

## A Catalytic and Iterative Route to *b*-Substituted Esters via Highly Enantioselective Conjugate Addition of Dimethylzinc to Unsaturated Malonates

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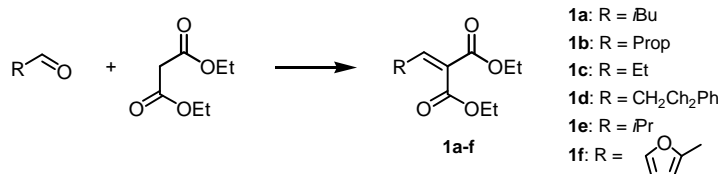
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### Supporting Information

**General Information.** All reactions were carried out under an argon atmosphere using flame-dried glassware. Toluene and ether were distilled from sodium, heptane and dichloromethane from calciumhydride. Dimethylzinc (2.0 M in toluene) and copper(II)-triflate were purchased from Aldrich and used without purification. Phosphoramidite ligands **L1-L8** were synthesized according to the protocol developed in our group.<sup>1</sup> Purification of reaction products was carried out by flash chromatography using Merck silica gel Type 9385 (230-400 mesh). Thin layer chromatography was performed on Merck silica gel 60 TLC-plates F254 and visualized with UV light and permanganate or phosphomolybdic acid staining. <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were recorded on a Varian Unity 300 or Varian Unity 200 spectrometer using CDCl<sub>3</sub> as the solvent. Chemical shifts are reported in ppm using the solvent as an internal standard ( $\delta = 7.24$  for <sup>1</sup>H,  $\delta = 77.0$  for <sup>13</sup>C). Data are reported as follows: chemical shift (multiplicity: s = singlet, d = doublet, t = triplet, q = quartet or m = multiplet, coupling constants, integration). For carbon spectra the number of attached protons were assigned by recording APT spectra. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Mass spectra were recorded on a AEI-MS-902 mass spectrometer. GC measurements were performed on a HP 6890 Plus gas chromatograph using a flame ionisation detector. HPLC analysis was carried out on a Water 600E system controller with a Water 991 photodiode array detector.

**General procedure A** for preparation of unsaturated malonic esters **1**.<sup>2</sup> A mixture of 0.2 mL of piperidine, 0.6 mL of glacial acetic acid and 10-50 mmol of diethylmalonate in 15-30 mL of toluene was stirred at room temperature for 15 min. 1.1 equivalent of the aldehyde was added and the reaction mixture was refluxed under Dean-Stark conditions for 4-24 h. The reaction mixture was cooled to room temperature, diluted with MTBE and washed with water and brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and the solvents were evaporated. The crude product was purified by flash chromatography.

**General procedure B** for preparation of unsaturated malonic esters **1**.<sup>3</sup> A mixture of 60  $\mu$ L (0.6 mmol) of pyridine, 34  $\mu$ L of (0.6 mmol) acetic acid anhydride and 7 mmol of diethylmalonate in 4 mL of toluene was stirred for 15 min at rt. 7 mmol of the aldehyde was added and stirring was continued for 24h. In some cases for complete conversion heating to 70°C was advantageous. The reaction mixture was then diluted with 5 mL of H<sub>2</sub>O and 5 mL of MTBE. After extraction of the aqueous layer with 2x 5 mL MTBE the combined organic layers were washed with water and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvents were evaporated and the crude product was purified by flash chromatography.



Diethyl isopentylidenemalonate (**1a**).<sup>4,5</sup> According to general procedure A obtained as a colorless oil in 68% yield. *R<sub>f</sub>* (hexane/EtOAc 20/1) = 0.25; GC (HP5): *t<sub>R</sub>* = 9.7 min (100-170°C, 5°C/min); <sup>1</sup>H NMR (200 MHz):  $\delta$  = 0.92 (d, *J* = 6.6 Hz, 6H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.69-1.89 (m, 1H), 2.17 (dd, *J* = 7.8, 6.8 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 4H), 4.28 (q, *J* = 7.1 Hz, 4H), 6.99 (t, *J* = 7.8 Hz, 1H); <sup>13</sup>C NMR (50 MHz):  $\delta$  = 14.1, 22.4 (CH<sub>3</sub>), 28.1 (CH), 38.5, 61.1, 61.2 (CH<sub>2</sub>), 129.2 (C), 148.2 (CH), 163.9, 165.6 (C); HRMS (EI): C<sub>12</sub>H<sub>20</sub>O<sub>4</sub> [*M*<sup>+</sup>] calcd 228.1361, found 228.1366.

<sup>1</sup> Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346-353; e.g.: Boiteau, J.-G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 681-684.

<sup>2</sup> Allan, C. F. H.; Spangler, F. W. *Org. Synth. Coll. Vol. III* **1955**, 377-379.

<sup>3</sup> Tadano, K.-i.; Maeda, H.; Hoshino, M.; Iimura, Y.; Suami, T. *J. Org. Chem.* **1987**, *52*, 1946-1956.

<sup>4</sup> Fraser, W.; Suckling, C. J.; Wood, H. C. S. *J. Chem. Soc. Perkin Trans. 1* **1990**, 3137-3144.

<sup>5</sup> Utley, J. H. P.; Elinson, M.; Güllü, M.; Ludwig, R.; Motevallı, M. *Acta. Chem. Scand.* **1999**, *53*, 901-909.

Diethyl butyridenemalonate (**1b**).<sup>4</sup> According to general procedure A obtained as a colorless oil in 42% yield.  $R_f$  (hexane/EtOAc 20/1) = 0.31; GC (HP1):  $t_R$  = 19.7 min (100°C); <sup>1</sup>H NMR (200 MHz):  $\delta$  = 0.91 (t,  $J$  = 8.1 Hz, 3H), 1.26 (t,  $J$  = 7.8 Hz, 3H), 1.29 (t,  $J$  = 7.9 Hz, 3H), 1.40-1.56 (m, 2H), 2.16-2.32 (m, 2H), 4.20 (q,  $J$  = 7.8 Hz, 2H), 4.26 (q,  $J$  = 7.8 Hz, 2H), 6.96 (t,  $J$  = 8.6 Hz, 1H); <sup>13</sup>C NMR (50 MHz):  $\delta$  = 13.7, 14.0, 14.1 (CH<sub>3</sub>), 21.6, 31.6, 61.1, 61.2 (CH<sub>2</sub>), 128.8 (C), 149.1 (CH), 163.9, 165.5 (C); HRMS (EI): C<sub>11</sub>H<sub>18</sub>O<sub>4</sub> [M<sup>+</sup>] calcd 214.1205, found 214.1211.

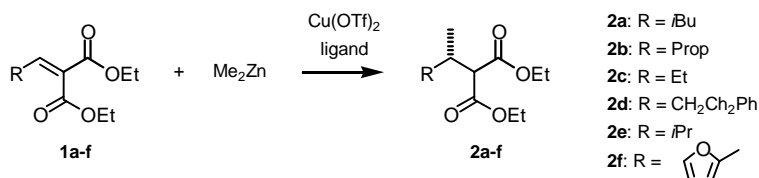
Diethyl propylidenemalonate (**1c**).<sup>4</sup> According to general procedure A obtained as a colorless oil in 43% yield.  $R_f$  (hexane/EtOAc 20/1) = 0.28; GC (HP1):  $t_R$  = 8.1 min (110°C); <sup>1</sup>H NMR (200 MHz):  $\delta$  = 1.06 (t,  $J$  = 7.6 Hz, 3H), 1.15-1.34 (m, 6H), 2.18-2.32 (m, 2H), 4.10-4.32 (m, 4H), 6.94 (t,  $J$  = 8.1 Hz, 1H); <sup>13</sup>C NMR (50 MHz):  $\delta$  = 12.7, 13.9, 14.0 (CH<sub>3</sub>), 23.1, 61.1, 61.4 (CH<sub>2</sub>), 128.1 (C), 150.4 (CH), 163.9, 165.4 (C); HRMS (EI): C<sub>10</sub>H<sub>17</sub>O<sub>4</sub> [MH<sup>+</sup>] calcd 201.1127, found 201.1118.

Diethyl 3-phenyl-propylidenemalonate (**1d**).<sup>6</sup> According to general procedure B obtained as a colorless oil in 27% yield.  $R_f$  (hexane/EtOAc 40/1) = 0.22; GC (HP1):  $t_R$  = 21.4 min (100-210°C, 5°C/min); <sup>1</sup>H NMR (200 MHz):  $\delta$  = 0.69, 0.72 (2x t,  $J$  = 7.8 Hz, 6H), 2.07-2.23 (m, 2H), 2.28-2.41 (m, 2H), 3.89, 3.96 (2x q,  $J$  = 7.8 Hz, 4H), 6.97 (t,  $J$  = 8.4 Hz, 1H), 7.10-7.32 (m, 5H); <sup>13</sup>C NMR (50 MHz):  $\delta$  = 13.9, 14.0 (CH<sub>3</sub>), 31.3, 34.3, 61.1 (CH<sub>2</sub>), 126.2, 128.2, 128.4 (CH), 129.0, 140.3 (C), 148.0 (CH), 163.7, 165.4 (C); HRMS (EI): C<sub>16</sub>H<sub>20</sub>O<sub>4</sub> [M<sup>+</sup>] calcd 276.1361, found 276.1374.

Diethyl isobutyridenemalonate (**1e**).<sup>4,5</sup> According to general procedure A obtained as a colorless oil in 68% yield.  $R_f$  (hexane/EtOAc 20/1) = 0.47; GC (HP1):  $t_R$  = 9.2 min (110°C); <sup>1</sup>H NMR (200 MHz):  $\delta$  = 1.02 (d,  $J$  = 6.6 Hz, 6H), 1.17-1.31 (m, 6H), 2.56-2.69 (m, 1H), 4.10-4.29 (m, 4H), 6.73 (d,  $J$  = 10.6 Hz, 1H); <sup>13</sup>C NMR (50 MHz):  $\delta$  = 14.1, 21.8 (CH<sub>3</sub>), 29.4, 61.1 (CH<sub>2</sub>), 126.5 (C), 154.8 (CH), 164.1, 165.6 (C); HRMS (EI): C<sub>11</sub>H<sub>18</sub>O<sub>4</sub> [M<sup>+</sup>] calcd 214.1205, found 214.1203.

Diethyl 2-furyl-methylidenemalonate (**1f**).<sup>7</sup> According to general procedure A obtained as a colorless oil in 66% yield.  $R_f$  (pentane/EtOAc 20/1) = 0.38; GC (HP1):  $t_R$  = 13.5 min (100-210°C, 5°C/min); <sup>1</sup>H NMR (300 MHz):  $\delta$  = 1.27, 1.32 (2x t,  $J$  = 7.3 Hz, 6H), 4.23, 4.35 (2x q,  $J$  = 7.3 Hz, 4H), 6.44 (dd,  $J$  = 3.7, 1.8 Hz, 1H), 6.72 (d,  $J$  = 3.7 Hz, 1H), 7.40 (s, 1H), 7.46 (s, 1H); <sup>13</sup>C NMR (75 MHz):  $\delta$  = 14.0, 14.1 (CH<sub>3</sub>), 61.4, 61.5 (CH<sub>2</sub>), 112.5, 117.8 (CH), 122.0 (C), 127.4, 146.0 (CH), 148.9, 164.1, 166.2 (C); HRMS (EI): C<sub>12</sub>H<sub>14</sub>O<sub>5</sub> [M<sup>+</sup>] calcd 238.0841, found 238.0828.

**General procedure C.** Conjugate addition of dimethylzinc to unsaturated malonic esters **1**. A solution of flamed dried Cu(OTf)<sub>2</sub> (2 mg, 0.006 mmol, 2 mol%) and phosphoramidite ligand (0.012 mmol, 4 mol%) in 2 mL of freshly distilled solvent was stirred at room temperature for 1-2 h. After cooling to -60°C 20  $\mu$ L of dodecane (internal standard) and 0.28 mmol of the unsaturated malonic ester were added. 0.21 mL of Me<sub>2</sub>Zn (1.5 eq., 2M in toluene) were added slowly. The progress of the reaction was monitored by GC. For quenching the reaction mixture was poured into 5 mL of saturated NH<sub>4</sub>Cl solution and 3 mL of EtOAc. The mixture was vigorously stirred at room temperature for 15 min. The organic layer was then separated and dried over Na<sub>2</sub>SO<sub>4</sub>. For ee determination the crude product was subjected to the next step without further purification.



(*S*)-Diethyl (1,3-dimethylbutyl)malonate (**2a**).<sup>8,9</sup> According to general procedure C obtained as a colorless oil.  $R_f$  (hexane/EtOAc 40/1) = 0.36; GC (HP5):  $t_R$  = 9.5 min (100-170°C, 5°C/min); <sup>1</sup>H NMR (200 MHz):  $\delta$  = 0.84, 0.87 (2x d,  $J$  = 7.1 Hz, 6H), 0.93 (d,  $J$  = 7.4 Hz, 3H), 1.04-1.17 (m, 2H), 1.23 (t,  $J$  = 7.8 Hz, 6H), 1.51-1.72 (m, 1H), 2.18-2.36 (m, 1H), 3.17 (d,  $J$  = 8.7 Hz, 1H), 4.16 (q,  $J$  = 7.8 Hz, 4H); <sup>13</sup>C NMR (50 MHz):  $\delta$  = 14.1, 16.9, 21.4, 23.7, 25.2 (CH<sub>3</sub>, CH), 31.2 (CH), 43.6 (CH<sub>2</sub>), 58.1 (CH), 61.1, 61.5 (CH<sub>2</sub>), 168.8, 168.9 (C); MS (CI): C<sub>13</sub>H<sub>28</sub>NO<sub>4</sub> [M+NH<sub>4</sub><sup>+</sup>] 262.2; [ $\alpha$ ]<sub>D</sub><sup>25</sup> -9.3° (95% ee),  $c$  = 5.6 (CHCl<sub>3</sub>).

(*S*)-Diethyl (1-methylbutyl)malonate (**2b**).<sup>10</sup> According to general procedure C obtained as a colorless oil.  $R_f$  (hexane/EtOAc 20/1) = 0.41. GC (HP1):  $t_R$  = 19.9 min (100°C); <sup>1</sup>H NMR (300 MHz):  $\delta$  = 0.85 (t,  $J$  = 6.4 Hz, 3H), 0.94 (d,  $J$  = 6.6 Hz, 3H), 1.10-1.39 (m, 4H), 1.23 (t,  $J$  = 7.1 Hz, 6H), 2.15-2.24 (m, 1H), 3.18 (d,  $J$  = 8.1 Hz, 1H), 4.15 (q,  $J$  = 7.1 Hz, 4H); <sup>13</sup>C NMR (75 MHz):  $\delta$  = 14.0, 14.1, 16.9 (CH<sub>3</sub>), 19.9 (CH<sub>2</sub>), 33.1 (CH), 36.5 (CH<sub>2</sub>), 57.8 (CH), 61.1 (CH<sub>2</sub>), 169.0 (C); HRMS (EI): C<sub>10</sub>H<sub>17</sub>O<sub>3</sub> [M<sup>+</sup>-OEt] calcd 185.1171, found 185.1178; MS (CI): C<sub>12</sub>H<sub>26</sub>NO<sub>4</sub> [M+NH<sub>4</sub><sup>+</sup>] 248.2; [ $\alpha$ ]<sub>D</sub><sup>26</sup> -1.1° (96% ee),  $c$  = 2.5 (CHCl<sub>3</sub>).

<sup>6</sup> Hon, Y.-S.; Lu, L. *Tetrahedron* **1995**, *51*, 7937-7942.

<sup>7</sup> Fujii, T.; Takahashi, O.; Furukawa, N. *J. Org. Chem.* **1996**, *61*, 6233-6239.

<sup>8</sup> Maas, S.; Stamm, A.; Kunz, H. *Synthesis* **1999**, 1792-1798.

<sup>9</sup> Rice, K. C. *J. Org. Chem.* **1982**, *47*, 3617-3622.

<sup>10</sup> Cook, C. E.; Tallent, C. R. *J. Heterocycl. Chem.* **1969**, *6*, 203-206.

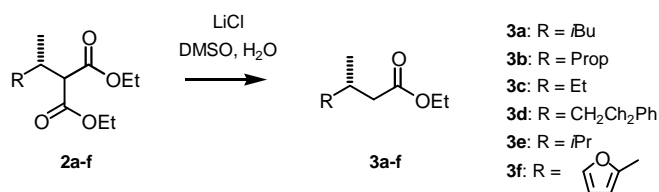
(*S*)-Diethyl (1-methylpropyl)malonate (**2c**).<sup>8,11</sup> According to general procedure C obtained as a colorless oil in 90% yield after flash chromatography.  $R_f$  (hexane/EtOAc 20/1) = 0.45; GC (HP1):  $t_R$  = 8.5 min (110°C);  $^1\text{H NMR}$  (200 MHz):  $\delta$  = 0.89 (t,  $J$  = 7.4 Hz, 3H), 0.96 (d,  $J$  = 6.8 Hz, 3H), 1.10-1.56 (m, 2H), 1.25 (t,  $J$  = 7.1 Hz, 6H), 2.06-2.23 (m, 1H), 3.22 (d,  $J$  = 8.3 Hz, 1H), 4.17 (q,  $J$  = 7.1 Hz, 4H);  $^{13}\text{C NMR}$  (50 MHz):  $\delta$  = 11.2, 14.1, 16.4 (CH<sub>3</sub>), 27.1 (CH<sub>2</sub>), 34.9, 57.5 (CH), 61.0, 61.1 (CH<sub>2</sub>), 168.8, 169.0 (C); HRMS (EI): C<sub>11</sub>H<sub>20</sub>O<sub>4</sub> [M<sup>+</sup>-OEt] calcd 171.1021, found 171.1028;  $[\alpha]_D^{23}$  +8.5° (92% ee),  $c$  = 2.0 (CHCl<sub>3</sub>).

(*S*)-Diethyl (1-methyl-3-phenylpropyl)malonate (**2d**).<sup>12</sup> According to general procedure C obtained as a colorless oil.  $R_f$  (hexane/EtOAc 40/1) = 0.25;  $^1\text{H NMR}$  (200 MHz):  $\delta$  = 1.07 (d,  $J$  = 6.8 Hz, 3H), 1.16-1.31 (m, 6H), 1.42-1.62 (m, 1H), 1.66-1.852 (m, 1H), 2.22-2.38 (m, 1H), 2.49-2.81 (m, 2H), 3.33 (d,  $J$  = 9.8 Hz, 1H), 4.19 (q,  $J$  = 7.3 Hz, 4H);  $^{13}\text{C NMR}$  (50 MHz):  $\delta$  = 14.1, 16.9 (CH<sub>3</sub>), 33.1 (CH), 33.2, 36.2 (CH<sub>2</sub>), 57.5 (CH), 61.1 (CH<sub>2</sub>), 125.8, 128.2, 128.3 (CH), 142.0, 168.6 (C); HRMS (EI) C<sub>17</sub>H<sub>24</sub>O<sub>4</sub> [M<sup>+</sup>] calcd 292.1674, found 292.1670;  $[\alpha]_D^{25}$  -2.8° (86% ee),  $c$  = 5.0 (CHCl<sub>3</sub>).

(*R*)-Diethyl (1,2-dimethylpropyl)malonate (**2e**).<sup>8,13</sup> According to general procedure C obtained as a colorless oil.  $R_f$  (hexane/EtOAc 40/1) = 0.37; GC (HP1):  $t_R$  = 11.9 min (110°C);  $^1\text{H NMR}$  (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 0.80, 0.85, 0.91 (3x d,  $J$  = 6.8 Hz, 9H), 1.23 (t,  $J$  = 7.1 Hz, 6H), 1.58-1.71 (m, 1H), 2.10-2.24 (m, 1H), 3.31 (d,  $J$  = 9.3 Hz, 1H), 4.16 (q,  $J$  = 6.8 Hz, 4H);  $^{13}\text{C NMR}$  (50 MHz, CDCl<sub>3</sub>):  $\delta$  = 11.7, 14.0, 14.1, 16.6, 21.2 (CH<sub>3</sub>), 29.6, 38.8, 56.4 (CH), 61.0, 61.1 (CH<sub>2</sub>), 169.0, 169.1 (C).

(*R*)-Diethyl 1-(2-furyl)-ethylmalonate (**2f**).<sup>14</sup> According to general procedure C obtained as a colorless oil.  $R_f$  (hexane/EtOAc 20/1) = 0.21;  $^1\text{H NMR}$  (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.08, 1.19 (2x t,  $J$  = 7.2 Hz, 6H), 1.23-1.30 (m, 3H), 3.52-3.61 (m, 2H), 4.01, 4.13 (2x q,  $J$  = 7.3 Hz, 4H), 5.99 (d,  $J$  = 2.9 Hz, 1H), 6.19 (dd,  $J$  = 3.3, 1.8 Hz, 1H), 7.20-7.25 (m, 1H);  $^{13}\text{C NMR}$  (75 MHz):  $\delta$  = 13.8, 14.0, 16.9 (CH<sub>3</sub>), 33.4, 56.9 (CH), 61.2, 61.3 (CH<sub>2</sub>), 105.4, 109.9, 141.3 (CH), 156.0, 167.9 (C);  $[\alpha]_D^{27}$  -13.5° (78% ee),  $c$  = 5.4 (CHCl<sub>3</sub>); HRMS (EI) C<sub>13</sub>H<sub>18</sub>O<sub>5</sub> [M<sup>+</sup>] calcd 254.1154, found 254.1149.

**General procedure D.**<sup>15</sup> Deethoxycarbonylation of malonic esters **2**. Typically, 0.56 mmol H<sub>2</sub>O and 1.12 mmol LiCl were added to a solution of 0.28 mmol diester in 1 mL of DMSO or DMF. The mixture was heated to 160°C for 8-12 h. After cooling to room temperature 3 mL of water was added. After extraction with ethyl acetate the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and subjected to ee determination.



(*S*)-Ethyl 3,5-dimethylhexanoate (**3a**).<sup>9</sup> According to general procedure D obtained as a yellowish oil.  $R_f$  (hexane/EtOAc 50/1) = 0.70; GC (Chiraldex G-TA): (*S*)-**3a**:  $t_R$  = 12.6 min, (*R*)-**3a**:  $t_R$  = 12.4 min (70-80°C, 0.5°C/min);  $^1\text{H NMR}$  (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 0.80-0.91 (m, 9H), 1.01-1.14 (m, 2H), 1.23 (t,  $J$  = 7.0 Hz, 3H), 1.53-1.67 (m, 1H), 1.93-2.10 (m, 2H), 2.17-2.28 (m, 1H), 4.08 (q,  $J$  = 7.0 Hz, 2H);  $^{13}\text{C NMR}$  (50 MHz, CDCl<sub>3</sub>):  $\delta$  = 14.3, 19.8, 22.1, 23.2, 25.2, 28.1 (CH<sub>3</sub>, CH), 42.2, 46.2, 60.0 (CH<sub>2</sub>), 173.3 (C); MS (CI): C<sub>8</sub>H<sub>20</sub>NO<sub>2</sub> [M+NH<sub>4</sub><sup>+</sup>] 190.3;  $[\alpha]_D^{26}$  -1.67° (95% ee),  $c$  = 7.2 (CHCl<sub>3</sub>).

(*S*)-Ethyl 3-methylhexanoate (**3b**).<sup>10,16</sup> According to general procedure D obtained after flash chromatography as a colorless oil in 91% yield (2 steps).  $R_f$  (pentane) = 0.14; GC (Chiraldex G-TA): (*S*)-**3b**:  $t_R$  = 10.3 min, (*R*)-**3b**:  $t_R$  = 10.0 min (70-80°C, 0.5°C/min);  $^1\text{H NMR}$  (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 0.78-0.92 (m, 6H), 1.10-1.35 (m, 7H), 1.85-1.97 (m, 1H), 2.06 (dd,  $J$  = 14.0, 8.3 Hz, 1H), 2.25 (dd,  $J$  = 14.4, 5.9 Hz, 1H), 4.09 (q,  $J$  = 7.1 Hz, 2H);  $^{13}\text{C NMR}$  (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 14.1, 14.2, 19.6 (CH<sub>3</sub>), 19.9 (CH<sub>2</sub>), 30.0 (CH), 38.9, 41.8, 59.9 (CH<sub>2</sub>), 173.3 (C); HRMS (EI): C<sub>9</sub>H<sub>18</sub>O<sub>2</sub> [M<sup>+</sup>] calcd 158.1307, found 158.1308; MS (CI): C<sub>9</sub>H<sub>22</sub>NO<sub>2</sub> [M+NH<sub>4</sub><sup>+</sup>] 176.2;  $[\alpha]_D^{23}$  -0.15° (neat, 96% ee).

(*S*)-Ethyl 3-methylpentanoate (**3c**).<sup>17</sup> According to general procedure D obtained as a colorless oil.  $R_f$  (hexane/MTBE 40/1) = 0.61; GC (Chiraldex G-TA): (*S*):  $t_R$  = 6.5 min, (*R*):  $t_R$  = 6.7 min (70-80°C, 0.5°C/min);  $^1\text{H NMR}$  (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 0.78-0.89 (m, 6H), 1.11-1.38 (m, 2H), 1.20 (t,  $J$  = 7.0 Hz, 3H), 1.76-1.89 (m, 1H), 2.04 (dd,  $J$  = 14.6, 8.1 Hz, 1H), 2.25 (dd,  $J$  = 14.6, 6.2 Hz, 1H), 4.07 (q,  $J$  = 7.0 Hz, 2H);  $^{13}\text{C NMR}$  (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 11.2, 14.2, 19.2 (CH<sub>3</sub>), 29.3 (CH<sub>2</sub>), 31.9 (CH), 41.5, 59.9 (CH<sub>2</sub>), 173.2 (C); MS (CI): C<sub>8</sub>H<sub>20</sub>NO<sub>2</sub> [M+NH<sub>4</sub><sup>+</sup>] 162.2;  $[\alpha]_D^{25}$  +10.0° (96% ee),  $c$  = 1.8 (cyclohexane).

<sup>11</sup> Alexakis, A.; Benhaim, C. *Tetrahedron: Asymmetry* **2001**, *12*, 1151-1157.

<sup>12</sup> Carter *J. Biol. Chem.* **1935**, *108*, 619, 624.

<sup>13</sup> Cahiez, G.; Alami, M. *Tetrahedron* **1989**, *45*, 4163-4176.

<sup>14</sup> Holmberg, G.-A.; Karlsson, M.; Ulfstedt, O.; Olli, M. *Acta Chem. Scand.* **1972**, *26*, 3483-3491.

<sup>15</sup> Krapcho, A. P. *Synthesis* **1982**, 805-822.

<sup>16</sup> Sakata, H.; Aoki, Y.; Kuwajima, I. *Tetrahedron Lett.* **1990**, *31*, 1161-1164.

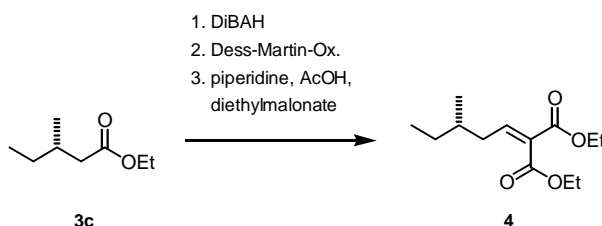
<sup>17</sup> Brown, H.C.; Joshi, N. N.; Pyun, C.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 1754-1758.

(*S*)-Ethyl 3-methyl-5-phenylpentanoate (**3d**).<sup>18</sup> According to general procedure D obtained as a colorless oil.  $R_f$  (hexane/EtOAc 40/1) = 0.56; HPLC (Chiracel OB-H, hexane/*i*PrOH 99:1, 0.5 mL/min): (*S*):  $t_R$  = 13.5 min, (*R*):  $t_R$  = 14.6 min;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.02 (d,  $J$  = 6.3 Hz, 3H), 1.26 (t,  $J$  = 7.1 Hz, 3H), 1.42-1.78 (m, 2H), 2.18 (dd,  $J$  = 15.6, 8.5 Hz, 1H), 2.32 (dd,  $J$  = 15.6, 6.5 Hz, 1H), 2.51-2.77 (m, 1H), 4.13 (q,  $J$  = 7.1 Hz, 2H), 7.08-7.42 (m, 5H);  $[\alpha]_D^{25}$  -11.6° (86% ee),  $c$  = 0.5 ( $\text{CHCl}_3$ ), HRMS (EI)  $\text{C}_{14}\text{H}_{20}\text{O}_2$  [ $\text{M}^+$ ] calcd 220.1463, found 220.1468.

(*R*)-Ethyl 3,4-dimethylpentanoate (**3e**).<sup>17</sup> According to general procedure D obtained as a colorless oil.  $R_f$  (hexane/EtOAc 40/1) = 0.69; (Chiraldex G-TA): (*R*):  $t_R$  = 9.7 min, (*S*):  $t_R$  = 9.4 min (70-80°C, 0.5°C/min);  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.78-0.98 (m, 9H), 1.23 (t,  $J$  = 7.8 Hz, 3H), 1.50-1.66 (m, 1H), 1.78-1.98 (m, 1H), 2.04 (dd,  $J$  = 15.7, 10.0 Hz, 1H), 2.32 (dd,  $J$  = 15.7, 5.5 Hz, 1H), 4.10 (q,  $J$  = 7.1 Hz, 2H);  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 14.2, 15.8, 18.2, 19.8 ( $\text{CH}_3$ ), 32.1, 35.9 (CH), 39.2, 60.1 ( $\text{CH}_2$ ), 173.8 (C);  $[\alpha]_D^{23}$  +6.1° (96% ee),  $c$  = 1.8 ( $\text{CHCl}_3$ ).

(*R*)-Ethyl 3-(2-furyl)-butanoate (**3f**). According to general procedure D obtained as a colorless oil.  $R_f$  (hexane/EtOAc 40/1) = 0.56; HPLC (Whelk-01, hexane/*i*PrOH 99.5:0.5, 1 mL/min) major:  $t_R$  = 5.9 min, minor:  $t_R$  = 6.3 min;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.17-1.37 (m, 6H), 1.23-1.30 (m, 3H), 2.44 (dd,  $J$  = 15.1, 6.6 Hz, 1H), 2.71 (dd,  $J$  = 15.1, 8.2 Hz, 1H), 4.13 (q,  $J$  = 7.3 Hz, 2H), 6.00 (d,  $J$  = 3.2 Hz, 1H), 6.27 (dd,  $J$  = 3.2, 1.7 Hz, 1H), 7.26-7.36 (m, 1H);  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 14.2, 18.8 ( $\text{CH}_3$ ), 30.1 (CH), 60.4, 40.5 ( $\text{CH}_2$ ), 103.8, 109.9, 141.0 (CH), 158.6, 172.1 (C);  $[\alpha]_D^{25}$  -7.6° (78% ee),  $c$  = 1.8 ( $\text{CHCl}_3$ ), HRMS (EI)  $\text{C}_{10}\text{H}_{14}\text{O}_3$  [ $\text{M}^+$ ] calcd 182.0943, found 182.0948.

**Synthesis of unsaturated diester 4.**<sup>19</sup> To a solution of 4 mmol crude **3c** in 20 mL  $\text{Et}_2\text{O}$  at -78°C were added 12 mL (3 eq) DiBALH (1M in hexanes) dropwise. The reaction mixture was stirred for additional 3h at -78°C. After warming to room temperature the solution was concentrated to 5 mL. 5g of  $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$  were added and after stirring for 30 min removed by filtration (5 mL  $\text{CH}_2\text{Cl}_2$  rinse). The obtained clear solution of the alcohol<sup>20</sup> ( $R_f$  (pentane/MTBE 20:1) = 0.14) was then cooled to -5°C and 2.2 g (1.3 eq) Dess-Martin periodinane<sup>21</sup> were added portionwise over 5 min. The cloudy solution was stirred for 2h at rt. The reaction mixture was poured into a mixture of 30 mL sat. aq.  $\text{NaHCO}_3$  solution and 6.8 g  $\text{Na}_2\text{S}_2\text{O}_3$  at 0°C. After extraction of the aqueous layer with  $\text{CH}_2\text{Cl}_2$  the combined organic fractions were concentrated to 7 mL. The obtained solution of pure aldehyde<sup>22</sup> ( $R_f$  (hexane/ $\text{Et}_2\text{O}$  10:1) = 0.26) was then cooled to 0°C and 610  $\mu\text{L}$  (1eq) diethylmalonate, 20  $\mu\text{L}$  glacial acetic acid and 40  $\mu\text{L}$  piperidine were added. The cooling bath was removed and the reaction mixture stirred at room temperature overnight. The reaction mixture was filtered over celite (3x 5 mL  $\text{CH}_2\text{Cl}_2$  rinse), washed with saturated  $\text{NaHCO}_3$  solution and brine and dried over  $\text{Na}_2\text{SO}_4$ . After concentration the crude product was purified by flash chromatography.



(*S*)-Ethyl 2-ethoxycarbonyl-5-methyl-hept-2-enoate (**4**). Obtained as a colorless oil in 43% yield (4 steps, starting from **2c**). GC (HP1):  $t_R$  = 11.1 min (100-210°C, 5°C/min);  $R_f$  (hexane/EtOAc 40/1) = 0.38;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.73-0.85 (m, 6H), 1.03-1.36 (m, 8H), 1.43-1.58 (m, 1H), 2.00-2.13 (m, 1H), 2.17-2.28 (m, 1H), 4.16, 4.22 (2x q,  $J$  = 7.0 Hz, 4H), 6.94 (t,  $J$  = 7.9 Hz, 1H);  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 11.2, 14.0, 14.1, 19.1 ( $\text{CH}_3$ ), 29.2 ( $\text{CH}_2$ ), 34.5 (CH), 36.4, 61.0, 61.1 ( $\text{CH}_2$ ), 129.2 (C), 148.3 (CH), 163.9, 165.6 (C); HRMS (EI)  $\text{C}_{13}\text{H}_{22}\text{O}_4$  [ $\text{M}^+$ ] calcd 242.1518, found 242.1524;  $[\alpha]_D^{24}$  -4.1° (96% ee),  $c$  = 2.4 ( $\text{CHCl}_3$ ).

<sup>18</sup> Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473-9474.

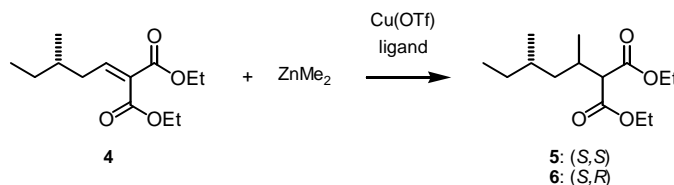
<sup>19</sup> Because of the high volatility of the ester **3c**, the corresponding alcohol and aldehyde these compounds were not isolated in pure form.

<sup>20</sup> Roeder, M.; Spiegelstein, O.; Schurig, V.; Bialer, M.; Yagun, B. *Tetrahedron: Asymm.* **1999**, *10*, 841-853.

<sup>21</sup> Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156.

<sup>22</sup> Tietze, L. F.; Schiemann, K.; Wegner, C.; Wulff, C. *Chem. Eur. J.* **1996**, *2*, 1164-1172.

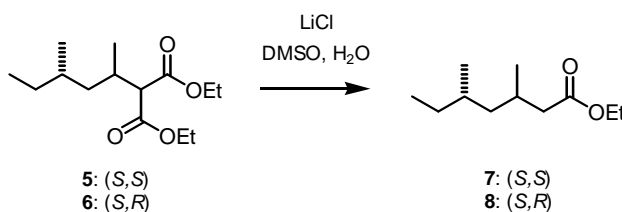
**General procedure E.** Conjugate addition of dimethylzinc to unsaturated malonic ester **4**. A solution of flamed dried  $\text{Cu}(\text{OTf})_2$  (7 mg, 0.02 mmol, 3 mol%) and phosphoramidite ligand (0.04 mmol, 6 mol%) in 6 mL of freshly distilled toluene was stirred at room temperature for 1-2 h. After cooling to  $-60^\circ\text{C}$  0.71 mmol of the unsaturated malonic ester were added. 0.54 mL of  $\text{Me}_2\text{Zn}$  (1.5 eq, 2M in toluene) were added slowly. The progress of the reaction was monitored by GC. For quenching the reaction mixture was poured into 15 mL of saturated  $\text{NH}_4\text{Cl}$  solution and 9 mL of EtOAc. The mixture was vigorously stirred at room temperature for 15 min. The organic phase was then separated and dried over sodium sulfate. For ee determination the crude product was subjected to the next step without further purification.



(*S,S*)-Diethyl (1,3-dimethylpentyl)malonate (**5**). According to general procedure E obtained as a colorless oil. GC (HP1):  $t_{\text{R}} = 10.9$  min (100-210 $^\circ\text{C}$ , 5 $^\circ\text{C}/\text{min}$ );  $R_{\text{f}}$  (hexane/EtOAc 20/1) = 0.34;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 0.77$ -0.84 (m, 6H), 0.95 (d,  $J = 7.0$  Hz, 3H), 0.96-1.09 (m, 2H), 1.23 (t,  $J = 7.0$  Hz, 3H), 1.20-1.45 (m, 3H), 2.21-2.38 (m, 1H), 3.18 (d,  $J = 7.7$  Hz, 1H), 4.15 (q,  $J = 7.0$  Hz, 4H);  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 10.8$ , 14.1, 17.2, 19.9 ( $\text{CH}_3$ ), 28.1 ( $\text{CH}_2$ ), 31.0, 31.4 (CH), 41.6, 61.0, 61.1 ( $\text{CH}_2$ ), 168.8, 169.0 (C); HRMS (EI)  $\text{C}_{12}\text{H}_{21}\text{O}_4$  [ $\text{M}^+ - \text{C}_2\text{H}_5$ ] calcd 229.1440, found 229.1430; MS (CI):  $\text{C}_{14}\text{H}_{30}\text{NO}_4$  [ $\text{M} + \text{NH}_4^+$ ] 276.3;  $[\alpha]_{\text{D}}^{24} -3.9^\circ$  (dr 97:3, 96% ee),  $c = 1.8$  ( $\text{CHCl}_3$ ).

(*S,R*)-Diethyl (1,3-dimethylpentyl)malonate (**6**). According to general procedure E obtained as a colorless oil. GC (HP1):  $t_{\text{R}} = 11.0$  min (100-210 $^\circ\text{C}$ , 5 $^\circ\text{C}/\text{min}$ );  $R_{\text{f}}$  (hexane/EtOAc 20/1) = 0.40;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 0.77$ -0.86 (m, 6H), 0.91 (d,  $J = 7.0$  Hz, 3H), 1.01-1.27 (m, 4H), 1.23 (t,  $J = 7.0$  Hz, 3H), 1.28-1.42 (m, 1H), 2.21-2.38 (m, 1H), 3.13 (d,  $J = 8.4$  Hz, 1H), 4.15 (q,  $J = 7.0$  Hz, 4H);  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 11.4$ , 14.1, 16.8, 18.4 ( $\text{CH}_3$ ), 30.5 ( $\text{CH}_2$ ), 31.0, 31.7 (CH), 41.3 ( $\text{CH}_2$ ), 58.5 (CH), 61.0, 61.1 ( $\text{CH}_2$ ), 168.8, 168.9 (C); HRMS (EI)  $\text{C}_{12}\text{H}_{21}\text{O}_4$  [ $\text{M}^+ - \text{C}_2\text{H}_5$ ] calcd 229.1440, found 229.1433; MS (CI):  $\text{C}_{14}\text{H}_{30}\text{NO}_4$  [ $\text{M} + \text{NH}_4^+$ ] 276.2;  $[\alpha]_{\text{D}}^{22} +15.5^\circ$  (dr 97:3, 96% ee),  $c = 2.2$  ( $\text{CHCl}_3$ ).

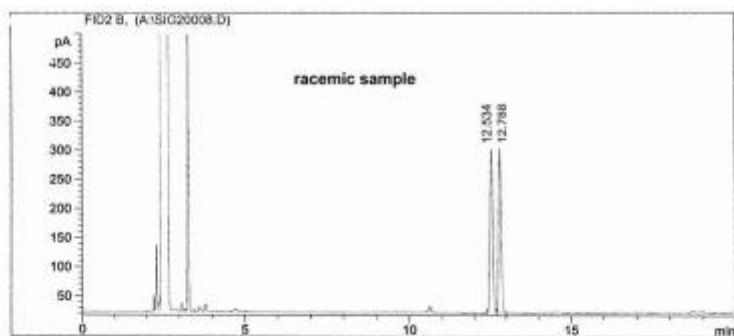
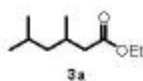
**General procedure F.** Deethoxycarbonylation of malonic esters **5** and **6**. Typically, 1.4 mmol  $\text{H}_2\text{O}$  and 2.8 mmol LiCl were added to a solution of 0.71 mmol diester in 2.5 mL DMSO. The mixture was heated to 160 $^\circ\text{C}$  for 8-12 h. After cooling to room temperature 3 mL of water were added. After extraction with ethyl acetate the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ . After concentration the crude product was purified by flash chromatography.



(*S,S*)-Ethyl 3,5-dimethylheptanoate (**7**).<sup>23</sup> According to general procedure F obtained as a colorless oil in 60% yield (2 steps). GC (HP1):  $t_{\text{R}} = 4.85$  min (100-160 $^\circ\text{C}$ , 5 $^\circ\text{C}/\text{min}$ ), (Chiraldex G-TA):  $t_{\text{R}} = 20.7$  min (70-80 $^\circ\text{C}$ , 0.5 $^\circ\text{C}/\text{min}$ );  $R_{\text{f}}$  (hexane/MTBE 40/1) = 0.63;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta = 0.77$ -0.86 (m, 6H), 0.90 (d,  $J = 6.2$  Hz, 3H), 0.90-1.13 (m, 2H), 1.23 (t,  $J = 7.0$  Hz, 3H), 1.18-1.43 (m, 3H), 1.96-2.08 (m, 2H), 2.20-2.31 (m, 1H), 4.10 (q,  $J = 7.1$  Hz, 2H, Et);  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 11.1$ , 14.3, 19.5, 20.3 ( $\text{CH}_3$ ), 27.9 (CH), 29.0 ( $\text{CH}_2$ ), 31.5 (CH), 41.8, 44.1, 60.0 ( $\text{CH}_2$ ), 173.4 (C); HRMS (EI)  $\text{C}_{11}\text{H}_{22}\text{O}_2$  [ $\text{M}^+$ ] calcd 186.1620, found 186.1632; MS (CI):  $\text{C}_8\text{H}_{20}\text{NO}_2$  [ $\text{M} + \text{NH}_4^+$ ] 204.3;  $[\alpha]_{\text{D}}^{22} -2.7^\circ$  (dr 97:3, 96% ee),  $c = 2.2$  ( $\text{CHCl}_3$ ).

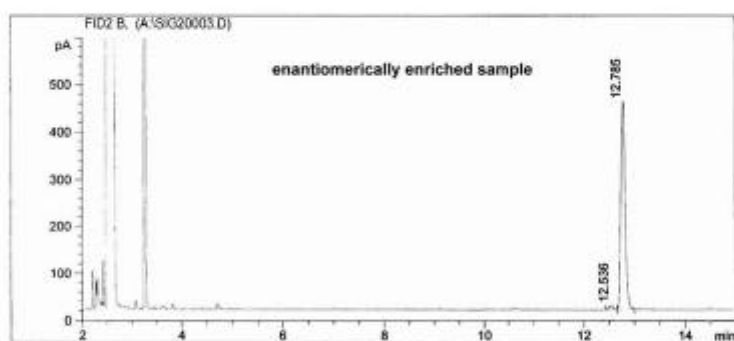
(*S,R*)-Ethyl 3,5-dimethylheptanoate (**8**). According to general procedure F obtained as a colorless oil in 62% yield (2 steps). GC (HP1):  $t_{\text{R}} = 4.89$  min (100-160 $^\circ\text{C}$ , 5 $^\circ\text{C}/\text{min}$ ), (Chiraldex G-TA):  $t_{\text{R}} = 20.9$  min (70-80 $^\circ\text{C}$ , 0.5 $^\circ\text{C}/\text{min}$ );  $R_{\text{f}}$  (hexane/MTBE 40/1) = 0.57;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 0.79$ -0.94 (m, 9H), 1.02-1.38 (m, 5H), 1.26 (t,  $J = 7.1$  Hz, 3H), 2.02-2.08 (m, 1H), 2.09 (dd,  $J = 14.6$ , 7.8 Hz, 1H), 2.22 (dd,  $J = 14.6$ , 5.9 Hz, 1H), 4.11 (q,  $J = 7.1$  Hz, 2H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 11.5$ , 14.4, 18.9, 19.5 ( $\text{CH}_3$ ), 27.9 (CH), 30.2 ( $\text{CH}_2$ ), 31.7 (CH), 42.7, 44.0, 60.1 ( $\text{CH}_2$ ), 173.2 (C); MS (CI):  $\text{C}_{11}\text{H}_{22}\text{NO}_2$  [ $\text{M} + \text{NH}_4^+$ ] 204.2;  $[\alpha]_{\text{D}}^{22} -1.4^\circ$  (dr 97:3, 96% ee),  $c = 2.3$  ( $\text{CHCl}_3$ ).

<sup>23</sup> Burke, R. L.; Herbst, R. M. *J. Org. Chem.* **1955**, *20*, 726-735.



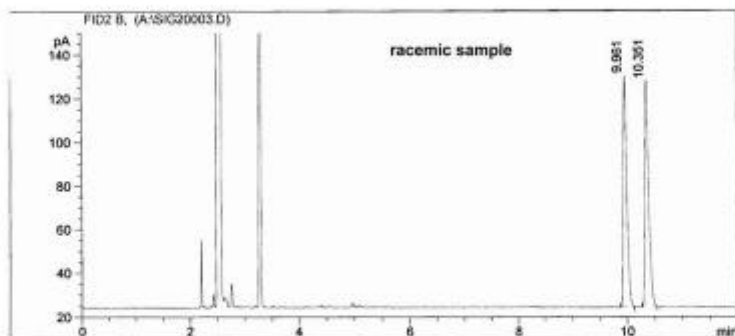
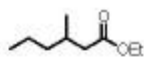
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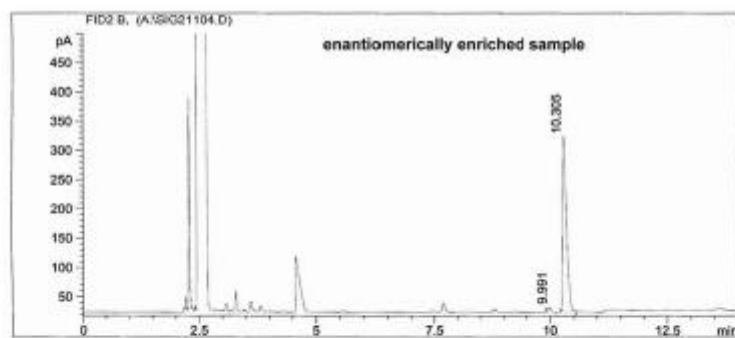
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2	12.785	BB		0.092	2603.545	98.319	0.000	0.000



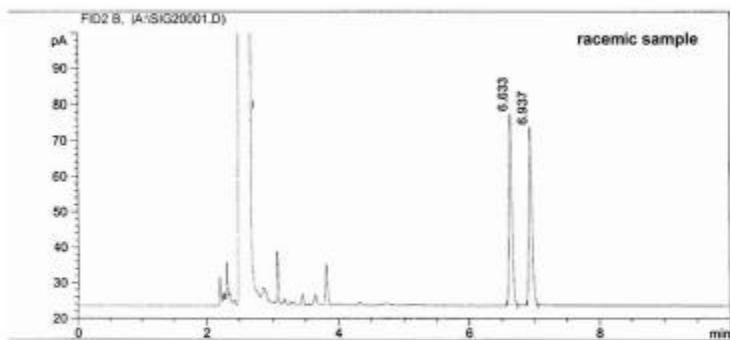
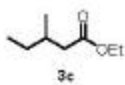
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2	0.000			0.000	0.000	0.000	0.000	0.000
3	9.961	PB		0.072	481.656	48.606	0.000	0.000
4	10.351	PB		0.073	509.280	51.394	0.000	0.000



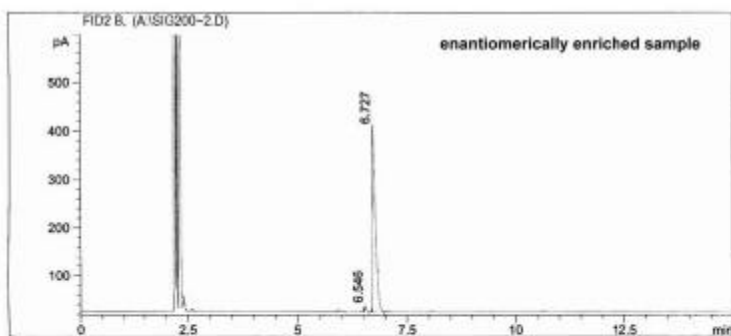
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2	10.305	PB		0.079	1611.237	98.172	0.000	0.000



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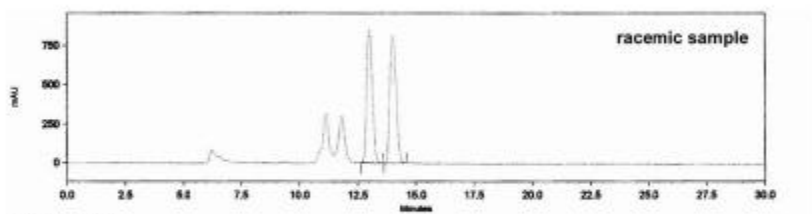
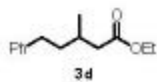
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2	6.937	PB		0.053	168.548	49.516	0.000	0.000



Signal 1: FID2 B,

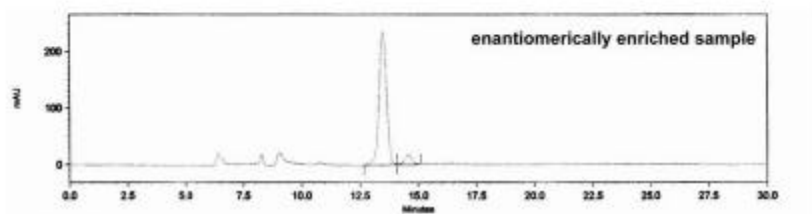
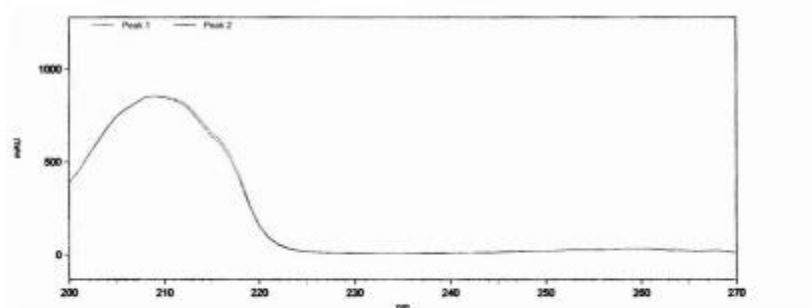
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2	6.727	PB		0.065	1808.759	98.149	0.000	0.000





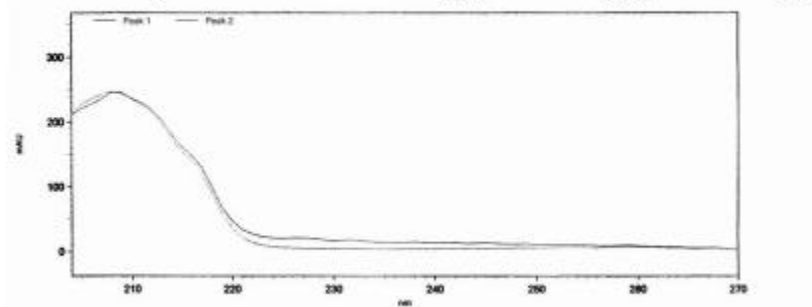
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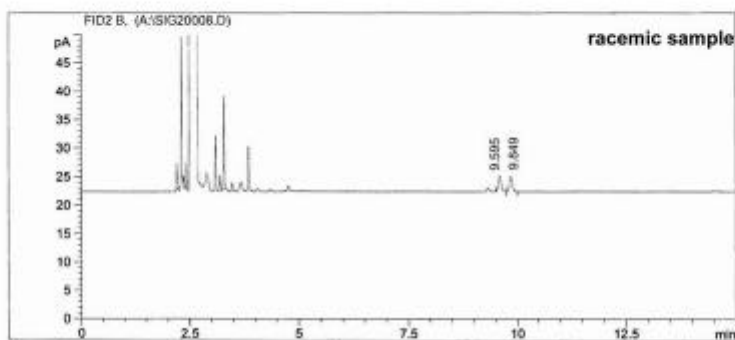
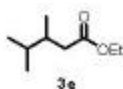
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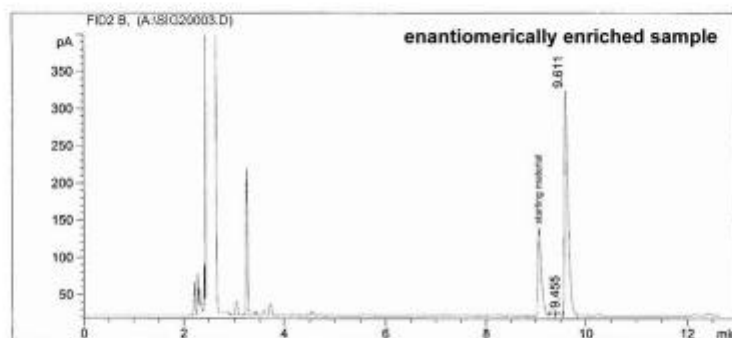
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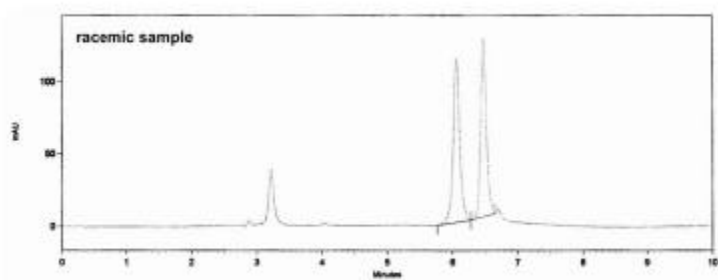
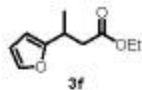
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1	0.000			0.000	0.000	0.000	0.000	0.000
2	0.000			0.000	0.000	0.000	0.000	0.000
3	9.595	BP		0.074	12.526	50.564	0.000	0.000
4	9.649	BB		0.075	12.247	49.436	0.000	0.000



Signal 1: FID2 B,

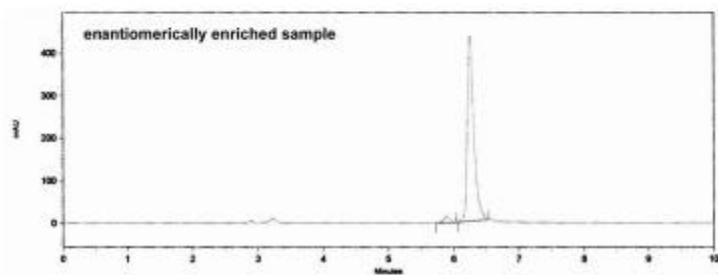
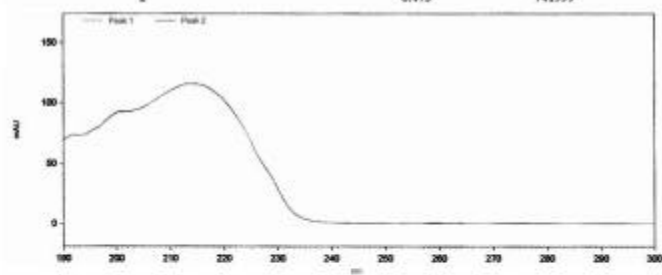
Peak #	RT [min]	Type	Name	Width [min]	Area	Area %	Response	Amount
1	9.339	BBA		0.059	12.034	0.802	0.000	0.000
2	9.455	BBA		0.056	13.802	0.920	0.000	0.000
3	9.611	BB		0.075	1474.504	98.278	0.000	0.000

} 99% ee



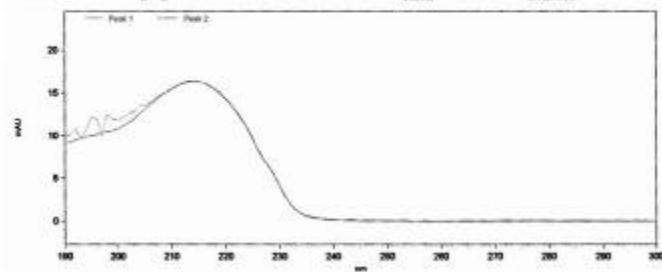
1: 215 nm, 2 nm

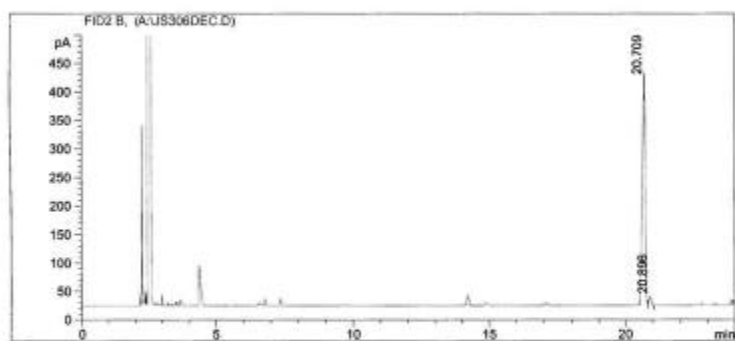
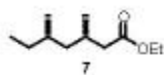
Pk #	Name	Retention Time	Area	Area Percent
1		6.059	798717	51.84
2		6.475	741999	48.16



1: 215 nm, 2 nm

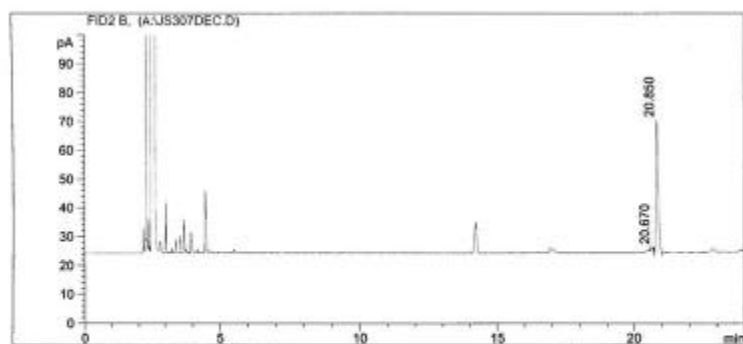
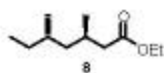
Pk #	Name	Retention Time	Area	Area Percent
1		5.899	92464	2.97
2		6.251	3019066	97.03





Signal 1: FID2 B.

Peak #	RT [min]	Type	Name	Width [min]	Area	Area %	Response	Amount
1	20.709	BV		0.096	2899.971	97.001	0.000	0.000
2	20.896	VB		0.085	89.656	2.999	0.000	0.000



Signal 1: FID2 B.

Peak #	RT [min]	Type	Name	Width [min]	Area	Area %	Response	Amount
1	20.670	PP		0.067	4.810	1.823	0.000	0.000
2	20.850	VB		0.087	259.002	98.177	0.000	0.000