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Synthesis of (*R*)-*ar*-turmerone and its conversion to (*R*)-*ar*-himachalene, a pheromone component of the flea beetle: (*R*)-*ar*-himachalene is dextrorotatory in hexane, while levorotatory in chloroform☆

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Abstract—(*R*)-*ar*-Turmerone was synthesized from (4-methylphenyl)acetic acid by employing Evans asymmetric alkylation as the key step. (*R*)-*ar*-Turmerone was converted to (*R*)-*ar*-himachalene, which was dextrorotatory in hexane while levorotatory in chloroform. Enantiomerically impure (75% ee) (*R*)-3-(4-methylphenyl)butanoic acid crystallized more readily than the enantiomerically pure one.

1. Introduction

Male-produced pheromone components of the flea beetle *Aphthona flava* were isolated and identified in 2001 by Bartelt et al.[1] They proposed himachalene-type sesquiterpene structures **1**–**4** (Fig. 1) to the components, and synthesized their racemates in 2003 to verify the proposed structures.[2] As to the absolute configuration of **1**–**4**, Bartelt proposed the stereochemistry opposite to those depicted in Figure 1.[1] Shortly afterwards in 2004, Mori et al. synthesized both the enantiomers of **1**–**4**, and the pheromone components were found to possess the absolute configuration as shown in Figure 1,[3] that is, opposite to those proposed by Bartelt et al.[1]

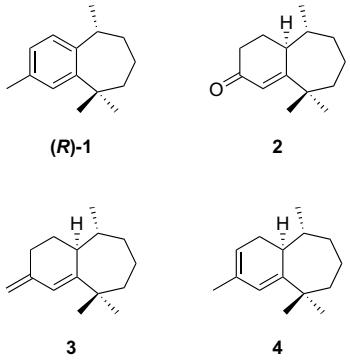

Figure 1. Structures of the pheromone components of the flea beetle.

Figure 2 summarizes the stereochemical correlations resulting in the assignment of the two different configurations to (+)-*ar*-himachalene **1** by Bartelt et al.[1] and Mori et al.,[3] respectively. The conclusion of Mori was based on their straightforward synthesis of (*R*)-(+)-*ar*-himachalene **1** starting from (*R*)-(+)-citronellal **5**, a popular building block in pheromone synthesis.[4] This monoterpene aldehyde **5** is a large-scale commercial product as manufactured by Takasago's asymmetric process developed by Noyori.[5]

On the other hand, Bartelt's proposal was based on Pandey and Dev's 1968 publication,[6] in which conversion of (*S*)-(+)-*ar*-turmerone **6** was reported to give (*S*)-(+)-*ar*-himachalene (**1**). The absolute configuration of (+)-*ar*-turmerone **6** had been established as *S* by Honwad and Rao, based on its stereochemical correlation to (*S*)-(+)-3-phenylbutanoic acid **7**.[7] An (*R*)-configuration was given to (−)-**7** by Prelog on the basis of its derivation from (*S*)-(+)-2-phenylpropanoic acid **8** by an

☆ Pheromone synthesis, Part 228. For Part 227, see: Ref. 27.
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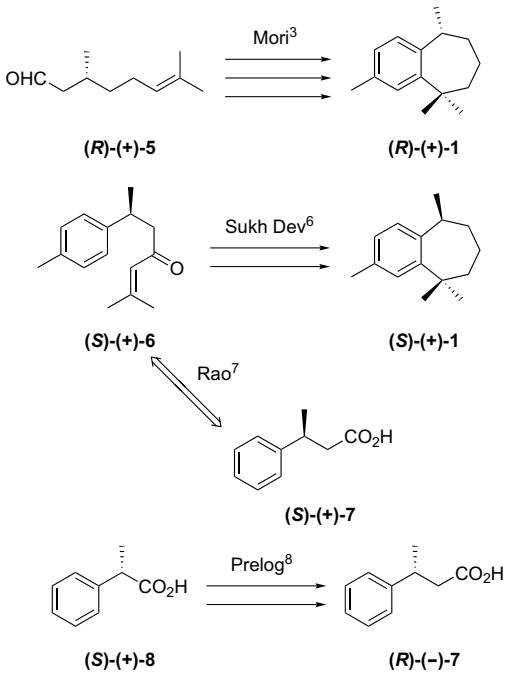


Figure 2. Stereochemical correlations for the assignments of the opposite absolute configuration to (+)-*ar*-himachalene **1**.

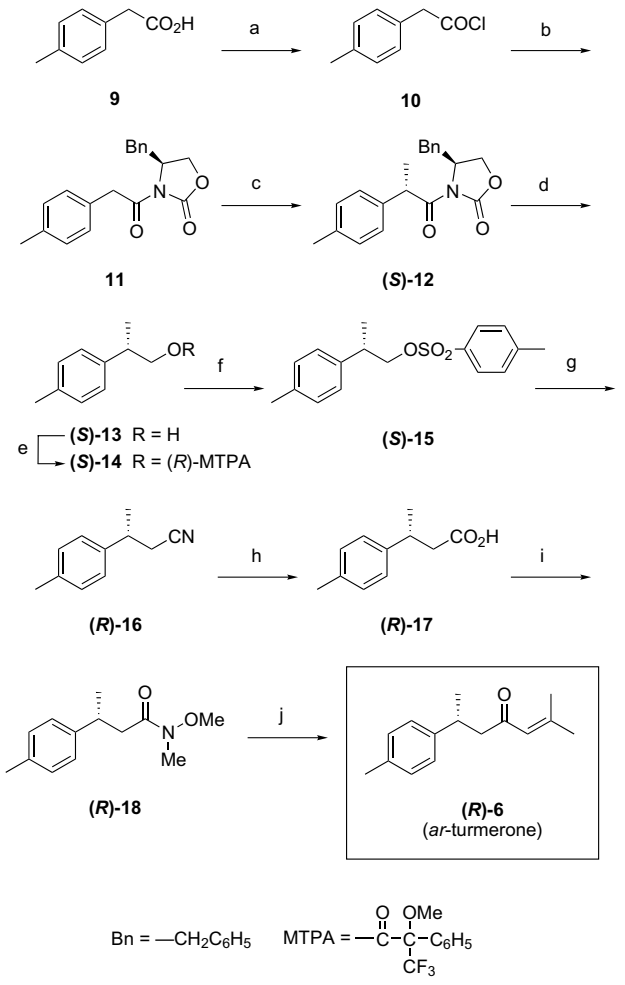
Arndt–Eistert reaction, which was known to give the product with retention of the original configuration.[8]

Since careful examination of the latter two papers[7,8] brought about nothing unusual, a decision was made to check the reproducibility of Pandey and Dev's work recording the preparation of (*S*)-**1** from (*S*)-**6**.[6] In the present experiment, attempts were made to synthesize the pheromone component (*R*)-**1** from the unnatural (*R*)-**6** secured by an asymmetric synthesis. Herein we report (i) synthesis of (*R*)-*ar*-himachalene **1** via (*R*)-*ar*-turmerone **6**, (ii) the crystallization behavior of enantiomerically enriched (*R*)-3-(4-methylphenyl)butanoic acid **17**, and (iii) the effect of solvents on the sign of the optical rotation of (*R*)-*ar*-himachalene **1**. This solvent effect turned out to be the origin of Bartelt's erroneous stereochemical assignment to the pheromone component **1**.

2. Results and discussion

2.1. Synthesis of (*R*)-*ar*-turmerone

Aromatic bisabolene sesquiterpenes, including *ar*-turmerone **6** are popular synthetic targets even now.[9,10] (*S*)-(+)-*ar*-Turmerone **6** is known as a spice flavor of turmeric.[11] Although there are many syntheses of (±)-**6**,[9] only a few enantioselective syntheses of (*S*)-(+)-**6** have been reported,[9,12–15] including our own.[16] Due to the (*R*)-configuration of the flea beetle pheromone component **1**, it was necessary to synthesize the unnatural (−)-*ar*-turmerone (*R*)-**6**. Scheme 1 summarizes the present asymmetric synthesis of (*R*)-**6**, which employs Evans asymmetric alkylation[17] of (*S*)-4-benzyl-3-(4-methylphenylacetyl)-2-oxazolidinone **11** as the key step to introduce the stereogenic center of (*R*)-**6**.



Scheme 1. Synthesis of (*R*)-*ar*-turmerone **6**. Reagents and conditions: (a) $SOCl_2$, C_6H_6, reflux, quant.; (b) (*S*)-4-benzyl-2-oxazolidinone, *n*-BuLi, THF, −78 °C, 30 min, then room temp, 79%; (c) NaHMDS, MeI, THF, −78 °C, 3 h, then room temp, 97%; (d) $LiAlH_4$, THF, 0 °C to room temp, 69%; (e) (*S*)-MTPACl, C_5H_5N, DMAP; (f) TsCl, DMAP, C_5H_5N, 0–5 °C, 2 h, 95%; (g) NaCN, NaI, DMSO, 110 °C, 30 min, 78%; (h) KOH, $HO(CH_2)_2OH$, H_2O, 100 °C, 3 h, 91%; (i) MeNHOMe·HCl, EDC, DMAP, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 0 °C, 4 d, 84%; (j) $Me_2C{=}CHMgBr$, THF, −20 °C to room temp, 2 h, 88%.

Commercially available 4-methylphenylacetic acid **9** was heated with thionyl chloride in benzene to give the corresponding acyl chloride **10**. Acylation of (*S*)-4-benzyl-2-oxazolidinone with **10** afforded crystalline **11**, which was methylated with methyl iodide and sodium hexamethyldisilazanide (NaHMDS) in THF at −78 °C to furnish gummy (*S*)-**12**. Judging from the ^1H NMR signals due to the newly generated methyl group at $\delta = 1.53$ (d, $J = 6.9$ Hz, 2.85H) and $\delta = 1.51$ (d, $J = 6.9$ Hz, 0.15H), the diastereomeric ratio of the products was about 95:5. The major isomer was assigned as (*S*)-**12** according to the established stereochemical outcome of the Evans alkylation.[17] Reduction of (*S*)-**12** with lithium aluminum hydride gave oily alcohol (*S*)-**13** in 53% yield based on **9** (four steps). The enantiomeric purity of (*S*)-**13** was determined as 89% ee by NMR analysis of the corresponding (*R*)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester) (*S*)-**14**.

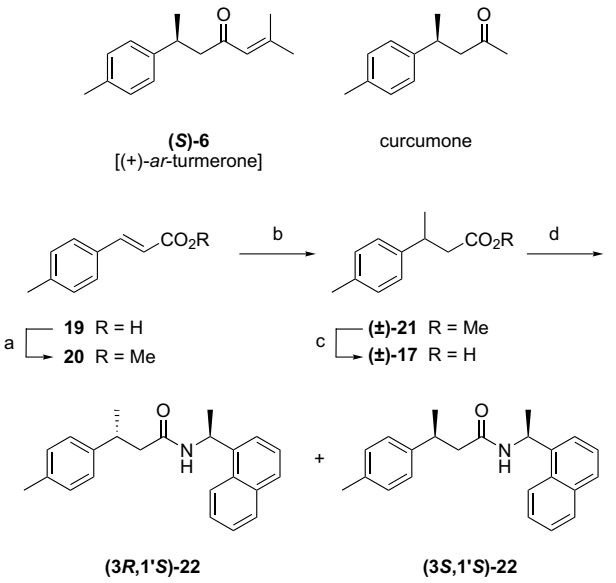
One-carbon chain-elongation of (*S*)-**13** was executed in a standard manner via nitrile (*R*)-**16**. Accordingly, (*S*)-**13** was treated with tosyl chloride in pyridine to furnish crystalline tosylate (*S*)-**15**. Sodium cyanide and a small amount of sodium iodide in DMSO converted (*S*)-**15** to oily nitrile (*R*)-**16**, which was hydrolyzed with potassium hydroxide in hot aqueous ethylene glycol to give (*R*)-**17**, the so-called Rupe's acid.[18] The yield of (*R*)-**17** as a semi-solid was 67% based on (*S*)-**13** (three steps). Purification of the semi-solid mass by silica gel chromatography followed by recrystallization from hexane gave crystalline **17** and oily **17** in a ratio of 45:55. The solid and oily samples of (*R*)-**17** were processed separately to the final product.

The next step was the conversion of acid (*R*)-**17** to Weinreb amide[19] (*R*)-**18** by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride and 1-ethyl-3-(3-*N*,*N*-dimethylaminopropyl)carbodiimide hydrochloride (EDC) in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and *N*-ethyldiisopropylamine. The resulting oily amide (*R*)-**18** was then treated with 2-methylpropenylmagnesium bromide in THF to give oily (*R*)-*ar*-turmerone **6** in 74% yield based on (*R*)-**17** (two steps). The IR, ^{1}H, and ^{13}C NMR spectra of (*R*)-**6** were identical with those reported previously for (*S*)-**6**.[16] The overall yield of (*R*)-**6** based on **4** was 26% (nine steps), while that of our previous synthesis of (*S*)-**6** was 25% (seven steps) based on ethyl (*R*)-3-hydroxybutanoate. It should be noted that crystalline (*R*)-**17** yielded (*R*)-**6** of 75% ee {determined by GC analysis on a chiral stationary phase; $[\alpha]_D^{24} = -47.0$ ($CHCl_3$)}, while oily (*R*)-**17** gave (*R*)-**6** of 98% ee {$[\alpha]_D^{22} = -60.6$ ($CHCl_3$); lit.[6] $[\alpha]_D^{25} = +66.4$ ($CHCl_3$) for (*S*)-**6**}.

2.2. Crystallization behavior of optically active 3-(4-methylphenyl)butanoic acid

Chemists tend to assume a crystalline sample to be purer than an oily sample. Contrary to that common belief, crystalline (*R*)-**17** gave (*R*)-*ar*-turmerone **6** with lower enantiomeric purity than (*R*)-**6** derived from oily (*R*)-**17**. The crystallization behavior of optically active 3-(4-methylphenyl)butanoic acid **17** was therefore examined in detail. The racemate and the (*S*)-isomer of this acid **17** were first reported in 1924 by Rupe and Wiederkehr.[18] They synthesized (±)-**17**, mp 91 °C, from *p*-methylacetophenone.[18] Scheme 2 shows the present and new synthesis of (±)-**17** as a reference sample. Commercially available 4-methylcinnamic acid **19** was methylated to give crystalline ester **20**. Conjugate addition of lithium dimethylcuprate to **20** gave oily ester (±)-**21** in 96% yield. Saponification of (±)-**21** afforded (±)-**17**, mp 87–88 °C. Rupe obtained (*S*)-**17** as crystals, mp 41–42 °C;[18] $[\alpha]_D = +45.0$ ($CHCl_3$),[20] by oxidation of curcumone isolated from curcuma oil.[18]

As already stated in Section 2.1, alkaline hydrolysis of (*R*)-**16** gave acid (*R*)-**17** in 91% yield, from which crystalline (*R*)-**17**, mp 65–75 °C {41% yield, $[\alpha]_D^{21} = -31.1$ ($CHCl_3$)}, and oily (*R*)-**17** {50% yield, $[\alpha]_D^{23} = -43.7$ ($CHCl_3$)} were obtained. Further fractionation of the solid and oily (*R*)-**17** revealed the following:



Scheme 2. Synthesis of (±)-3-(4-methylphenyl)butanoic acid **17** and its derivatization to amide **22**. Reagents and conditions: (a) K_2CO_3, MeI, DMF, 0–10 °C to room temp, quant.; (b) Me_2CuLi, Et_2O, −78 °C to room temp, 2 h, 96%; (c) KOH, $HO(CH_2)_2OH$, H_2O, reflux, 1 h, room temp, 3 d, 74%; (d) (i) $SOCl_2$, C_6H_6, reflux; (ii) (*S*)-1-(1-naphthylethyl)amine, C_6H_6, Et_2O.

(1) Recrystallization of the original crystalline crop of (*R*)-**17** (mp 65–75 °C) gave crystals with higher mp and lower enantiomeric excess. After three recrystallizations there was obtained a highest melting crop (mp 89–91 °C) with about 12% enantiomeric excess. (2) Crystals separated from the original mother liquor were enantiomerically pure; the low-melting one (mp 45–50 °C) was obtained first, followed by the higher melting ones with lower enantiomeric excesses. This therefore means that (*R*)-**17** and (±)-**17** make mixed crystals, and a mixture with about 75% ee more prone to separate. The fact that (*R*)-**17** and (±)-**17** make mixed crystals was first observed by Takeuchi et al. in 1994.[21] They obtained (*R*)-**17** in about 6% ee, mp 84.3–86.0 °C, $[\alpha]_D^{25} = -3.8$ (C_6H_6).[21]

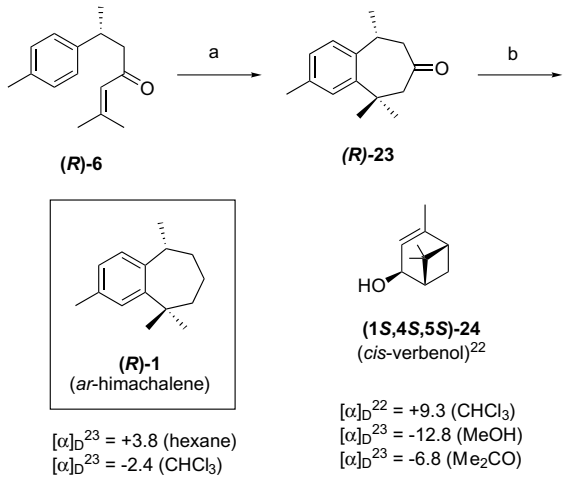
In order to determine the enantiomeric purity of the crystalline samples of (*R*)-**17**, some of them were derivatized to the corresponding (*S*)-1-(1-naphthyl)ethylamide **22**. Racemic acid (±)-**17** yielded a 1:1 mixture of two diastereomeric amides, (3*R*,1′*S*)- and (3*S*,1′*S*)-**22**. As reported previously, these two isomers of **22** could be distinguished from each other by 300 MHz ^{1}H NMR[13] and HPLC[16] comparisons. HPLC analysis of **22** derived from (*R*)-**17** with mp 45–50 °C and $[\alpha]_D^{20} = -45.2$ ($CHCl_3$) showed its enantiomeric purity to be 98% ee. Similarly, the enantiomeric purity of (*R*)-**17** with mp 65–75 °C and $[\alpha]_D^{21} = -31.1$ ($CHCl_3$) was determined to be 74% ee. Since the authentic (3*R*,1′*S*)-**22** was available from (*R*)-**17**, assignment of the absolute configuration to each of the diastereomers of **22** was possible. ^{1}H NMR analysis of the amide **22** prepared from a large plate-like crystal (mp 58–60 °C; size 2 × 10 mm) revealed the crystal to be heterogeneous with a purity of about 75% ee [= (*R*)-**17**/(*S*)-**17** (molar

ratio) = 7:1]. Accordingly, even a beautifully shaped crystal can be enantiomerically impure.

Such a phenomenon of anomalous crystallization is recorded in literatures.[22] The two enantiomers may form molecular combinations whose stoichiometry is not equal.[22] Chemists should not have excessive confidence on the purity of their crystalline samples. Nevertheless, chemists should not despise their traditional skill of recrystallization in view of recent trends among them to report crystalline samples of **17** without mentioning their mps.[12,23]

2.3. Synthesis of (*R*)-*ar*-himachalene and its specific rotation

As shown in Scheme 3, conversion of (*R*)-*ar*-turmerone **6** to (*R*)-*ar*-himachalene **1** was carried out according to Pandey and Dev.[6] Thus, (*R*)-**6** in carbon disulfide was treated with aluminum chloride (18 equiv) for 1 h at −40 to −20 °C, and then the mixture heated under reflux (46 °C) for 1 h. Chromatographic purification of the product gave oily ketone (*R*)-**23**, $[\alpha]_D^{22} = -52.7$ (*c* 0.85, $CHCl_3$) {lit.[6] $[\alpha]_D^{25} = +56.4$ (*c* 0.76, $CHCl_3$) for (*S*)-**23**}, in 40% yield and the recovered (*R*)-**6** in 40% yield. The initial low temperature was essential for the success of this cyclization step. Wolff–Kishner reduction of the ketone (*R*)-**23** afforded oily (*R*)-*ar*-himachalene **1** in 42% yield. The IR, ^1H, and ^{13}C NMR spectra of (*R*)-**1** were identical to those previously reported by us.[3] The above conversion was executed twice, first using (*R*)-**6** of 75% ee and then using (*R*)-**6** of 98% ee.



Scheme 3. Synthesis of (*R*)-*ar*-himachalene **1**. Reagents and conditions: (a) $AlCl_3$, CS_2, −40 to −20°C, 1 h, then reflux (46 °C), 4 h, 40%; (b) $N_2H_4{\cdot}H_2O$, KOH, diethylene glycol, 200–210 °C, 3 h, 42%.

The specific rotation of (*R*)-**1** prepared from (*R*)-**6** of 98% ee was first determined as a chloroform solution according to Pandey and Dev,[6] and it was $[\alpha]_D^{23} = -2.4$ (*c* 1.19, $CHCl_3$) {lit.[6] $[\alpha]_D^{27} = +5.9$ (*c* 1.35. $CHCl_3$) for (*S*)-**1**}. Accordingly, (*R*)-**1** was levorotatory in chloroform. Then the specific rotation of (*R*)-**1** was determined as a hexane solution according to Bartelt et al.[1] and Mori and co-workers.[3] The value was: $[\alpha]_D^{23} = +3.8$ (*c* 1.18, hexane). We reported it as $[\alpha]_D^{25} = +7.8$ (*c* 0.45, hexane),[3] while Bartelt's observation on **1** of the flea beetle origin was $[\alpha]_D$ <+10 (*c* 0.001, hexane).[1] He also prepared another enantiomer of **1**, antipodal to that produced by the flea beetle, from a terpene of Nordmann fir (*Abies nordmanniana*), and proved levorotatory in hexane, $[\alpha]_D = -2.2$ (*c* 0.4, hexane).[1] As to the enantiomeric purity of (*R*)-**1** [prepared from (*R*)-**6** of 98% ee], this was determined to be 97.7% ee by Bartelt's GC analysis using a CDX-B column.

It is now clear that (*R*)-*ar*-himachalene **1** is dextrorotatory in hexane, while levorotatory in chloroform. Indeed, this unique chiroptical behavior of (*R*)-**1** was the origin of the initial misassignment of the stereochemistry of the naturally occurring (*R*)-**1**. A similar example of different signs of specific rotations in different solvents had already been reported by Mori et al. in 1976, when they synthesized (1*S*,4*S*,5*S*)-*cis*-verbenol **24**.[24] Alcohol **24** is a pheromone component of *Ips* bark beetles. Prior to Mori's work some people called it (+)-*cis*-verbenol, while others referred to it as (−)-*cis*-verbenol. After its synthesis and measurements of specific rotations in different solvents, it became clear that **24** was dextrorotatory in acetone or methanol but levorotatory in chloroform. A different sign of specific rotation can be observed at different temperatures as reported by Mori and Uenishi.[25] It is therefore of utmost importance to use the same solvent as reported by others at a temperature similar to that described, when one compares the sign of the specific rotation of one's sample with previous data.

3. Conclusion

(*R*)-*ar*-Himachalene **1** (97.7% ee) was synthesized by using Evans asymmetric alkylation as the key step. The hydrocarbon (*R*)-**1** was dextrorotatory in hexane, while levorotatory in chloroform. The crystallization behavior of (*R*)-3-(4-methylphenyl)butanoic acid **17** (about 89–90% ee) has been studied. The acid **17** gave enantiomerically impure but well-shaped crystalline materials. Another approach to solve the present stereochemical problem on the absolute configuration of *ar*-himachalene of the flea beetle will be reported separately by Bartelt in due course.

4. Experimental

4.1. General

Melting points (Yanaco MP-S3) and boiling points are uncorrected values. Optical rotations were measured on a Jasco DIP-320 polarimeter. IR spectra were recorded on a Horiba FT-720 spectrometer. ^1H NMR spectra (300 MHz, TMS at $\delta = 0.00$ or $CHCl_3$ at $\delta = 7.26$ as internal standard) and ^{13}C NMR spectra (75 MHz, $CDCl_3$ at $\delta = 77.0$ as internal standard) were recorded on a Varian Mercury-300 spectrometer. Col-

umn chromatography was carried out on Merck Kieselgel 60 Art 1.07734.

4.2. (*S*)-4-Benzyl-3-(4-methylphenylacetyl)-2-oxazolidinone 11

Commercially available **9** (16.5 g, 110 mmol) was converted to the corresponding acyl chloride **10** (ca. 21 g, 110 mmol) by heating under reflux with excess $SOCl_2$ in C_6H_6. *n*-Butyllithium (1.5 M in hexane, 68 mL, 102 mmol) was added dropwise over 10 min to a stirred and cooled soln of (*S*)-4-benzyl-2-oxazolidinone (17.7 g, 100 mmol) in THF (300 mL) at −78 °C under Ar. To this was added **10** (ca. 21 g) in one portion through a syringe. The mixture was stirred at −78 °C for 30 min, and left to stand for 2 h at room temperature. The reaction was quenched by the addition of satd NH_4Cl aq soln (60 mL), and the mixture concentrated in vacuo to remove THF and hexane. The residue was extracted with Et_2O. The extract was washed with 1 M NaOH soln and brine, dried over $MgSO_4$, and concentrated in vacuo to give 23.8 g (79%) of **11** as crystals. Recrystallization from hexane gave prisms, mp 62–64 °C; $[\alpha]_D^{23} = +71.3$ (*c* 3.31, $CHCl_3$). ν_{max} (Nujol): 1780 (s, CO), 1690 (s, CO), 1615 (m); δ_H ($CDCl_3$): 2.35 (3H, s, $ArCH_3$), 2.75 (1H, dd, *J* 3.3, 13.5, PhCH), 3.22 (1H, dd, *J* 3.3, 13.5, PhCH), 4.15–4.28 (4H, m), 4.63 (1H, m, NCH), 7.10–7.35 (9H, m, ArH); δ_C ($CDCl_3$): 21.1, 37.8, 41.2, 55.4, 66.1, 127.3, 128.9, 129.30, 129.44, 129.75, 130.4, 135.2, 136.9, 153.4, 171.5. Anal. Calcd for $C_{19}H_{19}NO_3$ (309.4): C, 73.76; H, 6.19; N, 4.53. Found; C, 73.43; H, 6.21; N, 4.53.

4.3. (4*S*,2′*S*)-4-Benzyl-3-[(4-methylphenyl)-2-propanoyl]-2-oxazolidinone 12

A solution of NaHMDS (1.9 M in THF, 45 mL, 82.5 mmol) was added dropwise to a stirred and cooled solution of **11** (23.4 g, 75.7 mmol) in THF (300 mL) at −78 °C under Ar. After stirring for 1.2 h at −78 °C, a solution of MeI (53 g, 370 mmol) in THF (50 mL) was added dropwise to the stirred mixture at −78 °C. This was kept at −78 °C for 3 h, and then left to stand overnight at room temperature. The reaction was quenched by the addition of satd NH_4Cl aq soln, and the mixture concentrated in vacuo to remove THF and hexane. The residue was extracted with Et_2O. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed over SiO_2 (160 g) in hexane. Elution with hexane/EtOAc (10:1) gave 23.8 g (97%) of **12** as a viscous oil; $n_D^{28} = 1.5185$; $[\alpha]_D^{25} = +108$ (*c* 3.72, $CHCl_3$). ν_{max} (film): 1780 (s, CO), 1695 (s, CO), 1605 (w, Ar), 1375 (m), 1210 (m): δ_H ($CDCl_3$): 1.51 (0.15H, d, *J* 6.9, $CHCH_3$), 1.53 (2.85H, d, *J* 6.9, $CHCH_3$), 2.30 (3H, s, $ArCH_3$), 2.79 (1 H, dd, *J* 3.6, 13.5, PhCH), 3.31 (1H, d, *J* 13.5, PhCH), 3.90–4.18 (2H, m, OCH_2), 4.55 (1H, t, *J* 1.5, NCH), 5.09 (1H, q, *J* 6.9, $PhCHCH_3$), 7.10–7.35 (9H, m, ArH); δ_C ($CDCl_3$): 19.4, 20.9, 37.8, 42.6, 55.6, 65.7, 127.2, 127.9, 128.9, 129.2, 129.3, 135.3, 136.7, 137.2, 152.8, 174.6. Anal. Calcd for $C_{20}H_{21}NO_3$ (323.4): C, 74.28; H, 6.55; N, 4.33. Found: C, 73.51; H, 6.61; N, 4.03.

4.4. (*S*)-2-(4-Methylphenyl)-1-propanol 13

A solution of **12** (23.8 g, 74 mmol) in THF (50 mL) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (6.5 g, 171 mmol) in Et_2O (100 mL) at 0–5 °C. The mixture was stirred for 2 days at room temperature. Water was then added dropwise to the mixture to remove the excess $LiAlH_4$. Subsequently, dil HCl and ice were added, and the mixture was extracted with Et_2O. The extract was washed with water, $NaHCO_3$ aq soln, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was distilled to give 7.6 g (69%) of (*S*)-**13** as a colorless oil, bp 94–95 °C/3 Torr; $n_D^{28} = 1.5066$; $[\alpha]_D^{24} = -14.6$ (*c* 3.11, $CHCl_3$). ν_{max} (film): 3370 (s, OH), 1650 (w, Ar), 1035 (s, C–O), 1020 (s, C–O), 815 (s); δ_H ($CDCl_3$): 1.25 (3H, d, *J* 7.2, $CHCH_3$), 1.30 (1H, br s, OH), 2.32 (3H, s, $ArCH_3$), 2.90 (1H, q, *J* 7.2, $CHCH_3$), 3.66 (2H, d, *J* 6.6, CH_2O), 7.12 (4H, s, ArH); δ_C ($CDCl_3$): 17.6, 21.0, 42.0, 68.7, 127.3, 129.3, 136.2, 140.4. Anal. Calcd for $C_{10}H_{14}O$ (150.2): C, 79.95; H, 9.39. Found C, 78.72; H, 9.33. This alcohol **13** was volatile, and did not give correct combustion analytical data. HRMS calcd for $C_{10}H_{14}O$ (M^+) 150.1045, found 150.1047. The enantiomeric purity of (*S*)-**13** was determined as 89% ee by 500 MHz ^1H NMR analysis of the corresponding (*S*)-**14** derived from (*S*)-**13** and (*S*)-MTPACl. δ_H ($CDCl_3$, 500 MHz): 3.42 (2.83H, OMe), 3.44 (0.17H, OMe).

4.5. (*S*)-2-(4-Methylphenyl)propyl *p*-toluenesulfonate 15

TsCl (10.4 g, 55 mmol) and DMAP (10 mg) were added to a stirred and ice-cooled soln of **13** (6.3 g, 42 mmol) in pyridine (35 mL). The mixture was stirred for 2 h at 0–5 °C, poured into ice and dil HCl, and extracted with Et_2O. The extract was washed with water, satd $NaHCO_3$ soln, and brine, dried over $MgSO_4$, and concentrated in vacuo to give 12.2 g (95%) of **15** as a solid. Recrystallization from EtOAc/pentane gave prisms, mp 59–60 °C; $[\alpha]_D^{23} = +8.3$ (*c* 3.38, $CHCl_3$). ν_{max} (Nujol): 1660 (w, Ar), 1595 (w, Ar), 1175 (s), 970 (s); δ_H ($CDCl_3$): 1.25 (3H, d, *J* 6.9, $CHCH_3$), 1.57 (1H, s, OH), 2.31 (3H, s, $ArCH_3$), 2.43 (3H, s, $SO_2C_6H_4CH_3$), 3.04 (1H, dq, *J* 6.9, 11, $CHCH_3$), 4.02 (2H, m, CH_2O), 6.99 (2H, d, *J* 5.4, ArH). 7.09 (2H, d, *J* 5.4, ArH), 7.27 (2H, d, *J* 9.8, ArH), 7.67 (2H, d, *J* 9.0, ArH); δ_C ($CDCl_3$): 17.6, 21.0, 21.6, 38.7, 75.0, 127.1, 127.8, 129.2, 129.7, 133.0, 136.6, 138.5, 144.5. Anal. Calcd for $C_{17}H_{20}SO_3$ (304.4): C, 67.07; H, 6.62. Found C, 67.23; H, 6.49.

4.6. (*R*)-3-(4-Methylphenyl)butanenitrile 16

NaCN (6.0 g, 122 mmol) and NaI (1.0 g, 6.7 mmol) were added to a stirred solution of **15** (14.9 g, 49 mmol) in DMSO (40 mL). The stirred mixture was heated at 110 °C for 30 min. After cooling, it was poured into ice-water, and extracted with hexane. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed over SiO_2 (50 g) in hexane. Elution with hexane gave 2-(4-methylphenyl)propene (0.5 g). Further elution with hexane/EtOAc (20:1) gave **16** as an oil. Distillation afforded 6.1 g (78%) of pure **16**, bp 113–114 °C/3 Torr;

$n_D^{25} = 1.5088$; $[\alpha]_D^{23} = +4.1$ (*c* 3.11, hexane). ν_{max} (film): 2245 (m, CN), 820 (s); δ_H ($CDCl_3$): 1.43 (3H, d, *J* 6.9, $CHCH_3$), 2.33 (3H, s, $ArCH_3$), 2.45–2.62 (2H, m, CH_2CN), 3.12 (1H, dq, *J* 6.9, 11.4, $CHCH_3$), 7.15 (4H, m, ArH); δ_C ($CDCl_3$): 20.7, 21.0, 26.4, 36.1, 118.6, 126.4, 129.5, 136.9, 140.1. Anal. Calcd for $C_{11}H_{13}N$ (159.2): C, 82.97; H, 8.23; N, 8.80. Found C, 82.38; H, 8.14; N, 8.63.

4.7. (*R*)-3-(4-Methylphenyl)butanoic acid 17

A solution of KOH (85%, 5 g, 76 mmol) in water (5 mL) was added to a stirred solution of **16** (5.0 g, 31.4 mmol) in ethylene glycol (20 mL). The mixture was stirred and heated at reflux for 3 h, cooled, diluted with water, and extracted with hexane to remove neutral impurities. The aq layer was acidified with dil HCl, and extracted with Et_2O. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give 5.6 g (quant.) of crude **17** as an oil. This was chromatographed over SiO_2 (25 g) in hexane. Elution with hexane/EtOAc (4:1) gave **17** (2.3 g, 41%) as rhombs (from pentane), mp 65–75 °C; $[\alpha]_D^{24} = -31.1$ (*c* 3.10, $CHCl_3$). ν_{max} (Nujol): 2800 (m, CO_2H), 1710 (s, CO), 960 (m, CO_2H), 815 (m); δ_H ($CDCl_3$): 1.30 (3H, d, *J* 7.2, $CHCH_3$), 2.32 (3H, s, $ArCH_3$), 2.60 (2H, dq, *J* 7.2, 14, CH_2CO_2H), 3.23 (1H, dq, *J* 7.2, 14, $CHCH_3$), 7.11 (4H, s, ArH), 7.25 (1H, s, CO_2H); δ_C ($CDCl_3$): 21.0, 21.9, 35.8, 42.6, 126.6, 129.2, 136.0, 142.4, 178.2. Anal. Calcd for $C_{11}H_{14}O_2$ (178.2): C, 74.13; H, 7.92. Found C, 73.87; H, 7.83. The mother liquor was concentrated to give a further amount of **17** (2.8 g, 50%) as an oil, $[\alpha]_D^{23} = -43.7$ (*c* 3.61, $CHCl_3$). Crystalline (*R*)-**17** was then recrystallized from hexane repeatedly. Properties of the harvested crystalline crops are listed in Table 1. On the other hand, oily (*R*)-**17** was left to stand at room temperature (22–24 °C) to cause crystallization. The separated crystals were then collected, and the mother liquor again left to stand at room temperature to wait crystallization. The properties of the separated crystals are also listed in Table 1. The final mother liquor solidified after standing to give rods, mp 34–36 °C.

4.8. (*R*)-*N*-Methyl-*N*-methoxy-3-(4-methylphenyl)-butanamide 18

To a stirred and ice-cooled solution of **17** (2.5 g, 14 mmol) in CH_2Cl_2 (50 mL) were added MeNH(OMe)·HCl (1.8 g, 18 mmol), $(i\text{-Pr})_2NEt$ (3.3 mL), EDC (3.0 g, 16 mmol), and DMAP (3 mg). The mixture was left to stand in a refrigerator for 4 days. It was then poured into water, and extracted with CH_2Cl_2. The extract was washed with dil HCl, water, and satd $NaHCO_3$ aq solution, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed over SiO_2 (25 g) in hexane. Elution with hexane/EtOAc (4:1) gave 2.9 g (84%) of **18** as an oil, $n_D^{25} = 1.5086$; $[\alpha]_D^{28} = +6.4$ (*c* 3.6, hexane; from crystalline **17**) or $[\alpha]_D^{28} = +8.6$ (*c* 3.37, hexane; from oily **17**). ν_{max} (film): 1665 (s, CO), 1000 (s), 815 (s); δ_H ($CDCl_3$): 1.29 (3H, d, *J* 6.9, $CHCH_3$), 2.31 (3H, s, $ArCH_3$), 2.58–2.75 (2H, m, CH_2CO), 3.13 (3H, s, NCH_3), 3.30–3.40 (1H, m, $CHCH_3$), 3.58 (3H, s, OCH_3), 7.05–7.20 (4H, m, ArH); δ_C ($CDCl_3$): 20.87, 20.88, 21.7, 35.3, 40.3, 61.0, 126.6, 129.0, 135.5, 143.4, 177.0. Anal. Calcd for $C_{13}H_{19}NO_2$ (221.3): C, 70.55; H, 8.65; N, 6.33. Found C, 69.91; H, 8.63; N, 6.22.

4.9. (*R*)-2-Methyl-6-(4-methylphenyl)-2-hepten-4-one (*ar*-turmerone) 6

A Grignard reagent was prepared from 1-bromo-2-methylpropene (6.75 g, 50 mmol), Mg (1.3 g, 54 mmol), and THF (25 mL) by stirring and heating at reflux under Ar in the presence of a small piece (5 mg) of iodine. This

Table 1. Mps, $[\alpha]_D$ values (as $CHCl_3$ solutions), and enantiomeric purities of (*R*)-3-(4-methylphenyl)butanoic acid **17** obtained by fractional crystallization of crystalline (*R*)-**17** and its mother liquor

	Recrystallization of crystalline (*R*)-**17**[a]			
	Original crop	Recrystallization		
		Once	Twice	Three times[b]
Shape	Rhombs	Prisms	Prisms	Rhombs
Mp (°C)	65–75	82–87	82–84	89–91
$[\alpha]_D^{20-26}$ (*c*)	−31.1 (3.10)	−21.5 (3.30)	−10.3 (3.40)	−5.3 (3.23)
Ee (%)	75,[d] 74,[e] 69[f]	48[f]	23[f]	12[f]
	Crystals separated from the mother liquor			
	Original oil	Separated crystals		
		First crop[c]	Second crop	Third crop
Shape	—	Rods	Plates	Prisms
Mp (°C)	—	45–50	57–58	60–65
$[\alpha]_D^{20-26}$ (*c*)	−43.7 (3.61)	−45.2 (3.10)	−41.5 (3.82)	−33.2 (1.96)
Ee (%)	98,[d] 97[f]	98,[e] 100[g]	92[f]	73[f]

[a] Recrystallized from hexane.
[b] (±)-**17**: mp 91 °C.[18]
[c] (*S*)-(+)-**17**: mp 41–42 °C.[18] $[\alpha]_D$ = +45.0 (*c* 6.5, $CHCl_3$).[20]
[d] Based on the ee of the derived (*R*)-**6**.
[e] Based on the HPLC analysis of the derived **22**.
[f] Calculated on the basis of the $[\alpha]_D$ value of pure (*R*)-**17** as −45.2.
[g] Thought to be ca. 100% based on the $[\alpha]_D$ value (+45.0) of (*S*)-**17** derived from the naturally occurring curcumone.[20]

Grignard reagent was added dropwise through a syringe to a stirred and cooled solution of **18** (2.6 g, 12 mmol) in THF (20 mL) at −20 °C under Ar. Stirring was continued for 2 h at room temperature, the mixture then poured into ice and dil HCl, and extracted with hexane. The extract was washed with water, satd $NaHCO_3$ aq soln, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed over SiO_2 (30 g) in hexane. Elution with hexane/EtOAc (20:1) gave 2.2 g (88%) of **6** as an oil, $n_D^{26} = 1.5172$; $[\alpha]_D^{24} = -50.6$ (*c* 3.47, hexane; from crystalline **17**); $[\alpha]_D^{23} = -47.0$ (*c* 3.34, $CHCl_3$; from crystalline **17**); $[\alpha]_D^{22} = -60.6$ (*c* 3.16, $CHCl_3$; from oily **17**). ν_{max} (film): 1685 (s, CO), 1620 (s, C=C), 1515 (m), 815 (m); δ_H ($CDCl_3$): 1.24 (3H, d, *J* 6.9, CHC*H*$_3$), 1.85 (3H, d, *J* 1.2, C=CC*H*$_3$), 2.11 (3H, d, *J* 0.3, C=CC*H*$_3$), 2.31 (3H, s, ArC*H*$_3$), 2.61 (1H, dd, *J* 8, 17, CHC*H*H), 2.71 (1H, dd, *J* 6, 17, CHC*H*H), 3.29 (1H, m, C*H*CH$_3$), 6.02 (1H, s, C=CH), 7.10 (4H, s, ArH); δ_C ($CDCl_3$): 20.7, 20.9, 21.9, 27.6, 35.2, 52.6, 124.0, 126.6, 129.1, 135.5, 143.6, 155.1, 199.8. Anal. Calcd for $C_{15}H_{20}O$ (216.3): C, 83.28; H, 9.32. Found C, 82.87; H, 9.23. HRMS calcd for $C_{15}H_{20}O$ (M^+) 216.1514, found 216.1516.

The enantiomeric purity of (*R*)-**6** was determined as 98% ee [from oily (*R*)-**17**] or 75% ee [from crystalline (*R*)-**17**] by Dr. S. Tamogami employing chiral GC technique. GC: Column, Chiramix,[26] 30 m × 0.25 mm; Column temp 40–180 °C (+0.5 °C/min); Carrier gas, N_2, 0.7 mL/min: t_R 238.9 min [(*R*)-**6**], 239.4 min [(*S*)-**6**] or 239.6 min [(*R*)-**6**], 240.2 min [(*S*)-**6**].

4.10. Methyl 4-methylcinnamate 20

K_2CO_3 (9.2 g, 66.7 mmol) was added portionwise to a stirred and ice-cooled solution of **19** (5.4 g, 33.3 mmol) in DMF (40 mL) at 0–10 °C. MeI (10 g, 70 mmol) was then added to the mixture, and stirring continued for 3 days at room temperature. The mixture was poured into ice-water, and extracted with hexane. The hexane extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give 6.0 g (quant.) of **20** as prisms, mp 52–53 °C. ν_{max} (Nujol): 1710 (s, CO), 1630 (s, C=C), 1320 (s), 1170 (s), 1000 (m), 820 (s); δ_H ($CDCl_3$): 2.38 (3H, s, ArC*H*$_3$), 3.80 (3H, s, CO$_2$C*H*$_3$), 6.38 (1H, d, *J* 16, C=CH), 7.20 (2H, d, *J* 6, ArH), 7.43 (2H, d, *J* 6, ArH), 7.68 (1H, d, *J* 16, C=CH). Anal. Calcd for $C_{11}H_{12}O_2$ (176.2): C, 74.97; H, 6.86. Found C, 74.86; H, 6.84.

4.11. Methyl (±)-3-(4-methylphenyl)butanoate 21

A solution of MeLi in Et_2O (2.1 M, 45 mL, 94 mmol) was added dropwise over 30 min to a stirred and cooled suspension of CuI (8.6 g, 45 mmol) in Et_2O (100 mL) at −78 °C under Ar. To the resulting homogeneous solution of Me_2CuLi was added dropwise a solution of **20** (6.0 g, 34 mmol) in Et_2O (50 mL) with stirring and cooling at −78 °C. The mixture turned dark red and then yellow. This was stirred for 1 h at −78 to −40 °C, and then warmed to room temperature over 1 h. The mixture was poured into ice and satd NH_4Cl aq solution, and extracted with Et_2O. The extract was washed with water, satd $NaHCO_3$ aq solution, and brine, dried over $MgSO_4$, and concentrated in vacuo to give 6.3 g (96%) of **21** as an oil, $n_D^{25} = 1.5083$. ν_{max} (film): 1740 (s, CO), 1630 (w, Ar), 1165 (s), 820 (m); δ_H ($CDCl_3$): 1.27 (3H, d, *J* 6.9, CHC*H*$_3$), 2.30 (3H, s, ArC*H*$_3$), 2.55 (1H, dd, *J* 9, 16, CHCO), 2.58 (1H, dd, *J* 8, 16, CHCO), 3.26 (1H, m, C*H*CH$_3$), 3.60 (3H, s, CO$_2$C*H*$_3$), 7.10 (4H, s, ArH); δ_C ($CDCl_3$): 20.9, 21.8, 35.9, 42.7, 51.4, 126.5, 129.1, 135.8, 142.6, 172.8. HRMS calcd for $C_{12}H_{16}O_2$ (M^+) 192.1150, found 192.1151.

4.12. (±)-3-(4-Methylphenyl)butanoic acid 17

To a stirred solution of **21** (6.2 g, 32.3 mmol) in ethylene glycol (20 mL) was added a solution of KOH (85%, 5.0 g, 76 mmol) in water (10 mL). The mixture was stirred and heated under reflux for 1 h, and left to stand at room temperature for 3 days. This was then diluted with water, and extracted with hexane to remove neutral impurities. The aq layer was acidified with dil HCl, and extracted with Et_2O. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give 4.2 g (74%) of crystalline (±)-**17**. Three recrystallizations from EtOAc/hexane yielded 3.8 g of prisms, mp 87–88 °C. Its IR spectrum was almost indistinguishable from that of (−)-**17**, and its ^1H NMR spectrum was identical to that of (−)-**17**. Anal. Calcd for $C_{11}H_{14}O_2$ (178.2): C, 74.13; H, 7.92. Found C, 74.17; H, 7.75.

4.13. (3*R*,1′*S*)-(1′-Naphthylethyl)-3-(4-methylphenyl)-butanamide 22

A small amount (10–100 mg) of almost pure and oily (*R*)-**17**, $[\alpha]_D^{23} = -43.7$ (*c* 3.61, $CHCl_3$), crystalline but impure (*R*)-**17**, $[\alpha]_D^{24} = -31.1$ (*c* 3.10, $CHCl_3$), or (±)-**17**, respectively, was stirred and heated under reflux for 1 h in a solution of $SOCl_2$ in C_6H_6. The mixture was concentrated in vacuo, and the residual acyl chloride was dissolved in C_6H_6. To the resulting solution was added a solution of (*S*)-(−)-1-(1-naphthyl)ethylamine (2.5 equiv) in Et_2O with stirring and ice-cooling. After stirring for 1 h at 0–5 °C, the mixture was diluted with ether, washed with dil HCl, water, and brine, and dried over $MgSO_4$. The filtered solution was concentrated in vacuo, and the residual solid was analyzed by HPLC and ^1H NMR. HPLC: Column, Pegasil Senshu, 25 cm × 4.6 mm; eluent, hexane/THF = 6:1; flow rate, 1 mL/min; UV detection at 254 nm: t_R 21.6 min [(3*R*,1′*S*)-**22**]. 33.0 min [(3*S*,1′*S*)-**22**]. The enantiomeric purity of the almost pure (*R*)-**17** was 96% ee and that of impure (*R*)-**17** was 74% ee. δ_H ($CDCl_3$): 1.24 (3H, d, *J* 6.9, CH$_2$CHC*H*$_3$), 1.44 (3H, d, *J* 6.9, HNCHC*H*$_3$) for (3*R*,1′*S*)-**22**; 1.21 (3H, d, *J* 6.6, CH$_2$CHC*H*$_3$), 1.53 (3H, d, *J* 6.9, HNCHC*H*$_3$) for (3*S*,1′*S*)-**22**. These two 3H doublets could be employed for the determination of ee of **17**. Recrystallization of (3*R*,1′*S*)-**22** from EtOAc/hexane gave needles, mp 136–137 °C; $[\alpha]_D^{25} = -26.5$ (*c* 1.16, $CHCl_3$). ν_{max} (Nujol): 3290 (m, NH), 3245 (m, NH), 1630 (s, CONH, amide I), 1555 (s, CONH, amide II), 1455 (m), 780 (m); δ_H ($CDCl_3$): 1.24 (3H, d, *J* 6.9, CH$_2$CHC*H*$_3$), 1.44 (3H, d, *J* 6.6, HNCHC*H*$_3$), 2.31 (3H, s, ArC*H*$_3$), 2.37 (2H, d, *J* 7.5,

$COCH_2$), 3.26 (1H, m, CH_2CHCH_3), 5.42 (1H, d, *J* 8.1, NH), 5.83 (1H, m, $HNCHCH_3$), 7.07–8.06 (11H, m, ArH); δ_C ($CDCl_3$): 20.3, 21.0, 21.8, 36.7, 44.4, 46.0, 122.5, 123.5, 125.1, 125.8, 126.5, 126.7, 128.3, 128.7, 129.2, 131.0, 133.8, 135.9, 138.1, 142.7, 170.5. Anal. Calcd for $C_{23}H_{22}NO$ (331.5): C, 83.34; H, 7.60; N, 4.23. Found C, 83.25; H, 7.62; N, 4.19.

4.14. (*R*)-1,2,5,8-Tetramethyl-1,2,3,4,5-pentahydrobenzo[*a*][7]annulen-3-one 23

To a stirred and cooled solution of (*R*)-**6** (1.0 g, 4.6 mmol) in CS_2 (15 mL) was added powdered $AlCl_3$ (1.1 g, 83 mmol) portionwise over 1 h at −40 to −20 °C under Ar. The mixture was then stirred and heated under reflux (46 °C = bp of CS_2) for 1 h. After cooling, the mixture was poured into ice and dil HCl, and extracted with hexane. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed over SiO_2 (30 g) in hexane. Elution with hexane/EtOAc (20:1) first gave the recovered (*R*)-**6** (0.4 g, 40%), and then the desired **23** (0.4 g, 40%) as a colorless oil, $n_D^{26} = 1.5174$; $[\alpha]_D^{22} = -52.7$ (*c* 0.85, $CHCl_3$). ν_{max} (film): 1710 (s, CO), 1305 (m), 815 (m); δ_H ($CDCl_3$): 1.41 (3H, s, CH_3): 1.44 (3H, d, *J* 6.9, $CHCH_3$), 1.49 (3H, s, CH_3), 2.31 (3H, s, $ArCH_3$), 2.32 (1H, dd, *J* 11, 13, CH*H*), 2.51 (1H, d, *J* 12, CH*H*), 2.67 (1H, dd, *J* 3, 13, CH*H*), 3.26 (1H, d, *J* 12, CH*H*), 3.61 (1H, m, $CHCH_3$), 7.01 (1H, dd, *J* 1, 8, ArH), 7.14 (1H, d, *J* 8, ArH), 7.21 (1H, d, *J* 1, ArH); δ_C ($CDCl_3$): 20.6, 21.0, 32.3, 33.0, 33.5, 38.7, 52.6, 53.9, 126.3, 127.2, 128.7, 136.0, 138.9, 145.3, 211.0. Anal. Calcd for $C_{15}H_{20}O$ (213.3): C, 83.28; H, 9.32. Found C, 83.13, H, 9.39.

4.15. (*R*)-1,1,5,8-Tetramethyl-1,2,3,4,5-pentahydrobenzo[*a*][7]annulene (*ar*-himachalene) 1

A solution of KOH (2.0 g) in water (2 mL) and $N_2H_4{\cdot}H_2O$ (2 mL) were added to a solution of (*R*)-**23**, (390 mg, 1.9 mmol) in diethylene glycol (20 mL). The mixture was stirred and heated under reflux for 1 h, and then heated at 200–210 °C for 3 h with removal of the volatile materials. After cooling, the mixture was diluted with water and extracted with hexane. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed over SiO_2 (5 g) in hexane. Elution with hexane gave 154 mg (42%) of (*R*)-**1** as a colorless oil, $n_D^{26} = 1.5068$; $[\alpha]_D^{23} = -2.4$ (*c* 1.19, $CHCl_3$); $[\alpha]_D^{23} = +3.8$ (*c* 1.18, hexane). ν_{max} (film): 1610 (w, Ar), 810 (s); δ_H ($CDCl_3$): 1.33 (3H, s, CH_3), 1.34 (3H, d, *J* 6.9, $CHCH_3$), 1.42 (3H, s, CH_3), 1.45–1.60 (1H, m, CH*H*), 1.60–1.69 (1H, m, CH*H*), 1.70–1.86 (4H, m, CH_2), 2.31 (3H, s, $ArCH_3$), 3.25 (1H, m, $CHCH_3$), 6.99 (1H, dd, *J* 1, 8, ArH), 7.12 (1H, d, *J* 8, ArH), 7.19 (1H, d, *J* 1.5, ArH); δ_C ($CDCl_3$): 21.0, 21.2, 24.0, 29.7, 33.9, 34.4, 36.5, 39.5, 41.1, 125.4, 126.5, 127.5, 134.9, 141.2, 147.7. Anal. Calcd for $C_{15}H_{22}$ (202.3): C, 89.04; H, 10.96. Found C, 88.65; H, 11.07. The enantiomeric purity of (*R*)-**1** was determined as 97.7% ee by Dr. Bartelt employing chiral GC technique. GC: Column, CDX-B at 120 °C; t_R 40.63 min [(*S*)-**1**, 1.1%], 41.18 min [(*R*)-**1**, 98.8%].

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