (3H, d, J = 7.0 Hz), 1.34 (3H, s), 1.49 (1H, dd, J = 9.5, 12.0 Hz), 2.13 (1H, dd, J = 7.0, 12.0 Hz), 2.34 (3H, s), 3.16-3.23 (1H, m), 6.95 (1H, s), 7.00 (1H, d, J = 7.5 Hz), 7.05 (1H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.73, 21.38, 28.81, 29.21, 36.00, 42.66, 51.28, 122.59, 122.87, 127.14, 135.99, 144.26, 152.48; HRMS (EI) m/z calcd for $C_{13}H_{18}$ M^+ 174.1409, found 174.1407.

*4.7. 1-(2,3-dihydro-1H-1,3,3,5-tetramethyl-6-indenyl)-1-ethanone **1a***

To a solution of **6** (0.050 g, 0.29 mmol) in dry CH_2Cl_2 (1 ml) were added acetyl chloride (0.051 g, 0.65 mmol) and $AlCl_3$ (0.077 g, 0.58 mmol) at 0 ºC. The reaction mixture was stirred at room temperature for 30 min. Aqueous saturated $NaHCO_3$ was added at 0 ºC, and the mixture was filtered with suction. The filtrate was extracted with CH_2Cl_2 and then dried over Na_2SO_4. After removal of the solvent, Kugelrohr distillation (115–166 ºC/1.5 mmHg) provided **1a** as a white solid (0.038 g,

61%). Mp 55-58 ºC; IR (KBr) 1672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (3H, s), 1.32 (1H, d, J = 7.0 Hz), 1.35 (1H, s), 1.52 (2H, dd, J = 9.5, 12.3 Hz), 2.18 (1H, dd, J = 7.5, 12.3 Hz), 2.52 (3H, s), 2.58 (3H, s), 3.19-3.27 (1H, m), 6.98 (1H, s), 7.47 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.54, 21.81, 28.42, 28.81, 29.43, 35.86, 42.82, 50.94, 124.21, 125.41, 136.10, 137.19, 144.56, 156.17, 201.33; HRMS (EI) *m*/*z* calcd for $C_{15}H_{20}O$ M^+ 216.1514, found 216.1512.

4.8. 1-(2,3-dihydro-1H-1,3,3,5-tetramethyl-6-indenyl)-1-propanone ***1b***

Compound **1b** was synthesized from **6** (0.089 g, 0.51 mmol) and propionyl chloride (0.102 g, 1.10 mmol) with $AlCl_3$ (0.133 g, 1.00 mmol) in 57% yield according to the procedure described in Section 4.7. Kugelrohr distillation (120-160 ºC/1.5 mmHg) provided **1b** as a colorless oil. IR (neat) 1684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (3H, s), 1.19 (3H, t, J = 7.2 Hz), 1.31 (3H, d, J = 7.0 Hz), 1.34 (3H, s), 1.52 (1H, dd, J = 9.5, 12.3 Hz), 2.17 (1H, dd, J = 7.5, 12.3 Hz), 2.48 (3H, s), 2.92 (2H, q, J = 7.2 Hz), 3.20-3.26 (1H, m), 6.98 (1H, s), 7.41 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.40, 19.57, 21.50, 28.49, 28.88, 34.53, 35.93, 42.83, 51.00, 123.14, 125.32, 136.58, 136.61, 144.53, 155.69, 204.86; HRMS (EI) *m*/*z* calcd for $C_{16}H_{22}O$ M^+ 230.1671, found 230.1672.

4.9. 1-(2,3-dihydro-1H-1,3,3,5-tetramethyl-6-indenyl)-1-butanone ***1c***

Compound **1c** was synthesized from **6** (0.150 g, 0.86 mmol) and butyryl chloride (0.203 g, 1.91 mmol) with $AlCl_3$ (0.229 g, 1.72 mmol) in 75% yield according to the procedure described in Section 4.7. Kugelrohr distillation (140-190 ºC/1.5 mmHg) provided **1c** as a colorless oil. IR (neat) 1684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.99

(3H, t, *J* = 7.3 Hz), 1.16 (3H, s), 1.31 (3H, d, *J* = 7.0 Hz), 1.34 (3H, s), 1.52 (1H, dd, *J* = 9.0, 12.2 Hz), 1.74 (2H, sextet, *J* = 7.3 Hz), 2.17 (1H, dd, *J* = 7.3, 12.2 Hz), 2.48 (3H, s), 2.87 (2H, t, *J* = 7.3 Hz), 3.20-3.26 (1H, m), 6.97 (1H, s), 7.39 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.77, 17.80, 19.56, 21.39, 28.46, 28.86, 35.90, 42.80, 43.34, 50.98, 123.11, 125.27, 136.52, 136.81, 144.47, 155.59, 204.47; HRMS (EI) *m*/*z* calcd for $C_{17}H_{24}O$ M^+ 244.1827, found 244.1825.

4.10. 1-(2,3-dihydro-1H-1,3,3,5-tetramethyl-6-indenyl)-2-methyl-1-propanone ***1d***

Compound **1d** was synthesized from **6** (0.089 g, 0.51 mmol) and isobutyryl chloride (0.110 g, 1.03 mmol) with $AlCl_3$ (0.133 g, 1.00 mmol) in 72% yield according to the procedure described in Section 4.7. Kugelrohr distillation (136-160 ºC/1.5 mmHg) provided **1d** as a colorless oil. IR (neat) 1684 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (3H, 3), 1.17 (6H, d, *J* = 7.0 Hz), 1.30 (3H, d, *J* = 6.5 Hz), 1.34 (3H, s), 1.51 (1H, dd, *J* = 9.5, 12.3 Hz), 2.17 (1H, dd, *J* = 7.0, 12.3 Hz), 2.42 (3H, s), 3.18-3.25 (1H, m), 3.38 (1H, septet, *J* = 7.0 Hz), 6.97 (1H, s), 7.29 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.69, 18.75, 19.61, 29.99, 28.54, 28.95, 35.95, 38.45, 42.83, 51.03, 122.32, 125.10, 136.21, 136.94, 144.42, 155.22, 209.20; HRMS (EI) *m*/*z* calcd for $C_{17}H_{24}O$ $(M)^+$ 244.1827, found 244.1833.

4.11. Diethyl 2-(4-methylphenyl)malonate ***7***

LiHMDS was prepared by the treatment of HMDS (2.432 g, 15.07 mmol) with *n*-BuLi (1.6 *M* solution in hexane, 9.4 mL, 15 mmol) in dry THF (30 mL) at 0 ºC for 30 min. To a solution of ethyl *p*-tolylacetate (1.778 g, 9.98 mmol) in dry THF (30 ml) was added the LiHMDS at -78 ºC. The mixture was stirred at -78 ºC for 30 min.

To the mixture, ethyl cyanoformate (1.110 g, 11.20 mmol) was added at -78 ºC, and then the mixture was allowed to warm to 0 ºC for 80 min. 10% HCl was added at 0 ºC, and the mixture was extracted twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography using silica gel (hexane/acetone = 25/1) to afford **7** as a colorless oil (2.396 g, 96%). ^{1}H NMR spectra data were identical to those reported in the literature.[28]

*4.12. 2-(4-Methylphenyl)-1,3-propanediol **8***

Compound **8** was synthesized from **7** (5.930 g, 23.69 mmol) with $LiAlH_4$ (1.800 g, 47.43 mmol) in 79% yield according to the procedure described in Section 4.3. The crude product was purified by column chromatography using silica gel (hexane/acetone = 3/1 to 1/1) to give **8** as a colorless oil. ^{1}H NMR spectra data were identical to those reported in the literature.[28]

*4.13. (R)-3-hydroxy-2-(4-methylphenyl)propyl acetate (R)-**9***

Diol **8** (2.900 g, 17.45 mmol) was dissolved in vinyl acetate (52 ml). PPL (1.360 g) was added to the solution, and the resulting suspension was stirred at room temperature for 3 h. The lipase was filtered off with suction. After removal of the solvent, the residue was purified by column chromatography using silica gel (hexane/EtOAc = 1/2) to afford (*R*)-**9** (3.283 g, 90%). ^{1}H NMR spectra data were identical to those reported in the literature.[28] The enantiomeric excess was determined by HPLC (CHIRALCEL OD-H, hexane/2-propanol = 9/1) and found to be 99%. $[\alpha]_D^{19}$ = +14.9 (*c* 0.75, $CHCl_3$), Lit.[28] $[\alpha]_D$ = -16.2 ($CHCl_3$), (*S*), 96% ee.

*4.14. (R)-3-methoxymethoxy-2-(4-methylphenyl)propyl acetate (R)-**10***

To a solution of (*R*)-**9** (1.790 g, 8.60 mmol) in dry CH_2Cl_2 (27ml) were added DIPEA (1.780 g, 13.77 mmol) and MOMCl (1.039 g, 12.91 mmol) at 0 ºC. The reaction mixture was stirred at room temperature overnight. After removal of the solvent, the residue was purified by column chromatography using silica gel (hexane/acetone = 3/2) to afford (*R*)-**10** as a colorless oil (2.090 g, 96%). IR (neat) 1740, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.01(3H, s), 2.33 (3H, s), 3.21 (1H, quintet, *J* = 6.6 Hz), 3.28 (3H, s), 3.77 (2H, d, *J* = 6.6 Hz), 4.31 (1H, dd, *J* = 6.6, 11.1 Hz), 4.36 (1H, dd, *J* = 6.6, 11.1 Hz), 4.59 (2H, s), 7.13 (2H, d, *J* = 8.6), 7.15 (2H, d, *J* = 8.6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.53, 20.74, 44.20, 54.84, 65.15, 68.28, 96.17, 127.64, 128.92, 136.20, 136.27, 170.53; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{21}O_4$ $(M+H)^+$ 253.1440, found 253.1438; $[\alpha]_D^{16}$ = -9.57 (*c* 0.40, $CHCl_3$).

*4.15. (S)-3-methoxymethoxy-2-(4-methylphenyl)-1-propanol (S)-**11***

To a solution of (*R*)-**10** (2.090 g, 8.28 mmol) in MeOH (30 ml) was added K_2CO_3 (2.290 g, 16.57 mmol). The solution was stirred at room temperature for 2 h. CH_2Cl_2 was added, and the mixture was filtered with suction. After removal of the solvent, the residue was purified by chromatography using silica gel (hexane/acetone = 5/1 to 3/1) to afford (*S*)-**11** as a colorless oil (1.740 g, quant). IR (neat) 3421, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.33 (3H, s), 3.14 (1H, quintet, *J* = 6.8 Hz), 3.35 (3H, s), 3.81-3.88 (3H, m), 3.97 (1H, dd, *J* = 6.8, 10.8 Hz), 4.64 (2H, s), 7.14 (4H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.81, 47.40, 55.05, 65.17, 69.83, 96.35, 127.72, 129.08, 136.29, 136.60; HRMS (FAB) *m*/*z* calcd for $C_{12}H_{19}O_3$ $(M+H)^+$ 211.1334, found 211.1333;

$[\alpha]_D^{16}$ = -20.74 (*c* 0.85, $CHCl_3$).

*4.16. (R)-3-methoxymethoxy-2-(4-methylphenyl)propyl p-toluenesulfonate (R)-**12***

To a solution of alcohol (*S*)-**11** (0.622 g, 2.96 mmol) in dry CH_2Cl_2 (9 ml) were added Et_3N (0.539 g, 5.33 mmol), TsCl (0.904 g, 4.74 mmol), and DMAP (0.072 g, 0.59 mmol) at 0 ºC. The reaction mixture was stirred at room temperature for 2 h, and the solvent was evaporated. The residue was purified by chromatography using silica gel (hexane/acetone = 10/1 to 7/1) to afford (*R*)-**12** as a colorless oil (1.080 g, quant). IR (neat) 1362, 1177, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, s), 2.43 (3H, s), 3.17 (1H, quintet, *J* = 6.5 Hz), 3.24 (3H, s), 3.72 (2H, d, *J* = 6.5 Hz), 4.21 (1H, dd, *J* = 6.5, 9.8 Hz), 4.31 (1H, dd, *J* = 6.5, 9.8 Hz), 4.53 (2H, s), 7.03 (2H, d, *J* = 8.0 Hz), 7.07 (2H, d, *J* = 8.0 Hz), 7.27 (2H, d, *J* = 8.8), 7.67 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.83, 21.39, 44.40, 55.03, 67.51, 70.70, 96.29, 127.64, 127.69, 129.03, 129.55, 132.56, 134.87, 136.68, 144.48; HRMS (FAB) *m/z* calcd for $C_{19}H_{25}O_5S$ $(M+H)^+$ 365.1423, found 365.1421; $[\alpha]_D^{18}$ = -6.02 (*c* 0.55, $CHCl_3$).

*4.17. (R)-1-methoxymethoxy-2-(4-methylphenyl)propane (R)-**13***

To a solution of (*R*)-**12** (1.080 g, 2.96 mmol) in DMSO (7 ml) was added $NaBH_4$ (0.224 g, 5.92 mmol) at room temperature, and the reaction mixture was stirred at 60 ºC for 5 h. Water was added at 0 ºC, and the mixture was extracted three times with EtOAc. The combined organic extracts were dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography using silica gel (hexane/acetone = 20/1) to afford (*R*)-**13** as a colorless oil (0.489 g, 85%). IR (neat) 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, d, *J* = 6.9 Hz), 2.32 (3H, s), 2.99

(1H, sextet, *J* = 6.9 Hz), 3.29 (3H, s), 3.57 (1H, dd, *J* = 6.9, 9.5 Hz), 3.65 (1H, dd, *J* = 6.9, 9.5 Hz), 4.59 (2H, s), 7.13 (4H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.50, 20.89, 39.49, 54.96, 73.31, 96.28, 127.04, 128.95, 135.67,141.20, HRMS (EI) *m*/*z* calcd for $C_{11}H_{15}O$ $(M\text{-}OCH_3)^+$ 163.1123, found 163.1119; $[\alpha]_D^{17}$ = -14.27 (*c* 0.60, $CHCl_3$).

*4.18. (R)-2-(4-methylphenyl)-1-propanol (R)-**14***

To a solution of (*R*)-**13** (1.550 g, 7.98 mmol) in MeOH (24 ml) was added three drops of concentrated hydrochloric acid. The mixture was refluxed for 3.5 h. Aqueous saturated $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography using silica gel (hexane/acetone = 2/1) to afford (*R*)-**14** as a colorless oil (1.142 g, 95%). ^{1}H NMR spectra data were identical to those reported in the literature.[29] The enantiomeric excess of (*R*)-**14** was determined by HPLC (CHIRALCEL OB-H, hexane/2-propanol = 95/5) and found to be 99%. $[\alpha]_D^{21}$ = +16.05 (*c* 1.0, $CHCl_3$), Lit.[29] $[\alpha]_D^{25}$ = +17.4 (*c* 1, $CHCl_3$), (*R*), 97.5% ee.

*4.19. (R)-1-iodo-2-(4-methylphenyl)propane (R)-**15***

Compound (*R*)-**15** was synthesized from (*R*)-**14** (1.817 g, 12.10 mmol) and iodine (4.291 g, 16.91 mmol) with imidazole (1.239 g, 17.68 mmol) and PPh_3 (3.803 g, 14.50 mmol) in 83% yield according to the procedure described in Section 4.4. The crude product was purified by column chromatography using silica gel (hexane) to give (*R*)-**15** as a colorless oil. ^{1}H NMR spectra data were identical to those reported in the literature.[29] $[\alpha]_D^{25}$ = +33.59 (*c* 1.1, $CHCl_3$), Lit.[29] $[a]_D^{25}$ = +30.1 (*c* 1, $CHCl_3$), (*R*).

*4.20. (S)-4-(4-methylphenyl)-1-pentene (S)-**16***

The Gilman reagent was prepared by slow addition of MeLi (1.08 *M* solution in hexane, 16 ml, 17 mmol) to tetravinyltin (0.946 g, 4.17 mmol) in dry Et_2O (2.5 mL) at 0 ºC and then stirred for 30 min. The solution was then transferred to a flask containing CuI (1.600 g, 8.40 mmol) and dry Et_2O (4 ml) at -78 ºC, and the reaction mixture was allowed to warm to -35ºC for 30 min. The mixture was cooled to -78 ºC and added to the solution of (*R*)-**15** (0.550 g, 2.11 mmol) in dry Et_2O (4 ml). The reaction mixture was allowed to warm to 0 ºC for 1.5 h. Aqueous saturated NH_4Cl was added at 0 ºC, and the mixture was filtered with suction. The filtrate was extracted with CH_2Cl_2, and the organic layer was dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography using silica gel (hexane) to afford (*S*)-**16** as a colorless oil (0.241 g, 71%). ^{1}H NMR spectra data were identical to those reported in the literature.[30] $[\alpha]_D^{24}$ = +21.65 (*c* 0.30, $CHCl_3$), Lit.[30] $[a]_D^{20}$ = +15.0 (*c* 1.0, $CHCl_3$), 98% ee (*S*).

*4.21. (S)-4-(4-methylphenyl)-2-pentanone (S)-**17***

To a solution of (*S*)-**16** (0.097 g, 0.61 mmol) in DMF (1.5 ml) and H_2O (0.5 ml), CuCl (0.060 g, 0.61 mmol) and $PdCl_2$ (0.032 g, 0.18 mmol) were added, and the resulting suspension was stirred at room temperature under an oxygen atmosphere overnight. Aqueous saturated $NaHCO_3$ was added, and the mixture was extracted three times with Et_2O. The combined organic extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography using silica gel (hexane/acetone = 50/1 to 30/1) to afford (*S*)-**17** a colorless oil (0.063 g, 59%). ^{1}H NMR spectra data were identical to those reported in

the literature.[31] $[\alpha]_D^{27}$ = +30.7 (*c* 0.15, CH_2Cl_2), Lit.[32] $[a]_D^{20}$ = -30.0 (*c* 1.0, CH_2Cl_2), 89% ee, (*R*).

*4.22. (S)-2-methyl-4-(4-methylphenyl)-1-pentene (S)-**5***

To a solution of $MePPh_3Br$ (2.357 g, 6.60 mmol) in dry THF (6 ml) was added *n*-BuLi (1.6 *M* solution in hexane, 3.9 mL, 6.2 mmol) at 0 ºC. The solution of (*S*)-**17** (0.231 g, 1.31 mmol) in dry THF (6 ml) was added dropwise at room temperature, and the mixture was stirred overnight. Aqueous saturated NH_4Cl was added at 0 ºC. The mixture was extracted with EtOAc, and the organic layer was dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography using silica gel (hexane) to afford (*S*)-**5** a colorless oil (0.160 g, 70%). ^{1}H NMR spectra were identical to those of (±)-**5**. The enantiomeric excess was determined by GC (CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column, 70 ºC) and found to be 99%. $[\alpha]_D^{25}$ = -1.61 (*c* 1.35, $CHCl_3$).

*4.23. Cyclialkylation of (S)-**5***

The alkene (*S*)-**5** (0.053 g, 0.30 mmol) was treated with $AlCl_3$ (0.008 g, 0.06 mmol) in dry benzene (0.9 mL) at room temperature for 3 h according to the procedure described in Section 4.6. ^{1}H NMR spectra data of the product (*S*)-**6** were identical to those of (±)-**6**. The enantiomeric excess was determined by GC (CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column, 100 ºC) and found to be 93%. The cyclialkylation was conducted under the same conditions once again, and the ee of the product (*S*)-**6** was 86%.

*4.24. Treatment of (S)-**6** with $AlCl_3$*

To the solution of (*S*)-**6** (0.052 g, 0.30 mmol) with 99% ee (See Section 4.34) in dry benzene (0.9 ml), $AlCl_3$ (0.008 g, 0.060 mmol) was added at 0 ºC, and the mixture was stirred at room temperature for 3 h. Aqueous saturated $NaHCO_3$ was then added at 0 ºC, and the resulting precipitate was filtered off with suction. The filtrate was extracted with EtOAc and then dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography using silica gel (hexane/EtOAc = 20/1) to recover (*S*)-**6**. ^{1}H NMR spectra data of the recovered (*S*)-**6** were identical to those of (±)-**6**. The enantiomeric excess was determined by GC (CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column, 100 ºC) and found to be 98%.

*4.25. Ethyl 3,3,5-trimethylindane-1-carboxylate **21***

To the solution of **2** (2.637 g, 11.35 mmol) in dry benzene (34 ml), $AlCl_3$ (3.800 g, 28.50 mmol) was added at 0 ºC. The mixture was stirred at room temperature for 3.5 h. Aqueous saturated $NaHCO_3$ was added at 0 ºC, and the resulting precipitate was filtered off with suction. The filtrate was extracted with EtOAc, and the organic layer was dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography using silica gel (hexane/EtOAc = 20/1) to afford **21** (2. 290 g, 87%). IR (neat) 1737 cm^{-1}; ^{1}H MNR (400 MHz, $CDCl_3$) δ 1.21 (3H, s), 1.30 (3H, t, J = 7.0 Hz), 1.36 (3H, s), 2.18 (1H, dd, J = 8.5, 12.6 Hz), 2.30 (1H, dd, J = 8.5, 12.6 Hz), 2.35 (3H, s), 4.03 (1H, t, J = 8.5 Hz), 4.21 (2H, q, J = 7.0 Hz), 6.97 (1H, s), 7.01 (1H, d, J = 7.4 Hz), 7.23 (1H, d, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.16, 21.23, 28.76, 29.35, 43.04, 44.25, 47.33, 60.50, 122.76, 124.30, 127.38, 136.27, 137.21, 152.29, 173.81; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{21}O_2$ $(M+H)^+$ 233.1542, found 233.1539.

*4.26. 2,3-dihydro-1H-3,3,5-trimethyl-1-indenylmethanol **22***

Compound **22** was synthesized from **21** (1.248 g, 5.37 mmol) with $LiAlH_4$ (0.306 g, 8.06 mmol) in 95% yield according to the procedure described in Section 4.3. The crude product was purified by chromatography using silica gel (hexane/EtOAc = 3/1). IR (neat) 3344 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, s), 1.35 (3H, s), 1.77 (1H, dd, J = 8.4, 12.6 Hz), 2.12 (1H, dd, J = 7.6, 12.6 Hz), 2.35 (3H, s), 3.35-3.42 (1H, m), 3.82-3.39 (2H, m), 6.98 (1H, s), 7.01 (1H, d, J = 7.6 Hz), 7.14 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.27, 29.15, 29.79, 42.70, 44.39, 45.00, 60.04, 122.92, 123.40, 127.16, 136.66, 139.35, 153.24; HRMS (FAB) m/z calcd for $C_{13}H_{18}O$ M^+ 190.1358, found 190.1357.

*4.27. Lipase-catalyzed transesterification of **22** (screening experiments)*

In a typical run, a dry THF solution (1 mL) containing racemic primary alcohol **22** (0.045 mmol) and vinyl acetate (1.0 mmol) was added to a vial in which Sigma PPL (100 mg) was placed. The resulting suspension was then stirred at room temperature. The time-courses of the reaction were monitored by GC using InertCap 1 capillary column (220 °C). The reaction was stopped by the filtration of the lipase at a conversion of approximately 50%. The conversion was calculated from the ratio of the peak area of ester **23** in gas chromatogram to the total of the peak areas of **22** and **23**. The peak areas of the two compounds were corrected on the basis of the number of carbon atoms in the molecules.[33] The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 10/1 to 1/1) packed in a short column (10 mm ϕ × 80 mm) to afford (*R*)-**22** and (*S*)-**23**. The enantiomeric

excess of (*R*)-**22** was determined by GC using CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column (150 °C). The enantiomeric excess of (*S*)-**23** was determined by HPLC using the OJ-H column (hexane/2-propanol = 9/1). The *E*-value and the conversion of the reaction were calculated from the ee of (*R*)-**22** and (*S*)-**23**.[22]

*4.28. Preparative kinetic resolution of **22** (preparation of (R)-**22** and (S)-**22**)*

PPL (11.12 g) was added to the solution of **22** (2.764 g, 14.53 mmol) and vinyl acetate (25.00 g, 290.40 mmol) in dry THF (120 ml). The resulting suspension was stirred at room temperature for 3.5 h. PPL (1.700 g) was added to the mixture and stirring continued for a further 3.5 h. The conversion, which was calculated by GC using InertCap 1 capillary column (220 °C), was then approximately 56%. The lipase was filtered off with suction. After removal of the solvent, the residue was purified by chromatography using silica gel (hexane/EtOAc = 5/1 to 1/1) to afford (*R*)-**22** (1.225 g, 44%) and (*S*)-**23** (1.885 g, 56%) as colorless oils.

(*R*)-**22**: ^{1}H NMR spectra data were identical to those of (±)-**22**. The enantiomeric excess was determined by GC (CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column, 150 °C) and found to be >99%. $[\alpha]_D^{19}$ = +8.55 (*c* 1.0, $CHCl_3$).

(*S*)-**23**: IR (neat) 1741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, s), 1.34 (3H, s), 1.67 (1H, dd, *J* = 8.6, 12.7 Hz), 2.10 (3H, s), 2.14 (1H, dd, *J* = 7.6, 12.7 Hz), 2.35 (3H, s), 3.45-3.52 (1H, m), 4.19 (1H, dd, *J* = 7.2, 10.8 Hz), 4.34 (1H, dd, *J* = 6.4, 10.8 Hz), 6.97 (1H, s), 6.99 (1H, d, *J* = 7.8 Hz), 7.14 (1H, d, *J* = 7.8 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.03, 21.41, 29.22, 29.68, 41.18, 42.87, 45.58, 68.08, 122.99, 123.70, 127.35, 137.07, 139.11, 152.96, 171.22; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{21}O_2$ $(M+H)^+$ 233.1542, found 233.1543.

6 *M* NaOH (3.0 mL, 18 mmol) was added to the solution of (*S*)-**23** (1.850 g, 7.96 mmol) in EtOH (15 mL), and the reaction mixture was stirred at room temperature overnight. The ethanol was removed under reduced pressure, and H_2O was added to the residue. The mixture was extracted three times with Et_2O. The combined organic extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography using silica gel (hexane/EtOAc = 1/1) to afford (*S*)-**22** as a colorless oil (1.490 g, 98%, 76% ee). ^{1}H NMR spectra data were identical to those of (±)-**22**.

PPL (5.400 g) was added to the solution of (*S*)-**22** (1.460 g, 7.67 mmol) and vinyl acetate (13.200 g, 153.33 mmol) in dry THF (60 ml). The resulting suspension was stirred at room temperature for 1.5 h. The conversion, which was calculated by GC using InertCap 1 capillary column (220 °C), was then approximately 50%. The lipase was filtered off with suction. After removal of the solvent, the residue was purified by chromatography using silica gel (hexane/EtOAc = 5/1) to afford (*S*)-**23** as a colorless oil (0.964 g, 54%). ^{1}H NMR spectra data were identical to those of (*S*)-**23** prepared in the first PPL-catalyzed transesterification.

The ester (*S*)-**23** (0.913 g, 3.93 mmol) obtained above was hydrolyzed with 6 *M* NaOH (1.5 mL, 9 mmol) to (*S*)-**22** (0.733 g, 98%) according to the procedure described above. ^{1}H NMR spectra data were identical to those of (±)-**22**. The enantiomeric excess was determined by GC (CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column, 150 °C) and found to be 99%. $[\alpha]_D^{20}$ = -10.20 (*c* 1.0, $CHCl_3$).

*4.29. (R)-2,3-dihydro-1H-3,3,5-trimethyl-1-indenylmethyl methanesulfonate (R)-**24***

MsCl (1.512 g, 13.20 mmol) was slowly added to the solution of (*R*)-**22** with >99%

ee (1.225 g, 6.44 mmol) and dry pyridine (1.566 g, 19.80 mmol) in dry CH_2Cl_2 (20 ml) at 0 ºC. The reaction mixture was stirred at room temperature overnight, and then water was added to the mixture at 0 ºC. The resulting mixture was extracted with Et_2O. The organic layer was washed three times with $NaHCO_3$, brine in this order and then dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography using silica gel (hexane/EtOAc = 3/1) to afford (*R*)-**24** (1.535 g, 89%). IR (neat) 1176, 1359 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, s), 1.35 (3H, s), 1.73 (1H, dd, *J* = 8.4, 12.8 Hz), 2.20 (1H, dd, *J* = 8.0, 12.8 Hz), 2.35 (3H, s), 3.01 (3H, s), 3.56-3.63 (1H, m), 4.31 (1H, dd, *J* = 7.2, 9.6 Hz), 4.48 (1H, dd, *J* = 6.0, 9.6 Hz), 6.98 (1H, s), 7.01 (1H, d, *J* = 8.0 Hz), 7.13 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.42, 29.22, 29.78, 37.40, 41.63, 42.94, 45.07, 73.02, 123.20, 123.63, 127.55, 137.50, 137.62, 153. 01; HRMS (FAB) *m/z* calcd for $C_{14}H_{21}O_3S$ $(M+H)^+$ 269.1211, found 269.1204; $[\alpha]_D^{18}$ = +12.10 (*c* 0.50, $CHCl_3$).

*4.30. (R)-1,3,3,5-Tetramethylindane (R)-**6***

To a suspension of $LiAlH_4$ (0.298 g, 7.85 mmol) in dry Et_2O (5 mL), was slowly added a solution of (*R*)-**24** (1.053 g, 3.92 mmol) in dry Et_2O (13 mL) at 0 ºC. The reaction mixture was stirred at room temperature overnight. Water was added to the mixture at 0 ºC, and then 6 *M* HCl was added to the resulting mixture at 0 ºC. The mixture was extracted three times with Et_2O. The combined organic extracts were washed with brine and then dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography using silica gel (hexane) to afford (*R*)-**6** as a colorless oil (0.619 g, 91%). ^1H NMR spectra data were identical to those of (±)-**6**. The enantiomeric excess was determined by GC using

CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column (100 °C) and found to be >99%. $[\alpha]_D^{16}$ = +9.43 (*c* 1.0, $CHCl_3$).

*4.31. (R)-1-(2,3-dihydro-1H-1,3,3,5-tetramethyl-6-indenyl)ethanone (R)-**1a***

To a suspension of $AlCl_3$ (0.153 g, 1.15 mmol) in dry CH_2Cl_2 (1 ml) was added acetyl chloride (0.098 g, 1.25 mmol) at 0 ºC. After the mixture was stirred at room temperature for 5 min, the solution of (*R*)-**6** (0.100 g, 0.57 mmol) in CH_2Cl_2 (2 ml) was added at 0 ºC. The reaction mixture was stirred at room temperature for 15 min. Aqueous saturated $NaHCO_3$ was added at 0 ºC, and the mixture was filtered off with suction. The filtrate was extracted three times with Et_2O. The combined organic extracts were washed twice with $NaHCO_3$, brine in this order and then dried over Na_2SO_4. After removal of the solvent, the residue was purified by chromatography using silica gel (hexane/EtOAc = 10/1) and subsequent distillation (118-146 ºC/2.1 mmHg) to afford (*R*)-**1a** as a colorless oil (0.113 g, 91%). ^{1}H NMR spectra data were identical to those of (±)-**1a**. The enantiomeric excess was determined by HPLC using CHIRALPACK AS-H column (hexane/2-propanol = 99/1) and found to be >99%. $[\alpha]_D^{18}$ = -17.64 (*c* 1.0, $CHCl_3$); mp 70-72 °C.

*4.32. (R)-1-(2,3-dihydro-1H-1,3,3,5-tetramethyl-6-indenyl)propanone (R)-**1b***

Compound (*R*)-**1b** was synthesized from (*R*)-**6** (0.101 g, 0.58 mmol) and propionyl chloride (0.118 g, 1.28 mmol) with $AlCl_3$ (0.155 g, 1.16 mmol) in 89% yield according to the procedure described in Section 4.31. The crude product was purified by chromatography using silica gel (hexane/EtOAc = 10/1) and subsequent distillation (120-155 ºC/2.0 mmHg) to afford (*R*)-**1b** as a colorless oil. ^{1}H NMR spectra data

were identical to those of (±)-**1b**. The enantiomeric excess was determined by HPLC using CHIRALCEL OJ-H column (hexane/2-propanol = 99/1) and found to be 99%. $[\alpha]_D^{16}$ = -16.27 (*c* 1.0, $CHCl_3$).

*4.33. (S)-2,3-dihydro-1H-3,3,5-trimethyl-1-indenylmethyl methanesulfonate (S)-**24***

Compound (*S*)-**24** was synthesized from (*S*)-**22** (0.688 g, 3.62 mmol) with MsCl (0.829 g, 7.24 mmol) and dry pyridine (0.862 g, 10.90 mmol) in 96% yield according to the procedure described in Section 4.29, but with the proviso that the mixture of hexane and EtOAc (1/1) was used for the silica gel column chromatography. ^{1}H NMR spectra data were identical to those of (*R*)-**24**. $[\alpha]_D^{20}$ = -12.63 (*c* 0.65, $CHCl_3$).

*4.34. (S)-1,3,3,5-Tetramethylindane (S)-**6***

Compound (*S*)-**6** was synthesized from (*S*)-**24** (0.887 g, 3.31 mmol) with $LiAlH_4$ (0.251 g, 6.61 mmol) in 96% yield according to the procedure described in Section 4.30. ^{1}H NMR spectra data were identical to those of (±)-**6**. The enantiomeric excess was determined by GC using CP-Cyclodextrin-*β*-2,3,6-M-19 capillary column (100 °C) and found to be 99%. $[\alpha]_D^{16}$ = -8.86 (*c* 0.80, $CHCl_3$).

*4.35. (S)-1-(2,3-dihydro-1H-1,3,3,5-tetramethyl-6-indenyl)ethanone (S)-**1a***

Compound (*S*)-**1a** was synthesized from (*S*)-**6** (0.104 g, 0.60 mmol) and acetyl chloride (0.103 g, 1.31 mmol) with $AlCl_3$ (0.160 g, 1.20 mmol) in 71% yield according to the procedure described in Section 4.31. The crude product was purified by chromatography using silica gel (hexane/EtOAc = 5/1) and subsequent distillation (115-135 ºC/2.3 mmHg) to afford (*S*)-**1a** as a colorless oil. ^{1}H NMR spectra data

were identical to those of (±)-**1a**. The enantiomeric excess was determined by HPLC using CHIRALPACK AS-H column (hexane/2-propanol = 99/1) and found to be 98%. $[\alpha]_D^{18}$ = +16.07 (*c* 1.00, $CHCl_3$) ; mp 69-71 °C.

*4.36. (S)-1-(2,3-dihydro-1H-1,3,3,5-tetramethyl-6-indenyl)propanone (S)-**1b***

Compound (*S*)-**1b** was synthesized from (*S*)-**6** (0.107 g, 0.61 mmol) and propionyl chloride (0.123 g, 1.33 mmol) with $AlCl_3$ (0.164 g, 1.23 mmol) in 86% yield according to the procedure described in Section 4.32. ^{1}H NMR spectra data were identical to those of (±)-**1b**. The enantiomeric excess was determined by HPLC using CHIRALCEL OJ-H column (hexane/2-propanol = 99/1) and found to be 99%. Bp 118-181 ºC/2.3 mmHg; $[\alpha]_D^{20}$ = +14.26 (*c* 0.50, $CHCl_3$).

4.37. Odor profiles evaluation

An undiluted sample was attached to the tip of filter paper (5 mm × 10 cm) in small quantities and evaluated by trained panelists.

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21. Serra showed that the PPL-catalyzed transesterification of (±)-**14** in vinyl acetate proceeded enantioselectively (E^{22} = 33.3).[23] This finding means that (*R*)-**14** with 99% ee and the acetic acid ester of (*S*)-**14** with 73.5% ee can be theoretically obtained simultaneously in the transesterification.

We thought that we could obtain not only (*R*)-**14** in highly optically active form but also (*S*)-**14** in highly optically active form if only we prepared (*R*)-**9** in highly optically active form. We planned to synthesize (*S*)-**14** from (*R*)-**9** in two steps (the mesylation of (*R*)-**9** and the reduction of the resultant mesylate) and could actually obtain (*S*)-**14** with 99% ee from (*R*)-**9** with 99% ee in 83% yield in two steps.

If we follow Serra's report, we need to transform the acetic acid ester of (*S*)-**14** with 73.5% ee into (*S*)-**14** with higher ee. The transformation needs the enantioselective hydrolysis of the acetic acid ester of (*S*)-**14** to (*S*)-**14**, for example, the PPL-catalyzed hydrolysis of the ester in aqueous media. We newly need to find a suitable condition for the hydrolysis. We, therefore, followed Shishido's report to prepare (*R*)-**9** and used it for the synthesis of (*R*)-**14**.

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24. We tried the coupling of (*R*)-**15** with 2-bromo-1-propen three times. However, in our hand, the starting material (*R*)-**15** was recovered every time.

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Legends

Figure 1. Musk odorants.

Figure 2. Phantolide analogues **1a-1d**.

Figure 3. NOESY correlations for **1a**.

Scheme 1. Synthesis of racemic Phantolide analogues **1a-1d**.

Scheme 2. Synthesis of optically active intermediate (*S*)-**6**.

Scheme 3. Plausible mechanism of racemization.

Scheme 4. Syntheses of optically active Phantolide analogues **1a**, **1b**.

Table 1. Odor profiles of racemic Phantolide analogues **1a-1d**.

Table 2. PPL-catalyzed transesterification of **22**.

Table 3. Odor profiles of optically active Phantolide analogues **1a**, **1b**.