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Complete reversal of enantioselection using oxazoline-containing Schiff base ligands derived from L-serine in enantioselective addition of diketene to aldehydes

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Abstract—Starting from one stereogenic center (in this case from L-serine), we obtained two chiral Schiff bases possessing oxazoline moieties, each of which recognized a different enantioface of aldehydes with a high enantiomeric excess [up to 93% ee (*R*) and 89% ee (*S*)] in the addition reaction of diketene to 2-furfural.

1. Introduction

Attempts for obtaining both enantiomers in high enantiomeric excess are attractive and important challenges, because it is often the case that each enantiomer exhibits different bioactivity. Since our first report on the chiral Schiff base–Ti(O-*i*-Pr)$_4$-catalyzed trimethylsilylcyanation of aldehydes in 1991,[1] this catalyst system was proven to be efficient in a variety of asymmetric reactions. One such reaction is the enantioselective addition of diketene to aldehydes.[2] We succeeded in obtaining optically active 5-hydroxy-3-ketoesters in up to 92% ee.[3,4] Herein, we report the first example of complete reversal of enantioselection using oxazoline-containing Schiff bases derived from L-serine, that is, from one stereogenic center of L-serine, both enantiomers of 5-hydroxy-3-ketoesters were obtained in high enantiomeric excess (89–93% ee).

2. Results and discussion

2.1. Synthesis of chiral ligands

The chiral Schiff base ligands containing oxazoline moieties were synthesized according to Scheme 1. The reaction of an amino diol possessing a tertiary hydroxy group derived from L-serine with 3,5-di-*tert*-butyl-2-hydroxybenzonitrile in ethylene glycol–glycerol (2:1) at 120 °C for 24 h afforded a mixture of **1** and **2** in ratios of 1:1.3–3.3:1, which were easily separated by silica-gel column chromatography. The ratio of ligands **1** and **2** results from which one of the two hydroxy groups will attack the imino group after nucleophilic attack of the amino group to the nitrile.[5]

2.2. Enantioselective addition of diketene to aldehydes

We first examined the reaction of diketene with benzaldehyde in the presence of Ti(O-*i*-Pr)$_4$–Schiff base **1a**–**c** and **2a**–**c**. As shown in Table 1, the use of ligand **1a**–**c** afforded the (*R*)-product. Among **1a**–**c**, **1a**, which possessed the Me group as R^1, gave the product in 90% ee (67% yield), whereas in the case of the **2** series, **2b** (R^1 = Et) gave (*S*)-configured product in 87% ee (47% yield). The absolute configuration was determined by the transformation of optically active 5-hydroxy-3-ketoester into 4-hydroxy-6-phenyl-5,6-dihydro-2-pyrone derivatives, as shown in Scheme 2.[6] To the best of our knowledge, this is the first example of a complete reversal of enantioselection starting from one stereogenic center (in this case from L-serine), although there are some examples in which the change of metal,[7] solvent,[8] temperature[9] or substituent[10] reverses the enantioselectivity.

We then examined a variety of aldehydes, and found, without exception that when ligand **1a** was used, (*R*)-configured products were obtained, whereas (*S*)-products were pro-

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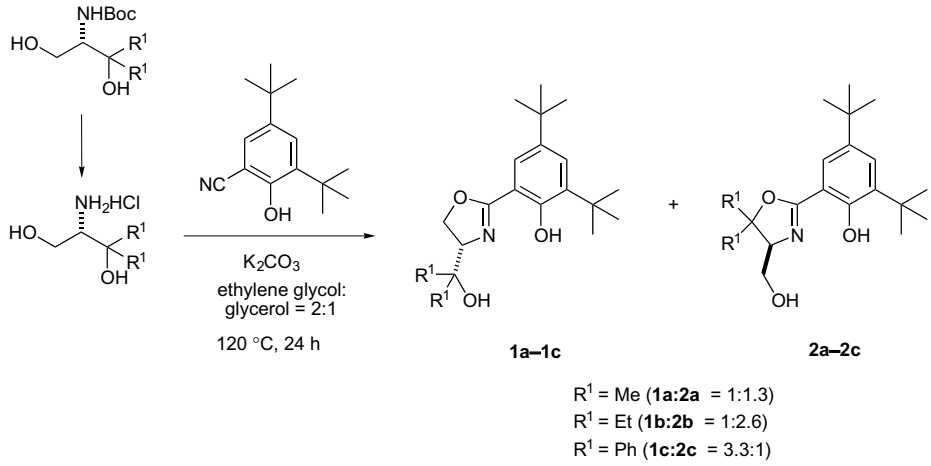
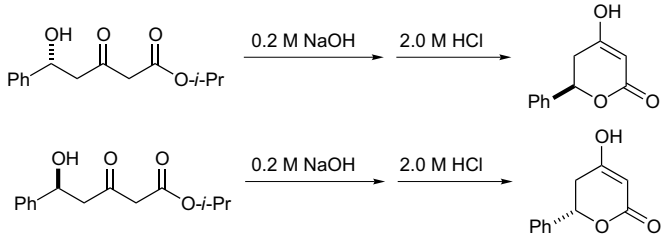


Scheme 1.

Table 1. Enantioselective addition of diketene to benzaldehydes promoted by Ti(O-*i*-Pr)$_4$–Schiff base (**1a**–**2c**) complex[a]

Entry	Schiff base	Yield[b]/%	ee[c,d]/%
1	**1a**	67	90
2	**1b**	46	77
3	**1c**	14	56
4	**2a**	55	62
5[e]	**2b**	47	87
6[e]	**2c**	77	62

[a] All reactions were carried out in CH_2Cl_2 at −40 °C for 48 h using 5 equiv of diketene unless otherwise noted.
[b] Isolated yield after silica-gel column chromatography.
[c] HPLC analysis using CHIRALPAK AD column.
[d] The absolute configurations of the products were determined as *R* (entries 1–3) and those of entries 4–6 were *S* after derivatization to the known enol ketone. $[\alpha]_D^{28} = +84.4$ (*c* 0.33, $CHCl_3$) for entry 1 (90% ee (*R*)), $[\alpha]_D^{28} = -80.8$ (*c* 0.2, $CHCl_3$) for entry 5 (87% ee (*S*)) [lit.[6] $[\alpha]_D^{20}$ +99.9 (*c* 1.0, $CHCl_3$) for 99.9% ee (*R*)].
[e] 2 equiv of diketene was used.

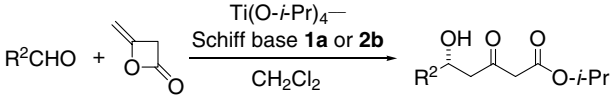


Scheme 2.

duced in the case of **2b**.[11] The highest ee was 93% (*R*), in the case of 2-furfural and 89% (*S*), respectively (Table 2).

Concerning the mechanism of the reaction between the aldehydes and diketene promoted by Schiff base–Ti(O-*i*-Pr)$_4$, we determined that the diketene directly attacked aldehydes without the formation of the intermediate titanium enolate based on careful NMR analysis.[12] The detailed reason for why chiral Schiff bases **1a** and **2b** recognize the opposite enantioface of the aldehyde is still not clear. However, judging from the outcome of the stereo-

Table 2. Enantioselective addition of diketene to aldehydes promoted by Schiff base **1a** (or **2b**)–Ti(O-*i*-Pr)$_4$ complex[a]



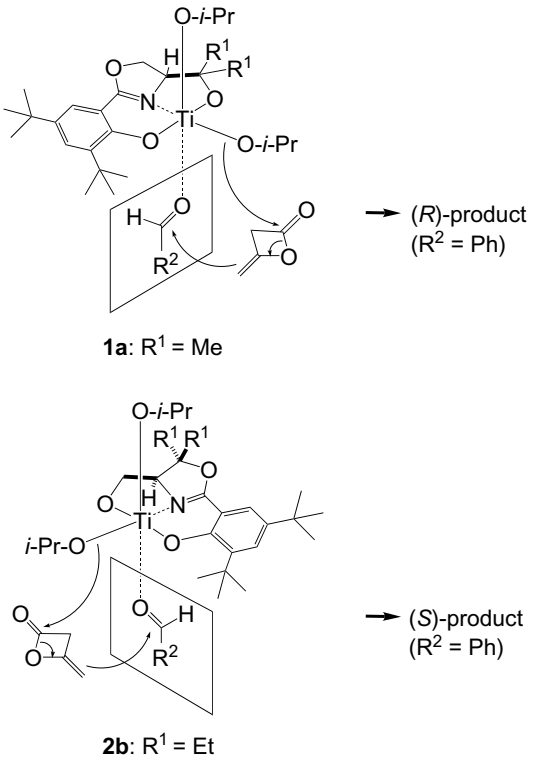
Entry	Aldehyde	Yield[b,c]/%	ee[c,d,e]/%
1	Benzaldehyde	67 (64)	90; *R* (87; *S*)
2	4-Methylbenzaldehyde	76 (57)	87; *R* (79; *S*)
3	4-Methoxybenzaldehyde	63 (66)	73; *R* (70; *S*)
4	(*E*)-Cinnamaldehyde	72 (46)	92; *R* (84; *S*)
5	3-Phenylpropionaldehyde	74 (51)	80; *S* (66; *R*)
6	Cyclohexanecarbaldehyde	57 (44)	73; *R* (47; *S*)
7	*n*-Butanal	60 (50)	79; *S* (60; *R*)
8	Methacrolein	75 (55)	88; *R* (73; *S*)
9	(*E*)-Crotonaldehyde	61 (59)	86; *R* (80; *S*)
10	2-Furfural	75 (56)	93; *R* (89; *S*)
11	2-Thiophenaldehyde	76 (62)	87; *R* (76; *S*)

[a] All reactions were carried out using 1.0 equiv of Ti(O-*i*-Pr)$_4$, 1.1 equiv of Schiff base **1a** or **2b**, and 5 equiv of diketene in CH_2Cl_2 at −40 °C for 48 h.
[b] Isolated yield after silica-gel column chromatography.
[c] The values in parentheses indicated in the case of ligand **2b** were used.
[d] HPLC analysis using CHIRALPAK AD column.
[e] In all cases, by using **2b**, the opposite enantiomer was obtained predominantly as indicated values.

chemistry of the products, we would like to propose the following mechanism (Scheme 3). The multiplier effect of the R^1 group and *tert*-butyl group at the *ortho*-position of phenolic hydroxy group may cause the high level of reversal in asymmetric induction.

3. Conclusion

In conclusion, starting from one stereogenic center (in this case from L-serine), we obtained two chiral Schiff base possessing oxazoline moieties, each of which recognized a different enantioface of the aldehyde in high enantiomeric excess [up to 93% ee (*R*) and 89% ee (*S*)] in the addition reaction of diketene to 2-furfural. This is the first example of complete reversal of enantioselection from the single chi-



Scheme 3.

rality of L-serine. It should be added that the products obtained by the present reaction, 5-hydroxy-3-ketoesters, can be used as the potential inhibitors of HMG coenzyme reductase.

4. Experimental

4.1. General

All melting points were measured on a Yanaco MP-500D and are uncorrected. ^{1}H and ^{13}C NMR spectra (400 and 100.6 MHz, respectively) were recorded on a JEOL JNM-LA 400 using Me_4Si as the internal standard. IR spectra were measured with a PERKIN ELMER FT-IR Spectrometer SPECTRUM 1000. Elemental analyses were performed with a Yanaco CHN Corder MT-5. Mass spectra were taken on a Shimadzu GCMS-QP 2000A. Preparative column chromatography was carried out on Fuji Silysia BW-820MH. Thin-layer chromatography (TLC) was carried out on foil plates, Silica Gel 60 F_{254} (E. Merck; layer thickness 0.2 mm). Chiral HPLC was performed in a Shimadzu LC-VP series instrument equipped with a diode array detector.

4.2. General procedure for the preparation of chiral Schiff base ligands

Chiral oxazoline ligands **1** and **2** were accessible from chiral 2-*N*-(Boc) amino-1,3-diol in two steps.

First step: Deprotection of Boc. With mechanical stirring, chiral 2-*N*-(Boc) amino-1,3-diol (23.4 mmol, 1.0 equiv), ethanol (70 mL), and 35% (w/w) aqueous HCl (20 mL) were combined in a 200-mL round bottomed flask, the mixture was stirred at room temperature for 10 h, removing the solvent to leave a residue, which was redissolved in ethanol, and the solvent was removed by vacuum distillation. This distillation was repeated several times to remove the hydrogen chloride, and then used in the synthesis of the oxazoline ligands.

Second step: Synthesis of the oxazoline ligands. With mechanical stirring, the residues from the first step, ethylene glycol/glycerol = 2:1 (30 mL), anhydrous K_2CO_3 (3.2 g, 23.4 mmol, 1.0 equiv), and 3,5-di-*tert*-butyl-2-hydroxyl benzonitrile (5.4 g, 23.4 mmol, 1.0 equiv), were combined in a 200-mL round bottomed flask. The mixture was stirred at 120 °C for 24 h. After the reaction, it was cooled to room temperature, and ethyl acetate (50 mL) and brine (50 mL) were added, collection of the organic layer and water was done with ethyl acetate (50 mL × 3). The combined organic phases were dried over anhydrous sodium sulfate and evaporated to a residue. The residue was purified on a silica gel column carefully (ethyl acetate–hexane 1:40) in order to obtain chiral oxazoline ligands **1** and **2** in pure form.

4.2.1. (4*S*)-4-[(1-Hydroxyl-1-methyl)-ethyl]-2-[(2-hydroxyl-3,5-di-*tert*-butyl)-phenyl]-4,5-dihydro-1,3-oxazoline 1a. Yield (24%, 1886 mg): mp 109–110 °C; $[\alpha]_D^{27} = +3.3$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 12.41 (br, 1H), 7.52 (d, $J = 2.8$ Hz, 1H), 7.46 (d, $J = 2.8$ Hz, 1H), 4.44–4.37 (m, 2H), 4.28 (dd, $J = 10.4$ Hz, $J = 7.6$ Hz, 1H), 1.44 (s, 9H), 1.38 (s, 3H), 1.30 (s, 9H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.7, 157.0, 140.2, 136.5, 128.4, 122.3, 110.5, 74.5, 71.3, 67.7, 35.1, 34.3, 31.5, 29.5, 27.0, 25.7; IR (KBr) *v* 3414, 2960, 1633; Mass *m*/*z* (relative intensity) 333 (48.1), 318 (61.9), 274 (21.6), 233 (54.8), 217 (47.7), 149 (49.1), 59 (34.1), 57 (100.0). Anal. Calcd for $C_{20}H_{31}NO_3$: C 72.04, H 9.37, N 4.20; found: C 71.94, H 9.51, N 4.13.

4.2.2. (4*S*)-4-Hydroxymethyl-5,5-dimethyl-2-[(2-hydroxyl-3,5-di-*tert*-butyl)-phenyl]-4,5-dihydro-1,3-oxazoline 2a. Yield (29%, 2264 mg): mp 132–133 °C; $[\alpha]_D^{27} = -30.8$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.52 (d, $J = 2.8$ Hz, 1H), 7.45 (d, $J = 2.8$ Hz, 1H), 3.99 (t, $J = 6.0$ Hz, 1H), 3.80 (d, $J = 6.0$ Hz, 2H), 1.52 (s, 3H), 1.49 (s, 3H), 1.44 (s, 9H), 1.31 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 166.5, 157.0, 140.0, 136.5, 128.2, 122.3, 110.0, 85.1, 74.0, 62.3, 35.1, 34.3, 31.5, 29.4, 29.0, 21.3; IR (KBr) *v* 3564, 2961, 1629; Mass *m*/*z* (relative intensity) 333 (51.9), 318 (55.8), 290 (29.3), 233 (41.8), 217 (100), 57 (60.3), 41 (71.0). Anal. Calcd for $C_{20}H_{31}NO_3$: C 72.04, H 9.37, N 4.20; found: C 71.83, H 9.42, N 3.92.

4.2.3. (4*S*)-4-[(1-Ethyl-1-hydroxyl-propyl)-2-[(2-hydroxyl-3,5-di-*tert*-butyl)-phenyl]-4,5-dihydro-1,3-oxazoline 1b. Yield (11%, 409 mg): mp 74–75 °C; $[\alpha]_D^{27} = -1.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 12.5 (s, 1H), 7.55 (d, $J = 2.8$ Hz, 1H), 7.45 (d, $J = 2.8$ Hz, 1H), 4.45–4.37 (m, 3H), 1.83–1.70 (m, 2H), 1.58–1.50 (m, 2H), 0.99–0.90 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 167.6, 156.9, 140.2, 136.5, 128.3, 122.3, 110.3, 109.7, 75.1, 71.3, 67.2, 35.1, 34.3, 29.5, 28.8, 26.8, 7.9, 7.6; IR (KBr) *v* 3457, 2965, 1636; Mass *m*/*z* (relative

intensity) 361 (32.0), 233 (85.0), 217 (42.1), 175 (29.1), 87 (32.0), 57 (100.0), 41 (66.6). Anal. Calcd for $C_{22}H_{35}NO_3$: C 73.09, H 9.76, N 3.87; found: C 72.92, H 9.90, N 3.68.

4.2.4. (4*S*)-4-Hydroxymethyl-5,5-diethyl-2-[(2-hydroxyl-3,5-di-*tert*-butyl)-phenyl]-4,5-dihydro-1,3-oxazoline 2b. Yield (31%, 1154 mg): mp 110–111 °C; $[\alpha]_D^{27} = -24.5$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 12.5 (br, 1H), 7.54 (d, $J = 2.8$ Hz, 1H), 7.45 (d, $J = 2.8$ Hz, 1H), 4.13–4.09 (m, 1H), 3.85–3.77 (m, 2H), 1.96–1.69 (m, 4H), 1.44 (s, 9H), 1.31 (s, 9H), 1.06 (t, $J = 7.2$ Hz, 3H), 0.96 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.3, 157.0, 140.0, 136.5, 128.1, 122.2, 109.9, 89.7, 72.5, 62.5, 35.1, 34.2, 31.5, 29.6, 29.5, 24.3, 8.3, 7.4; IR (KBr) *v* 3597, 2963, 1633; Mass *m*/*z* (relative intensity) 361 (43.8), 346 (21.8), 233 (52.3), 217 (70.9), 175 (23.9), 98 (93.9), 69 (25.0), 57 (100.0), 41 (85.5). Anal. Calcd for $C_{22}H_{35}NO_3$: C 73.09, H 9.76, N 3.87; found: C 73.21, H 9.77, N 3.86.

4.2.5. (4*S*)-4-[(Hydroxyl-diphenyl)-methyl]-2-[(2-hydroxyl-3,5-di-*tert*-butyl)-phenyl]-4,5-dihydro-1,3-oxazoline 1c. Yield (53%, 242.5 mg): mp 111–112 °C; $[\alpha]_D^{27} = -41.2$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.64–7.20 (m, 12H), 5.54 (t, $J = 9.2$ Hz, 1H), 4.30 (t, $J = 9.2$ Hz, 1H), 4.19 (t, $J = 9.2$ Hz, 1H), 1.40 (s, 9H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.0, 157.0, 145.5, 143.8, 140.2, 136.5, 128.5, 128.4, 128.3, 127.2, 127.0, 126.8, 125.6, 122.4, 109.5, 78.2, 72.1, 68.0, 35.1, 34.2, 31.4, 30.8, 29.4; IR (KBr) *v* 3426, 2961, 1631; Mass *m*/*z* (relative intensity) 457 (19.8), 275 (55.9), 260 (22.1), 233 (75.3), 217 (27.6), 183 (53.8), 105 (96.9), 77 (58.3), 57 (100.0), 41 (45.1). Anal. Calcd for $C_{30}H_{35}NO_3$: C 78.74, H 7.71, N 3.06; found: C 78.44, H 7.96, N 3.14.

4.2.6. (4*S*)-4-Hydroxymethyl-5,5-diphenyl-2-[(2-hydroxyl-3,5-di-*tert*-butyl)-phenyl]-4,5-dihydro-1,3-oxazoline 2c. Yield (16%, 73.2 mg): mp 88–89 °C; $[\alpha]_D^{27} - 232.5$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.79–7.25 (m, 12H), 5.09 (t, $J = 6.4$ Hz, 1H), 3.47 (d, $J = 6.4$ Hz, 2H), 1.45 (s, 9H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 169.1, 157.3, 146.3, 144.4, 140.3, 137.1, 128.5, 128.4, 127.3, 127.1, 126.8, 125.1, 122.4, 109.7, 77.7, 72.2, 68.1, 35.1, 34.2, 31.5, 30.7, 29.5; IR (KBr) *v* 3429, 2959, 1639; Mass *m*/*z* (relative intensity) 457 (15.0), 427 (6.4), 260 (22.2), 233 (30.8), 225 (33.5), 207 (22.0), 195 (100.0), 180 (24.3), 57 (29.6). Anal. Calcd for $C_{30}H_{35}NO_3$: C 78.74, H 7.71, N 3.06; found: C 78.63, H 7.94, N 2.94.

4.3. General procedure for the addition of diketene to aldehydes promoted by chiral Schiff base–Ti(O-*i*-Pr)$_4$ complexes

In a Schlenk tube were placed either Schiff base **1a** or **2b** (198.9 mg, 0.55 mmol), and CH_2Cl_2 (5 mL). To this solution was added Ti(O-*i*-Pr)$_4$ (0.5 mmol) at room temperature and stirred for 1 h, then the mixture was cooled to −40 °C. Aldehyde (0.5 mmol, 1.0 equiv) and diketene (2.5 mmol) were added to it and the whole mixture was stirred for 48 h at −40 °C. After this, isopropyl alcohol (2 mL) was added to the mixture, and then stirred for 3 h. The mixture was poured into a mixture of 1 M HCl (10 mL) and diethyl ether (10 mL), then stirred vigorously for 1 h at room temperature. The mixture was then extracted with ethyl acetate (30 mL × 3), and the combined extracts were washed with satd $NaHCO_3$ (30 mL × 3), brine (30 mL × 3), and dried over Na_2SO_4, then evaporated. The residue was column chromatographed on silica gel [eluent, hexane–ethyl acetate (5:1)] to give 5-hydroxy-3-oxoesters. The enantiomeric excess for each of the 5-hydroxy-3-oxoesters was determined by HPLC analysis (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min].

4.3.1. (*S*)-Isopropyl 5-hydroxy-5-phenyl-3-oxopentanoate. 59.3 mg (47%). The enantiomeric excess of the product was determined as 87% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 12 min; t_R of (*S*)-isomer, 19 min. Absolute configuration of the major isomer was determined as (*S*) by the comparison of the specific rotation value after conversion into (*S*)-4-hydroxy-6-phenyl-5,6-dihydro-2-pyrone.[6]

4.3.2. (*R*)-Isopropyl 5-hydroxy-5-phenyl-3-oxopentanoate. 84.3 mg (67%). $[\alpha]_D^{28} = +47.6$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 90% ee by HPLC analysis (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 12 min; t_R of (*S*)-isomer, 19 min. Absolute configuration of the major isomer was determined as (*R*) by the comparison of the specific rotation value after conversion into (*R*)-4-hydroxy-6-phenyl-5,6-dihydro-2-pyrone.[6]

4.3.3. (*S*)-Isopropyl 5-hydroxy-5-(4-methylphenyl)-3-oxopentanoate. 75.5 mg (57%). $[\alpha]_D^{28} = -41.3$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 79% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 12 min; t_R of (*S*)-isomer, 17 min. Absolute configuration of the major isomer was determined as (*S*) by the comparison of the specific rotation value and the order of the retention time in HPLC analysis.

4.3.4. (*R*)-Isopropyl 5-hydroxy-5-(4-methylphenyl)-3-oxopentanoate. 100.0 mg (76%). $[\alpha]_D^{27} = +38.9$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 87% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 12 min; t_R of (*S*)-isomer, 17 min. Absolute configuration of the major isomer was determined as (*R*) by the comparison of the specific rotation value and the order of the retention time in HPLC analysis.

4.3.5. (*S*)-Isopropyl 5-hydroxy-5-(4-methoxyphenyl)-3-oxopentanoate. 92.2 mg (66%). $[\alpha]_D^{27} = -40.9$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 70% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 22 min; t_R of (*S*)-isomer, 33 min. Absolute configuration of the major isomer was determined as (*S*) by the comparison of the specific

rotation value and the order of the retention time in HPLC analysis.

4.3.6. (*R*)-Isopropyl 5-hydroxy-5-(4-methoxyphenyl)-3-oxopentanoate. 88.2 mg (63%). $[\alpha]_D^{24} = +33.0$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 73% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 22 min; t_R of (*S*)-isomer, 33 min. Absolute configuration of the major isomer was determined as (*R*) by the comparison of the specific rotation value and the order of the retention time in HPLC analysis.

4.3.7. (*S*)-(*E*)-Isopropyl 5-hydroxy-7-phenyl-3-oxo-6-heptanoate. 64.0 mg (46%). $[\alpha]_D^{29} = -23.4$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 84% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 16 min; t_R of (*S*)-isomer, 24 min. Absolute configuration of the major isomer was determined as (*S*) by the comparison of the specific rotation value with those previously published.[2b]

4.3.8. (*R*)-(*E*)-Isopropyl 5-hydroxy-7-phenyl-3-oxo-6-heptanoate. 99.8 mg (72%). $[\alpha]_D^{28} = +18.2$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 92% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 16 min; t_R of (*S*)-isomer, 24 min. Absolute configuration of the major isomer was determined as (*R*) by the comparison of the specific rotation value with those previously published.[2b]

4.3.9. (*R*)-Isopropyl 5-hydroxy-7-phenyl-3-oxoheptanoate. 70.7 mg (51%). $[\alpha]_D^{29} = -10.5$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 66% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*S*)-isomer, 12 min; t_R of (*R*)-isomer, 19 min. Absolute configuration of the major isomer was determined as (*R*) by the comparison of the specific rotation value with those previously published.[2b]

4.3.10. (*S*)-Isopropyl 5-hydroxy-7-phenyl-3-oxoheptanoate. 103.2 mg (74%). $[\alpha]_D^{28} = +8.3$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 80% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (97.5:2.5) + trifluoroacetic acid (0.01%), 0.5 mL/min, 254 nm]. t_R of (*S*)-isomer, 43 min; t_R of (*R*)-isomer, 69 min. Absolute configuration of the major isomer was determined as (*S*) by the comparison of the specific rotation value with those previously published.[2b]

4.3.11. (*S*)-Isopropyl 5-hydroxy-5-cyclohexyl-3-oxopentanoate. 56.7 mg (44%). $[\alpha]_D^{28} = -18.8$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 47% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*S*)-isomer, 10 min; t_R of (*R*)-isomer, 15 min. ^1H NMR ($CDCl_3$) δ 5.05 (sept, $J = 6.1$ Hz, 1H), 3.9–3.8 (m, 1H), 3.45 (s, 2H), 2.71 (d, $J = 3.7$ Hz, 1H), 2.67 (d, $J = 6.6$ Hz, 1H), 2.2 (br s, 1H), 1.9–1.6 (m, 6H), 1.26 (d, $J = 6.1$ Hz, 6H), 1.5–1.1 (m, 5H). Absolute configuration of the major isomer was determined as (*S*) by the comparison of the specific rotation value and the order of the retention time in HPLC analysis.

4.3.12. (*R*)-Isopropyl 5-hydroxy-5-cyclohexyl-3-oxopentanoate. 72.5 mg (57%). $[\alpha]_D^{27} = +17.3$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 73% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 10 min; t_R of (*S*)-isomer, 15 min. Absolute configuration of the major isomer was determined as (*R*) by the comparison of the specific rotation value and the order of the retention time in HPLC analysis.

4.3.13. (*R*)-Isopropyl 5-hydroxy-3-oxooctanoate. 53.7 mg (50%). $[\alpha]_D^{27} = -20.0$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 60% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*S*)-isomer, 8 min; t_R of (*R*)-isomer, 11 min. Absolute configuration of the major isomer was determined as (*R*) by the comparison of the specific rotation value with those previously published.[2b]

4.3.14. (*S*)-Isopropyl 5-hydroxy-3-oxooctanoate. 64.5 mg (60%). $[\alpha]_D^{25} = +16.6$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 79% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*S*)-isomer, 8 min; t_R of (*R*)-isomer, 11 min. Absolute configuration of the major isomer was determined as (*S*) by the comparison of the specific rotation value with those previously published.[2b]

4.3.15. (*S*)-Isopropyl 5-hydroxy-6-methyl-3-oxo-6-heptanoate. 59.0 mg (55%). $[\alpha]_D^{27} = -28.7$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 73% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 8 min; t_R of (*S*)-isomer, 11 min. Absolute configuration of the major isomer was determined as (*S*) by the comparison of the specific rotation value and the order of the retention time in HPLC analysis.

4.3.16. (*R*)-Isopropyl 5-hydroxy-6-methyl-3-oxo-6-heptanoate. 80.0 mg (75%). $[\alpha]_D^{29} = +44.3$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 88% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 8 min; t_R of (*S*)-isomer, 11 min. Absolute configuration of the major isomer was determined as (*R*) by the comparison of the specific rotation value and the order of the retention time in HPLC analysis.

4.3.17. (*S*)-(*E*)-Isopropyl 5-hydroxy-3-oxo-6-octanoate. 62.7 mg (59%). $[\alpha]_D^{27} = -27.9$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 80% ee by

HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 8 min; t_R of (*S*)-isomer, 11 min. ^{1}H NMR ($CDCl_3$) δ 5.8–5.7 (m, 1H), 5.6–5.4 (m, 1H), 5.1–5.0 (m, 1H), 4.55 (dd, $J = 12.2$ Hz, 6.1 Hz, 1H), 3.45 (s, 2H), 2.75 (d, $J = 6.10$ Hz, 2H), 1.70 (d, $J = 6.10$ Hz, 3H), 1.6 (br s, 1H), 1.27 (d, $J = 6.1$ Hz, 6H). Absolute configuration of the major isomer was determined as (*S*) by the comparison of the specific rotation value with those previously published.[2b]

4.3.18. (*R*)-(*E*)-Isopropyl 5-hydroxy-3-oxo-6-octanoate. 66.8 mg (61%). $[\alpha]_D^{29} = +27.1$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 86% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 8 min; t_R of (*S*)-isomer, 11 min. Absolute configuration of the major isomer was determined as (*R*) by the comparison of the specific rotation value.

4.3.19. (*S*)-Isopropyl 5-hydroxy-5-(2-furyl)-3-oxopentanoate. 67.7 mg (56%). $[\alpha]_D^{28} = -33.4$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 89% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 15 min; t_R of (*S*)-isomer, 22 min. Absolute configuration of the major isomer was determined as (*S*) by the comparison of the specific rotation value and the order of the retention time in HPLC analysis.

4.3.20. (*R*)-Isopropyl 5-hydroxy-5-(2-furyl)-3-oxopentanoate. 89.9 mg (75%). $[\alpha]_D^{29} = +26.8$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 93% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 15 min; t_R of (*S*)-isomer, 22 min. Absolute configuration of the major isomer was determined as (*R*) by the comparison of the specific rotation value and the order of the retention time in HPLC analysis.

4.3.21. (*S*)-Isopropyl 5-hydroxy-5-(2-thienyl)-3-oxopentanoate. 80.0 mg (62%). $[\alpha]_D^{28} = -36.4$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 76% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 15 min; t_R of (*S*)-isomer, 22 min. Absolute configuration of the major isomer was determined as (*S*) by the comparison of the specific rotation value and the order of the retention time in HPLC analysis.

4.3.22. (*R*)-Isopropyl 5-hydroxy-5-(2-thienyl)-3-oxopentanoate. 97.6 mg (76%). $[\alpha]_D^{28} = +28.3$ (*c* 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 87% ee by HPLC analysis. (CHIRALPAK AD) [eluent, hexane–ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min, 254 nm]. t_R of (*R*)-isomer, 14 min; t_R of (*S*)-isomer, 25 min. Absolute configuration of the major isomer was determined as (*R*) by the comparison of the specific rotation value and the order of the retention time in HPLC analysis.

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