

Optical Resolution of Acyclic α -Hydroxy Ketone Derivatives by Inclusion Complexation

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A new method for the preparation of optically active acyclic α -hydroxy ketone derivatives by thermodynamic resolution using a chiral host compound is described. We examined the resolution of racemic 2-benzyloxy-3-pentanone with chiral host compounds in various solvents. After optimization of the reaction conditions, it has become apparent that the optical resolution could occur only under certain strict conditions about solvents, host compounds, and the concentration of the substrate. Stirring the suspension of the ketone with (–)-TADDOL bearing a cyclohexyl ring, derived from ethyl L-tartrate, in MeOH–H₂O (1:1) at room temperature produces the inclusion complex with high enantioselectivity to give (*S*)-ketone with up to 99% ee. On the other hand, the ee of (*R*)-ketone obtained from the filtrate could be improved by the same procedure using (+)-TADDOL; finally, both enantiomers of the ketone as an almost optically pure form were afforded. Analysis of the formed complex by ESI-TOFMS supposed that the host–guest ratio would be 1:1. This resolution procedure was also applied to other substrates to afford the corresponding optically active ketones.

Optically active acyclic α -substituted ketones are very important synthons in organic synthesis. Naturally occurring α -hydroxy and amino acids are important chiral sources for such classes of compounds, but are hardly sufficient to supply a variety of compounds. In previous papers, we reported on enzyme-mediated kinetic resolution via the hydrolysis of enol esters as masked ketones.¹ Although the reaction directly gives optically active acyclic α -substituted ketones, it does not always satisfactory work in terms of moderate enantioselectivity and a difficulty of regioselective preparation of the enol form as the substrate.

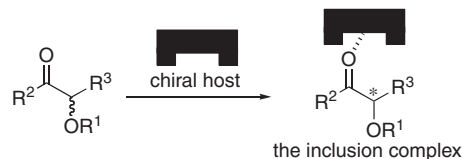
On the other hand, the thermodynamic resolution through the formation of inclusion complexes with chiral host compounds has been studied as an attractive approach to obtaining optically active compounds.^{2–4} In particular, separations have been accomplished with compounds bearing amino and hydroxy groups, which can readily undergo hydrogen bonding with host compounds. Recently, a few studies of the optical resolution of α -substituted cycloalkanones have been reported,^{5,6} and thus we have noticed that the method can be potentially useful for the preparation of optically active acyclic ketones, although the stereocontrol of the acyclic compounds should be more difficult than that of the cyclic ones.

We now report on a useful procedure for the preparation of optically active acyclic ketones with an α -substitution by optical resolution using the inclusion complexation methodology (Scheme 1).

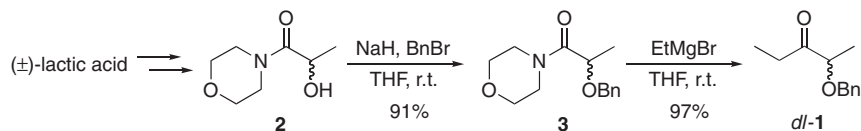
Results and Discussion

A racemic 2-benzyloxy-3-pentanone (*dl*-**1**) was chosen as the representative guest substrate, which was easily prepared from racemic lactic acid, as shown in Scheme 2.

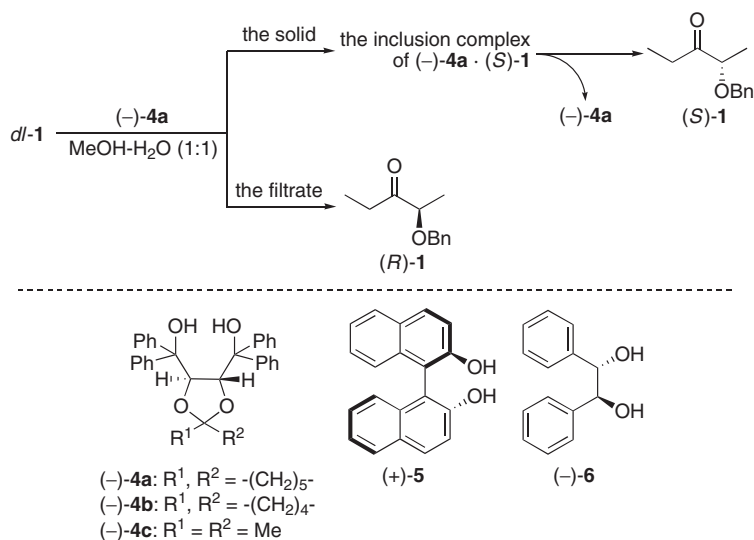
We first examined the resolution of *dl*-**1** with a (–)-TADDOL derivative bearing a cyclohexyl ring ((4*R*,5*R*)-(–)-2,2-pentamethylene- α,α,α' , α' -tetraphenyl-1,3-dioxolan-4,5-dimethanol, (–)-**4a**),⁷ derived from ethyl L-tartrate, as a typical chiral host compound for inclusion complexation (Scheme 3). After a suspension of *dl*-**1** (ca. 100 mg; sub. conc., 50 mM) and (–)-**4a** in a solvent (10 mL) was stirred for 72 h at room temperature, the solid was filtered. Then, after dissolving the solid into AcOEt, the host and guest were separated by column chromatography on silica gel. The results are summarized in Table 1. While **1** was not obtained from the solid in the cases of the reactions using hydrophobic (hexane, entry 1; cyclohexane, entry 2), and hydrophilic (MeOH, entry 3) organic solvents, the complexation of **1** with (–)-**4a** occurred in an aque-



Scheme 1.



Scheme 2.



Scheme 3.

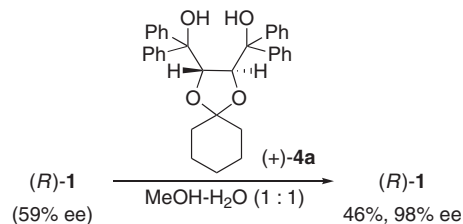
Table 1. Optical Resolution of α -Hydroxy Ketone Derivative $dl\text{-}1$ with $(-)\text{-}4a$ ^{a)}

Entry	Solvent	$(R)\text{-}1$ from the filtrate		$(S)\text{-}1$ from the solid	
		Yield/%	Ee/%	Yield/%	Ee/%
1	Hexane	98	0	0	—
2	Cyclohexane	92	0	0	—
3	MeOH	97	0	0	—
4	H ₂ O	16	29	79	6
5	MeOH–H ₂ O ^{b)}	68	38	26	97
6 ^{c)}	MeOH–H ₂ O ^{b)}	73	29	18	94
7	MeOH–H ₂ O ^{b,d)}	54	59	34	99

a) Unless otherwise specified, $dl\text{-}1$ (ca. 100 mg) was mixed with $(-)\text{-}4a$ (1 equiv.) in a solvent (10 mL) for 72 h at room temperature. b) MeOH/H₂O = 1/1. c) Using 2 equiv. of $(-)\text{-}4a$. d) Using 5 mL of the mixed solvent.

ous suspension (entry 4). However, the ee of **1** recovered in 79% yield from the solid was very low (6% ee, (S) -form). To our surprise, the highly enantioselective resolution proceeded only in a 1:1 mixed solvent of MeOH and H₂O (entries 5–7). After optimization of the reaction conditions, the reaction of $dl\text{-}1$ (ca. 100 mg; sub. conc., 100 mM) with 1 equiv. of $(-)\text{-}4a$ in MeOH–H₂O (1:1, 5 mL) (entry 7) afforded almost optically pure $(S)\text{-}1$ (34%, 99% ee) from the solid. The ee of $(S)\text{-}1$ was determined by an HPLC analysis of the compound with CHIRALCEL OJ (Daicel Chemical Industries, Ltd). The absolute configuration was confirmed by comparing the obtained optical rotation value of **1** ($[\alpha]_D^{22} = -45.0$ (c 0.98, CHCl₃)) with the reported one; lit.,^{1b} $[\alpha]_D^{24} = -45.9$ (c 1.16, CHCl₃), (S) -form. On the other hand, $(R)\text{-}1$ was reasonably obtained from the filtrate with a moderate ee (54%, 59% ee), $[\alpha]_D^{22} = +25.1$ (c 1.07, CHCl₃). It is noteworthy that the complexation of **1** did not occur in examinations using not only $(R)\text{-}(+)\text{-}1,1'\text{-bi-2-naphthol}$ (**5**) and $(S,S)\text{-}(+)\text{-hydrobenzoin}$ (**6**), but also the other TADDOL derivatives ($(-)\text{-}4b$ and $(-)\text{-}4c$) as chiral host compounds under the same conditions. In all cases, the chiral host was quantitatively recovered.

If the enantioselective resolution proceeded thermodynamically, repeating the reaction for obtaining $(R)\text{-}1$ with the $(+)\text{-}$ antipode **4a** derived from ethyl D-tartrate instead of $(-)\text{-}4a$



Scheme 4.

should improve the ee of $(R)\text{-}1$. We then examined the resolution of $(R)\text{-}1$ (59% ee) with $(+)\text{-}4a$ (Scheme 4). As expected, the sequential experiment delivered $(R)\text{-}1$ with 98% ee ($[\alpha]_D^{25} = +40.9$ (c 0.92, CHCl₃)) in 46% yield from the solid, although the uncomplexed **1** with 28% ee ((R) -form) was also recovered in 31% yield.

In order to study the relationship of $(S)\text{-}1$ and $(-)\text{-}4a$, the collected solid after the reaction was analyzed employing ESI-TOFMS. As a result, we detected the peak of $[1 + 4a + \text{Na}]^+$ ion (m/z , 721.34928; 721.35051 calcd for C₄₆H₅₀O₆Na) as well as the peaks of $[4a + \text{Na}]^+$ and $[4a + 4a + \text{Na}]^+$ (Fig. 1). Thus, we suppose that the ratio of $(-)\text{-}4a$ to $(S)\text{-}1$ of the inclusion complex would be 1:1, although there is no

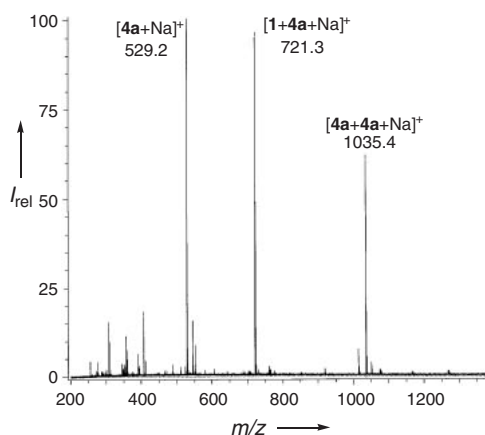
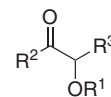


Fig. 1.



- 7: R¹ = Benzyloxymethyl (BOM), R² = Et, R³ = Me
 8: R¹ = *p*-Methoxybenzyl (MPM), R² = Et, R³ = Me
 9: R¹ = Bn, R² = Me, R³ = Me
 10: R¹ = Bn, R² = *n*-Pr, R³ = Me
 11: R¹ = Bn, R² = Bu, R³ = Me
 12: R¹ = Bn, R² = -CH₂CH₂CH=CH₂, R³ = Me
 13: R¹ = Bn, R² = Ph, R³ = Me
 14: R¹ = Bn, R² = Et, R³ = Et

Fig. 2.

Table 2. Optical Resolution of α -Hydroxy Ketone Derivatives with (–)-**4a**^{a)}

Entry	Substrate	Ketone from the filtrate			Ketone from the solid		
		Yield/%	$[\alpha]_D^{25}$ ^{b)}	Ee/% ^{c)}	Yield/%	$[\alpha]_D^{25}$ ^{b)}	Ee/% ^{c)}
1	<i>dl</i> - 7	72	—	22 (<i>R</i>)	26	—	59 (<i>S</i>)
2	(<i>S</i>)- 7 (59% ee)	72	—	48 (<i>S</i>)	20	–18.0 (<i>c</i> 0.73)	81 (<i>S</i>)
3	<i>dl</i> - 8	70	—	40 (<i>S</i>)	29	+35.0 (<i>c</i> 1.02)	90 (<i>R</i>)
4	<i>dl</i> - 9	39	—	27 (<i>S</i>)	45	+11.2 (<i>c</i> 1.04)	27 (<i>R</i>)
5	<i>dl</i> - 10	50	—	71 (<i>R</i>)	50	—	70 (<i>S</i>)
6	(<i>S</i>)- 10 (70% ee)	45	—	37 (<i>S</i>)	53	–46.7 (<i>c</i> 0.57)	98 (<i>S</i>)
7	<i>dl</i> - 11	33	+16.3 (<i>c</i> 1.00)	44 (<i>R</i>)	61	—	23 (<i>S</i>)
8	<i>dl</i> - 12	43	+17.8 (<i>c</i> 1.07)	44 (<i>R</i>)	57	—	33 (<i>S</i>)
9	<i>dl</i> - 13	35	+68.9 (<i>c</i> 0.97)	90 (<i>R</i>)	58	—	54 (<i>S</i>)
10	<i>dl</i> - 14	70	—	20 (<i>R</i>)	30	–29.1 (<i>c</i> 1.00)	42 (<i>S</i>)

a) Unless otherwise specified, the ketone (ca. 100 mg) was mixed with (–)-**4a** (1 equiv.) in MeOH–H₂O (1:1, 5 mL) for 72 h at room temperature. b) Measured in CHCl₃ at r.t. c) Determined by HPLC analysis (CHIRALCEL OJ or OB-H).

conclusive evidence of the host–guest ratio.

We applied the reaction to other acyclic α -hydroxy ketone derivatives. Reactions of substrates bearing different R¹, R², and R³ groups (Fig. 2) with the host (–)-**4a** were performed under the same conditions as in the case of *dl*-**1**; the results are summarized in Table 2. First, we tried to change the protecting group (R¹) of the hydroxy group. The complexation of the *dl*-**7** bearing a benzyloxymethyl group proceeded with moderate enantioselectivity (entry 1). As expected, the sequential reaction of (*S*)-**7** (59% ee) with (–)-**4a** also succeeded to improve the ee to 81% ee (entry 2). An excellent thermodynamic resolution was observed in the case of *dl*-**8** bearing a *p*-methoxybenzyl group to give (*R*)-**8** with 90% ee from the solid in 29% yield (entry 3). Although the details are not yet clear, the presence of a methoxy group on the benzene ring for **8** could change the enantioselective mode, and (–)-**4a** captured (*R*)-**8** with the opposite absolute configuration of those of the other substrates.

Second, we focused on changing the R² and R³ groups. It was found that the carbon number of the substituents of the substrates reflected the enantioselectivity. The reactions of *dl*-**9** (R² = Me), *dl*-**11** (R² = Bu), and *dl*-**14** (R³ = Et) showed low-to-moderate enantioselectivities (entry 4, 7, and 10, respectively), and the C=C double bond at the terminus of the

substituent (*dl*-**12**, R² = –CH₂CH₂CH=CH₂) did not affect the enantioselectivity (entry 8). Interestingly, the (*R*)-form of **9** was obtained from the solid as well as the case of the compound **8**. In the case of compound *dl*-**10**, having a propyl group at the R² position (entry 5), the complexation proceeded with good enantioselectivity to give (*S*)-**10** with 70% ee from the solid and (*R*)-**10** with 71% ee from the filtrate in 50% yields. After a sequential reaction for obtaining (*S*)-**10**, as in the method mentioned above, the ee of (*S*)-**10** was up to 98% ee (entry 6). On the other hand, in the case of *dl*-**13** (R² = Ph; entry 9), compound (*R*)-**13** with a high ee (90% ee) was produced from the filtrate in 35% yield and (*S*)-**13** with 54% ee from the solid was yielded in 58%. The relatively high yield of **13** from the solid is supposed to be due to the good affinity of the phenyl group with (–)-**4a**.

Conclusion

We have disclosed a facile method to prepare optically active acyclic ketones bearing an α -alkoxy group by thermodynamic optical resolution with a chiral host. The procedure is a quite simple and the chiral source could be quantitatively recovered. Thus, this convenient method is expected to be potentially useful in preparing optically active acyclic carbonyl compounds, although the details of the molecular-recognition

process are still unclear. Further investigations for applying the method and the analysis of the crystal structure of the inclusion complex are now in progress.

Experimental

General Procedure and Instruments. ^1H (300 and 500 MHz) and ^{13}C (75 and 125 MHz) NMR spectra were measured on JEOL JNM AL-300 and α -500, respectively, with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded with a Shimadzu IR Prestige-21 spectrometer. Mass spectra were obtained with a JEOL EI/FAB mate BU25 instrument (EI method) and a JEOL AccuTOF MS-50010BU instrument (ESI-TOFMS). The optical rotations were measured with a Jasco DIP-1000 polarimeter. HPLC data were obtained on Shimadzu LC-10AD_{VP}, SPD-10A_{VP}, and sic 480II data station (System Instruments Inc.). Kieselgel 60 F₂₅₄ Art.5715 (E. Merck) was used for analytical TLC. Preparative TLC was performed on a Kieselgel 60 F₂₅₄ Art.5744 (E. Merck). Flash column chromatography was performed with Silica Gel 60N (63–210 mm, Kanto Chemical Co. Inc.). The melting points were obtained on a Yanako melting-point apparatus, and were not corrected. The hosts ((–)-**4a**, (–)-**4b**, and (–)-**4c**) were prepared from diethyl L-tartrate by the same procedure as that reported.⁷ The compound (+)-**4a** was derived from D-tartaric acid. The spectral data of these compounds were in full agreement with the reported data.⁷ On the other hand, compounds (+)-**5** and (–)-**6** were purchased from Wako pure Chemical Industries, Ltd. and Kanto chemical Co. Inc., respectively. All other chemicals were also obtained from commercial sources.

Preparation of Racemic 2-Benzoyloxy-3-pentanone (*dl*-1). Under an argon atmosphere, to a suspension of NaH (60% in oil, 830 mg, 20.8 mmol) in THF (30 mL) were added a solution of 2-hydroxy-1-(morpholin-4-yl)-1-propanone (**2**, 2.99 g, 18.8 mmol) in THF (30 mL) and benzyl bromide (2.0 mL, 18.8 mmol) at 0 °C. The mixture was stirred for 2.5 h at room temperature, and the reaction was stopped with 0.1 M phosphate buffer (pH 6.5). The products were extracted with AcOEt ($\times 3$), and the organic layer was washed with brine, and dried over Na₂SO₄. After evaporation under reduced pressure, the residue was purified by flash column chromatography (hexane/AcOEt = 1/1 $\rightarrow$ AcOEt) to give 2-benzoyloxy-1-(morpholin-4-yl)-1-propanone (**3**) as a colorless oil (4.26 g, 91%); IR (neat) 2857, 1645, 1435, 1271, 1234, 1115, 1030, 741, 700 cm⁻¹; ^1H NMR (300 MHz, CDCl₃) δ 1.45 (3H, d, J = 7.0 Hz, CH₃), 3.50–3.75 (8H, m, NCH₂CH₂O), 4.33 (1H, q, J = 7.0 Hz, CH), 4.47 (1H, d, J = 11.5 Hz, PhCHH), 4.59 (1H, d, J = 11.5 Hz, PhCHH), 7.26–7.39 (5H, m, Ph); ^{13}C NMR (75 MHz, CDCl₃) δ 17.8, 42.5, 45.6, 66.7, 67.0, 71.1, 75.3, 127.8, 127.9, 128.5, 137.4, 170.5.

Under an argon atmosphere, to a solution of **3** (2.56 g, 10.3 mmol) in THF (30 mL) was added ethylmagnesium bromide (1.6 M in THF, 12.6 mL) at 0 °C. After stirring for 2 h at room temperature, the mixture was poured into a sat. NH₄Cl aqueous solution and the products were extracted with Et₂O ($\times 3$). The organic layer was washed with brine and dried over Na₂SO₄. After evaporation, the residue was purified by flash column chromatography (hexane/AcOEt = 10/1) to give *dl*-**1** as a colorless oil (1.91 g, 97%); IR (neat) 2980, 1717, 1456, 1369, 1105, 739, 698 cm⁻¹; ^1H NMR (500 MHz, CDCl₃) δ 1.05 (3H, t, J = 7.5 Hz, CH₃CH₂), 1.35 (3H, d, J = 7.0 Hz, CH₃CH), 2.52–2.67 (2H, m, CH₃CH₂), 3.95 (1H, q, J = 7.0 Hz, CH₃CH), 4.50 (1H, d, J = 11.5 Hz, PhCHH), 4.54 (1H, d, J = 11.5 Hz, PhCHH), 7.27–7.40 (5H, m, Ph); ^{13}C NMR (75 MHz, CDCl₃) δ 7.3, 17.5,

30.6, 71.8, 80.5, 127.7, 127.9, 128.5, 137.6, 213.5; MS m/z (EI) 192 (M⁺, 1.2%), 135 (100), 105 (47), 91 (100), 58 (100); HRMS m/z (EI) 192.1151 (192.1150 calcd for C₁₂H₁₆O₂, M⁺).

The other substrates were prepared by the same procedure mentioned above from the corresponding starting materials.

2-Benzoyloxymethoxy-3-pentanone (*dl*-7): IR (neat) 2856, 1653, 1437, 1234, 1115, 1028, 741, 700 cm⁻¹; ^1H NMR (300 MHz, CDCl₃) δ 1.04 (3H, t, J = 7.5 Hz, CH₃CH₂), 1.34 (3H, d, J = 7.0 Hz, CH₃CH), 2.46–2.66 (2H, m, CH₃CH₂), 4.21 (1H, q, J = 7.0 Hz, CH₃CH), 4.62 (2H, s, OCH₂O), 4.77 (1H, d, J = 11.5 Hz, PhCHH), 4.83 (1H, d, J = 11.5 Hz, PhCHH), 7.24–7.40 (5H, m, Ph); ^{13}C NMR (75 MHz, CDCl₃) δ 7.3, 17.6, 31.3, 70.0, 78.1, 93.9, 127.8, 128.4, 137.5, 212.1; MS m/z (EI) 192 (30%), 165 (M⁺ – CH₃CH₂CO, 37), 135 (100), 107 (100), 91 (100), 58 (100); HRMS m/z (EI) 222.1246 (222.1256 calcd for C₁₃H₁₈O₃, M⁺).

2-*p*-Methoxybenzyloxy-3-pentanone (*dl*-8): IR (neat) 2978, 1719, 1612, 1514, 1458, 1250, 1105, 1035, 822 cm⁻¹; ^1H NMR (300 MHz, CDCl₃) δ 1.04 (3H, t, J = 7.5 Hz, CH₃CH₂), 1.32 (3H, d, J = 7.0 Hz, CH₃CH), 2.51–2.65 (2H, m, CH₃CH₂), 3.80 (3H, s, CH₃O), 3.92 (1H, q, J = 7.0 Hz, CH₃CH), 4.44 (1H, d, J = 11.5 Hz, C₆H₄CHH), 4.46 (1H, d, J = 11.5 Hz, C₆H₄CHH), 6.85–6.92 (2H, m, C₆H₂H₂CHH), 7.23–7.30 (2H, m, C₆H₂H₂CHH); ^{13}C NMR (75 MHz, CDCl₃) δ 7.3, 17.5, 30.5, 55.3, 71.5, 80.2, 113.9, 129.4, 129.7, 159.4, 213.6; MS m/z (EI) 222 (M⁺, 22%), 178 (50), 137 (100), 122 (100), 107 (21), 91 (58), 77 (94), 58 (64); HRMS m/z (EI) 222.1250 (222.1256 calcd for C₁₃H₁₈O₃, M⁺).

3-Benzoyloxy-2-butanone (*dl*-9): IR (neat) 2986, 1717, 1456, 1356, 1240, 1124, 748, 698 cm⁻¹; ^1H NMR (300 MHz, CDCl₃) δ 1.34 (3H, d, J = 7.0 Hz, CH₃CH₂), 2.20 (3H, s, CH₃CO), 3.91 (1H, q, J = 7.0 Hz, CH₃CH), 4.50 (1H, d, J = 11.5 Hz, PhCHH), 4.55 (1H, d, J = 11.5 Hz, PhCHH), 7.25–7.39 (5H, m, Ph); ^{13}C NMR (75 MHz, CDCl₃) δ 17.2, 25.0, 71.8, 80.8, 127.7, 127.9, 128.5, 137.5, 211.2; MS m/z (EI) 178 (M⁺, 16%), 135 (56), 107 (34), 91 (100), 77 (100), 58 (77); HRMS m/z (EI) 178.1039 (178.0994 calcd for C₁₁H₁₄O₂, M⁺).

2-Benzoyloxy-3-hexanone (*dl*-10): IR (neat) 2962, 1717, 1456, 1369, 1117, 739, 698 cm⁻¹; ^1H NMR (300 MHz, CDCl₃) δ 0.92 (3H, t, J = 7.5 Hz, CH₃CH₂), 1.34 (3H, d, J = 7.0 Hz, CH₃CH), 1.50–1.68 (2H, m, CH₃CH₂), 2.42–2.64 (2H, m, CH₂CO), 3.93 (1H, q, J = 7.0 Hz, CH₃CH), 4.49 (1H, d, J = 11.5 Hz, PhCHH), 4.55 (1H, d, J = 11.5 Hz, PhCHH), 7.26–7.40 (5H, m, Ph); ^{13}C NMR (75 MHz, CDCl₃) δ 13.8, 16.6, 17.4, 39.2, 71.8, 80.6, 127.7, 127.8, 128.5, 137.6, 212.9; MS m/z (EI, rel intensity) 205 (M⁺, 8.3%), 135 (14), 105 (52), 91 (100), 71 (44), 58 (18); HRMS m/z (EI) 205.1211 (205.1229 calcd for C₁₃H₁₇O₂, M⁺ – H).

2-Benzoyloxy-3-heptanone (*dl*-11): IR (neat) 2959, 1717, 1456, 1369, 1117, 737, 698 cm⁻¹; ^1H NMR (300 MHz, CDCl₃) δ 0.91 (3H, t, J = 7.5 Hz, CH₃CH₂CH₂), 1.24–1.49 (2H, m, 2H, CH₃CH₂CH₂), 1.33 (3H, d, J = 7.0 Hz, CH₃CH), 1.49–1.65 (2H, m, CH₃CH₂CH₂), 2.45–2.66 (2H, m, CH₂CO), 3.93 (1H, q, J = 7.0 Hz, CH₃CH), 4.49 (1H, d, J = 11.5 Hz, PhCHH), 4.51 (1H, d, J = 11.5 Hz, PhCHH), 7.25–7.41 (5H, m, Ph); ^{13}C NMR (75 MHz, CDCl₃) δ 13.9, 17.4, 22.4, 25.3, 37.0, 71.8, 80.6, 127.7, 127.8, 128.5, 137.6, 213.0; MS m/z (EI, rel intensity) 220 (M⁺, 2.4%), 135 (100), 114 (100), 91 (100), 85 (100), 58 (100); HRMS m/z (EI) 221.1534 (221.1542 calcd for C₁₄H₂₁O₂, M⁺ + H).

2-Benzoyloxy-6-hepten-3-one (*dl*-12): IR (neat) 2980, 1717, 1454, 1369, 1113, 914, 737, 698 cm⁻¹; ^1H NMR (300 MHz,

CDCl_3) δ 1.34 (3H, d, $J = 7.0$ Hz, CH_3CH), 2.28–2.36 (2H, m, $\text{CHH}=\text{CHCH}_2$), 2.60–2.74 (2H, m, CH_2CO), 3.94 (1H, q, $J = 7.0$ Hz, CH_3CH), 4.50 (1H, d, $J = 11.5$ Hz, PhCHH), 4.55 (1H, d, $J = 11.5$ Hz, PhCHH), 4.98 (1H, tdd, $J = 2.0, 2.0, 10.5$ Hz, $\text{CHH}=\text{CHCH}_2$), 5.04 (1H, tdd, $J = 2.0, 2.0, 17.0$ Hz, $\text{CHH}=\text{CHCH}_2$), 5.81 (1H, tdd, $J = 6.5, 10.5, 17.0$ Hz, $\text{CHH}=\text{CHCH}_2$), 7.26–7.39 (5H, m, Ph); ^{13}C NMR (125 MHz, CDCl_3) δ 17.3, 27.2, 36.5, 71.8, 80.6, 115.2, 127.7, 127.9, 128.5, 137.2, 137.5, 2120; MS m/z (EI, rel intensity) 218 (M^+ , 5.5%), 188 (9.6), 135 (52), 112 (47), 105 (100), 91 (100), 77 (100), 56 (100); HRMS m/z (EI) 218.1295 (218.1307 calcd for $\text{C}_{14}\text{H}_{18}\text{O}_2$, M^+).

2-Benzoyloxy-1-phenyl-1-propanone (dl-13): IR (neat) 2984, 2868, 1693, 1448, 1227, 1105, 961, 739, 698 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.53 (3H, d, $J = 7.0$ Hz, CH_3CH), 4.44 (1H, d, $J = 11.5$ Hz, PhCHH), 4.65 (1H, d, $J = 11.5$ Hz, PhCHH), 4.79 (1H, q, $J = 7.0$ Hz, CH_3CH), 7.24–7.37 (5H, m, PhCH_2O), 7.40–7.61 (3H, m, PhCO), 8.01–8.07 (2H, m, PhCO); ^{13}C NMR (125 MHz, CDCl_3) δ 18.8, 71.6, 78.2, 127.8, 128.0, 128.4, 128.6, 128.8, 133.4, 134.9, 137.6, 200.7; MS m/z (EI, rel intensity) 240 (M^+ , 6.3%), 210 (47), 134 (99), 122 (100), 107 (72), 91 (100), 77 (100); HRMS m/z (EI) 240.1188 (240.1150 calcd for $\text{C}_{16}\text{H}_{16}\text{O}_2$, M^+).

4-Benzoyloxy-3-hexanone (dl-14): Derived from 2-hydroxybutanoic acid; IR (neat) 2972, 1715, 1454, 1331, 1111, 737, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.95 (3H, t, $J = 7.5$ Hz, $\text{CH}_3\text{CH}_2\text{CH}$), 1.05 (3H, t, $J = 7.5$ Hz, $\text{CH}_3\text{CH}_2\text{CO}$), 1.65–1.79 (2H, m, $\text{CH}_3\text{CH}_2\text{CH}$), 2.55 (3H, dq, $J = 2.5, 7.5$ Hz, $\text{CH}_3\text{CH}_2\text{CO}$), 3.75 (1H, dd, $J = 5.5, 7.0$ Hz, $\text{CH}_3\text{CH}_2\text{CH}$), 4.44 (1H, d, $J = 11.5$ Hz, PhCHH), 4.56 (1H, d, $J = 11.5$ Hz, PhCHH), 7.27–7.40 (5H, m, Ph); ^{13}C NMR (75 MHz, CDCl_3) δ 7.2, 9.6, 25.3, 31.0, 72.3, 86.1, 127.76, 127.83, 128.43, 137.7, 213.7; MS m/z (EI, rel intensity) 207 ($\text{M}^+ + \text{H}$, 3.6%), 149 (100), 105 (28), 100 (100), 91 (199), 58 (100); HRMS m/z (EI) 206.1212 (206.1307 calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2$, M^+).

Typical Procedure of Enantioselective Thermodynamic Resolution of dl-1 with (–)-4a. To a mixture of 101 mg (0.524 mmol) of *dl*-1 and 265 mg (0.524 mmol) of (–)-4a were added MeOH (2.65 mL) and H_2O (2.65 mL), and the suspension was stirred for 72 h at room temperature. After filtration, the solid was dissolved into AcOEt, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 20/1) to afford (S)-1 (34.3 mg, 34%, 99% ee) and (–)-4a (264 mg, quantitative). On the other hand, the compounds were extracted from the filtrate with AcOEt ($\times 3$), and the combined organic layer was washed with brine and dried over Na_2SO_4 . After evaporation, the residue was purified by the same procedure as mentioned above to give (R)-1 (54.4 mg, 54%, 59% ee). The ee of 1 was determined by HPLC analysis with CHIRALCEL OJ (Daicel Chemical Industries, Ltd.); eluent, hexane/2-propanol = 180/1; flow rate, 0.5 mL min^{-1} ; retention time, 40 (R) and 50 (S) min. The absolute configuration of 1 was determined by comparing the optical rotation sign with that of the published data.^{1b}

Enantioselective reactions of the other cases were carried out by the same procedure. All of the spectral data (^1H NMR, ^{13}C NMR, IR, and MS) were in full agreement with those of the racemates. The optical rotations of the obtained compounds are given in the text and Table 2. The ee's of the ketones were determined by HPLC analysis with CHIRALCEL OJ or OB-H (Daicel Chemical Industries, Ltd.). The conditions of the analyses are given below:

7: column, OJ; eluent, hexane/2-propanol = 2000/1; flow rate, 0.5 mL min^{-1} ; (S) 119 min, (R) 133 min.

8: column, OJ; eluent, hexane/2-propanol = 99/1; flow rate, 0.5 mL min^{-1} ; (S) 78 min, (R) 98 min.

9: column, OJ; eluent, hexane/2-propanol = 180/1; flow rate, 0.5 mL min^{-1} ; (R) 39 min, (S) 61 min.

10: column, OJ; eluent, hexane/2-propanol = 180/1; flow rate, 0.5 mL min^{-1} ; (R) 26 min, (S) 28 min.

11: column, OJ; eluent, hexane/2-propanol = 180/1; flow rate, 0.3 mL min^{-1} ; (R) 36 min, (S) 40 min.

12: column, OB-H; eluent, hexane/2-propanol = 92/8; flow rate, 0.5 mL min^{-1} ; (S) 14 min, (R) 31 min.

13: column, OJ; eluent, hexane/2-propanol = 90/10; flow rate, 0.5 mL min^{-1} ; (S) 23 min, (R) 29 min.

14: column, OJ; eluent, hexane/2-propanol = 2000/1; flow rate, 0.5 mL min^{-1} ; (R) 41 min, (S) 49 min.

The absolute configurations of 7, 8, 10, and 14 were determined by comparing the optical rotation signs with those of the published data.^{1b} In other cases, the absolute configurations were determined by comparing the optical rotation signs with those of synthesized authentic samples, which were prepared from optically active starting materials by the same procedure of preparing racemic substrates.

Analysis of the Inclusion Complex of (–)-4a with (S)-1 by ESI-TOFMS. After stirring a mixture of (–)-4a (104 mg, 0.21 mmol) and (S)-1 (153 mg, 0.80 mmol) in MeOH– H_2O (1:1, 8 mL) for 72 h at room temperature, the suspension was filtered. The methanol solution of the collected solid was injected directly to the ESI-TOFMS system. The exact mass of the sample was determined by the same system with PEG as an external standard. HRMS [$1 + 4a + \text{Na}$] $^+$ ion (m/z , 721.34928; 721.35051 calcd for $\text{C}_{46}\text{H}_{50}\text{O}_6\text{Na}$).

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