Catalytic Asymmetric Synthesis of α -Amino Phosphonates Using Enantioselective Carbon-Carbon Bond-Forming Reactions

Shū Kobayashi,* Hiroshi Kiyohara, Yoshitaka Nakamura, Ryosuke Matsubara

*Graduate School of Pharmaceutical Sciences, The University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

Supporting Information

Table of Contents	Pages
General	S-1
Preparation of α -iminophosphonate 1	S-1
Typical procedure for the reactions of N-acyl- α -iminophosphonate in the presence of HFIP)	S-3
Typical procedure for the reactions of N-acyl- α -iminophosphonate in the absence of HFIP	S-3
Transformation of 4a into compound 12	S-4
Determination of the ee of compound 4k	S-5
Transformation of 4g into 8g	S-6
Physical data	S-8
References	S-16

General. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400, or JNM-LA500 spectrometer in CDCl_3 unless otherwise noted. Tetramethylsilane (TMS)

served as internal standard ($\delta = 0$) for ^1H NMR, and CDCl_3 was used as internal standard ($\delta = 77.0$) for ^{13}C NMR. IR spectra were measured with a JASCO FT/IR-610 spectrometer. Optical rotations were measured with a JASCO P-1010 polarimeter. High-performance liquid chromatography was carried out using following apparatuses; SHIMADZU LC-10AT (liquid chromatograph), SHIMADZU SPD-10A (UV detector), and SHIMADZU C-R6A Chromatopac. Column chromatography was conducted on Silica gel 60 (Merck) and preparative thin-layer chromatography was carried out using Wakogel B-5F. All reactions were carried out under argon atmosphere in a dried glassware. All solvents were dried and distilled by standard procedures. Silicon enolates **2a**, **2b**, **2f**, **2h**, and **2i** were prepared from the corresponding ketones by standard protocols using LDA.¹ Silicon enolates **2c**, **2d**, **2e**, **2g**, **2j**, **2k**, and **2l** were prepared from the corresponding ketones by reported methods.^{2,3}

Preparation of α -iminophosphonate **1**

To a solution of [bromo-(2,2,2-trichloro-ethoxycarbonylamino)-methyl]-phosphonic acid diethyl ester⁴ (0.30 mmol) in CH_2Cl_2 (3.0 mL) was added piperidinomethylpolystyrene⁵ (3.70 mmol/g, 243 mg, 0.90 mmol) and molecular sieves 4A (30 mg). The reaction mixture was stirred at rt for 20 min, and the mixture was filtered under argon atmosphere through membrane filter (Whatman 0.15 μm). This solution was used immediately in the following reaction.

Typical procedure for the reactions of N-acyl- α -iminophosphonate in the presence of HFIP

To a mixture of $\text{Cu}(\text{OTf})_2$ (7.2 mg, 0.020 mmol) and ligand (*R,R*)-**3** (10.8 mg, 0.022 mmol) was added the indicated solvent (1.5 mL) under argon atmosphere. The reaction mixture was stirred for 6 h, then molecular sieve 3A (10.0 mg) was added, and the mixture was cooled to 0 °C. Silicon enolate (0.10 mmol) in the indicated solvent (0.5 mL) and HFIP (0.40 mmol) in the indicated solvent (0.5 mL) were added by using separate syringes. Then, an N-acyl- α -iminophosphonate dichloromethane solution (0.1 M, 2.0 mL, 0.2 mmol) and a silicon enolate solution (the indicated solvent, 0.1 M, 2.0 mL, 0.2 mmol) were slowly added over the indicated time, and the reaction mixture was stirred for another 1 h. A saturated NaHCO_3 aqueous solution was added, and then the mixture was stirred vigorously until the organic phase turned to blue. The aqueous layer was extracted with CH_2Cl_2 5 times and then the combined organic phase was washed with brine. The organic phase was dried over anhydrous sodium sulfate. After removal of the solvents, the crude mixture was purified by chromatography on silica gel.

Typical procedure for the reactions of N-acyl- α -iminophosphonate in the absence of HFIP

To a mixture of Cu(OTf)₂ (7.2 mg, 0.020 mmol) and ligand (*R,R*) **3** (10.8 mg, 0.022 mmol) was added toluene (1.5 mL) under argon atmosphere. The mixture was stirred for 6 h, then molecular sieve 3A (10.0 mg) was added, and the mixture was cooled to 0 °C. Silicon enolate (0.10 mmol) in toluene (1.0 mL) was added. Then, an N-acyl- α -iminophosphonate dichloromethane solution (0.1 M, 2.0 mL, 0.2 mmol) and a silicon enolate solution (toluene, 0.1 M, 2.0 mL, 0.2 mmol) were slowly added for 48 h, and the reaction mixture was stirred for another 1 h. A saturated NaHCO₃ aqueous solution was added, and the mixture was vigorously stirred until the organic phase turned to blue. The aqueous layer was extracted with CH₂Cl₂ 5 times, and then the combined organic phase was washed with brine. The organic phase was dried over anhydrous sodium sulfate. After removal of the solvents, the organics were dissolved in dichloromethane (2.0 mL) and hydrogen fluoride-pyridine (several drops, excess amount) was added. The mixture was stirred for 1 h. A saturated NaHCO₃ aqueous solution was added, and the aqueous layer was extracted with CH₂Cl₂ 5 times and then the combined organic phase was washed with brine. The organic phase was dried over anhydrous sodium sulfate. After removal of the solvents, the crude mixture was purified by chromatography on silica gel.

Transformation of 4a into compound 12

To a solution of compound **4a** (46.1 mg, 0.10 mmol) in acetic acid (1.0 mL) was added zinc powder (activated by HCl aq, 45.6 mg, 0.70 mmol).⁶ The mixture was vigorously stirred for 2 h and then filtered through celite, and washed with water. The water phase was washed with diethyl ether 3 times, then a 25% (w/w) NH_3 aqueous solution was added until pH was between 9 and 10, and NaCl was added to saturation. The aqueous layer was extracted with CH_2Cl_2 5 times, and then the combined organic phase was washed with brine. The organic phase was dried over anhydrous sodium sulfate. After removal of the solvents, compound **11** was obtained (27.3 mg, 96% yield).

To a solution of compound **11** (25.0 mg, 0.088 mmol) in ethyl acetate (1.0 mL) were added wet palladium on carbon (5% w/w, 18.2 mg, 0.0086 mmol), acetic acid (17.2 mg, 0.30 mmol) in ethanol (0.5 mL), and methanesulfonic acid (19.1 mg, 0.20 mmol) in ethanol (0.5 mL), successively, under argon atmosphere. Then, argon was replaced by hydrogen. The mixture was vigorously stirred for 12 h. The mixture was filtered through celite and washed with ethanol. To the mother liquid was added a saturated NaHCO_3 aqueous solution, and the aqueous layer was extracted with CH_2Cl_2 5 times. The combined organic phase was washed with brine. After removal of the solvents, the crude mixture was purified by chromatography on silica gel to afford compound **6** (15.5 mg, 65% yield).

Determination of the ee of compound **4k**

Compound **4k** was converted into compound **13** shown in the following equation⁷, because it was difficult to determine the ee of **4k** directly by using HPLC.

To a solution of compound **4k** (28.3 mg, 0.071 mmol) and (2-mercaptomethyl-phenyl)-methanethiol (12. mg, 0.072 mmol) in 1,4-dioxane (0.5 mL) was added a solution of 98% sulfuric acid in methanol (30% w/w, 1.0 mL), and the mixture was stirred for 2 h. A saturated NaHCO_3 aqueous solution was added. The aqueous layer was extracted with CH_2Cl_2 5 times, and then the combined organic phase was washed with brine. The organic phase was dried over anhydrous sodium sulfate. After removal of the solvents, the crude mixture was purified by chromatography on silica gel to afford compound **13** (28.5 mg, 73% yield). The ee of compound **13** was determined by using HPLC. From the knowledge of the ee of compound **13**, the ee of compound **4k** was determined.

Transformation of **4g** into **8g**

Compound **4g** (92% ee, 220 mg, 0.41 mmol) was dissolved in a concentrated hydrochloric acid aqueous solution (20 mL), and then the mixture was vigorously stirred for 18 h under reflux condition. After the mixture was cooled rt, the aqueous layer was washed with diethyl ether 3 times. After removal of the solvents, yellowish solid was obtained. Water (7.0 mL) was added and the resultant suspension was vigorously stirred for 2 h under reflux conditions, and filtered. After the filtrate was concentrated under vacuum condition, compound, **8g** was obtained (19.5 mg, 16% yield, 99% ee).

Compound **8j** was also prepared from **4j** (94% ee) following the same procedure (19 % yield, 99% ee).

Physical data

(1S)-[3-Oxo-3-phenyl-1-(2,2,2-trichloro-

ethoxycarbonylamino)-propyl]-phosphonic acid diethyl ester (4a): $[\alpha]_D^{27} -6.34$ (92% ee, c 0.99, CHCl_3); ^1H NMR (CDCl_3) δ = 7.96 (2H, m), 7.59 (1H, m), 7.47 (2H, m), 4.81 (1H, d, J = 12.0 Hz), 4.66 (1H, d, J = 12.2 Hz), 4.9-4.7 (1H, m), 4.2-4.1 (4H, m), 3.6-3.35 (2H, m), 1.32 (3H, t, J = 7.0 Hz), 1.29 (3H, t, J = 7.4 Hz); ^{13}C NMR (CDCl_3) δ = 196.0 (d, J = 10.7 Hz), 154.0 (d, J = 5.7 Hz), 136.2, 133.5, 128.7, 128.1, 95.3, 74.7, 63.2 (J = 6.5 Hz), 62.8 (J = 6.3 Hz), 44.4 (d, J = 160.0 Hz), 38.2 (d, J = 4.2 Hz), 16.4 (J = 5.8 Hz), 16.3 (J = 5.8 Hz); IR 3743, 3239, 3053, 2982, 1739, 1691, 1598, 1579, 1544, 1449, 1393, 1367, 1229, 1146, 1031, 972, 819, 757, 737 cm^{-1} ; Chiral HPLC, Daicel Chiralcel AD, hexane/ i PrOH = 9/1, flow rate = 1.0 mL/min; t_R = 18.4 min (*R*), t_R = 23.0 min (*S*).

(1S)-[3-Oxo-3-*p*-tolyl-1-(2,2,2-trichloro-

ethoxycarbonylamino)-propyl]-phosphonic acid diethyl ester (4b): $[\alpha]_D^{26} -4.50$ (85% ee, c 1.63, CHCl_3); ^1H NMR (CDCl_3) δ = 7.86 (2H, m), 7.27 (2H, m), 4.81 (1H, d, J = 12.0 Hz), 4.66 (1H, d, J = 12.2 Hz), 4.9-4.7 (1H, m), 3.6-3.35 (2H, m), 1.32 (3H, t, J = 7.0 Hz), 1.29 (3H, t, J = 7.4 Hz); ^{13}C NMR (CDCl_3) δ = 195.7 (d, J = 9.8 Hz), 154.1, 144.5, 133.8, 129.4, 128.3, 95.4, 74.7, 63.2 (d, J = 6.6 Hz), 62.8 (d, J = 6.5 Hz), 44.7 (d, J = 160.4 Hz), 38.1, 16.5 (d, J = 5.8 Hz), 16.3 (d, J = 5.8 Hz); IR 3432, 3241, 3047, 2981, 1739, 1686, 1607, 1545, 1439, 1410, 1367, 1231, 1183, 1147, 1031, 978, 817, 766, 736,

542, 465 cm^{-1} ; Chiral HPLC, Daicel Chiralcel AD, hexane/ i PrOH = 9/1, flow rate = 1.0 mL/min; t_R = 19.4 min (*R*), t_R = 25.9 min (*S*) Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{Cl}_3\text{NO}_6\text{P}$ C:43.01, H:4.88, N: 2.95. Found C:42.75, H:5.12, N:2.98.

(1S)- [3-(4-Chloro-phenyl)-3-oxo-1-(2,2,2-trichloro-

ethoxycarbonylamino)-propyl]-phosphonic acid diethyl ester (4c): $[\alpha]_D^{26} -2.71$ (91% ee, c 0.56, CHCl_3); ^1H NMR (CDCl_3) δ = 7.90 (2H, m), 7.46 (2H, m), 5.74 (1H, d, J = 9.8 Hz), 4.80 (1H, d, J = 12.0 Hz), 4.67 (1H, d, J = 12.0 Hz), 4.9-4.7 (1H, m), 4.2-4.1 (4H, m), 3.6-3.35 (2H, m), 1.32 (3H, t, J = 7.0 Hz), 1.29 (3H, t, J = 7.4 Hz); ^{13}C NMR (CDCl_3) δ = 194.9, 154.0, 135.0, 132.1, 129.7, 128.9, 95.3, 74.8, 63.3 (d, J = 7.5 Hz), 62.9 (d, J = 7.4 Hz), 44.5 (d, J = 160.5 Hz), 38.3, 16.5 (d, J = 5.8 Hz), 16.3 (d, J = 5.8 Hz); IR 3437, 3060, 2988, 1742, 1685, 1627, 1544, 1470, 1392, 1369, 1260, 1220, 1146, 1124, 1081, 1030, 968, 861 cm^{-1} ; Chiral HPLC, Daicel Chiralcel AD, hexane/ i PrOH = 9/1, flow rate = 1.0 mL/min; t_R = 21.8 min (*R*), t_R = 34.5 min (*S*) Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{Cl}_3\text{NO}_6\text{P}$ C: 38.81 H: 4.07 N: 2.83. Found C: 39.01 H: 4.37 N: 2.83.

(1S)-[3-(4-Bromo-phenyl)-3-oxo-1-(2,2,2-trichloro-

ethoxycarbonylamino)-propyl]-phosphonic acid diethyl ester (4d): $[\alpha]_D^{26} -5.63$ (92% ee, c 4.33, CHCl_3); ^1H NMR (CDCl_3) δ = 7.82 (2H, m), 7.62 (2H, m), 6.03-5.90 (1H, m), 4.80 (1H, d, J = 12.0 Hz), 4.66 (1H, d), 4.90-4.60 (1H, m), 4.20-4.11 (4H, m), 3.51-3.35

(2H, m), 1.32 (3H, t, $J = 7.1$ Hz), 1.30 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (CDCl_3) $\delta = 195.1$, 154.0, 135.0, 132.1, 129.7, 128.9, 95.3, 74.8, 63.3 (d, $J = 7.5$ Hz), 62.9 (d, $J = 7.4$ Hz), 44.5 (d, $J = 160.5$ Hz), 38.3, 16.5 (d, $J = 5.8$ Hz), 16.3 (d, $J = 5.8$ Hz); IR 3447, 2989, 1735, 1683, 1641, 1586, 1545, 1395, 1227, 1151, 1029, 976, 813, 728, 548 cm^{-1} ; HRMS (FAB); Exact mass calcd for $\text{C}_{16}\text{H}_{21}\text{BrCl}_3\text{NO}_6\text{P}$ $[\text{M}+\text{H}]^+$, 537.9355. Found 537.9343; Chiral HPLC, Daicel Chiralcel AD, hexane/ i PrOH = 9/1, flow rate = 1.0 mL/min, $t_R = 21.5$ min (R), $t_R = 34.5$ min (S).

(1S)-[3-(4-Iodo-phenyl)-3-oxo-1-(2,2,2-trichloro-

ethoxycarbonylamino)-propyl]-phosphonic acid diethyl ester (4e): $[\alpha]_D^{27} -5.67$ (89%

ee, c 1.89, CHCl_3); ^1H NMR (CDCl_3) $\delta = 7.84$ (2H, m), 7.66 (2H, m), 6.3-5.8 (1H, m), 4.80 (1H, d, $J = 12.1$ Hz), 4.66 (1H, d, $J = 11.9$ Hz), 4.9-4.6 (1H, m), 4.2-4.1 (4H, m), 3.55-3.30 (2H, m), 1.35-1.25 (6H, m); ^{13}C NMR (CDCl_3) $\delta = 195.4$, 154.0, 138.1, 135.5, 129.5, 101.8, 95.3, 74.7, 63.4 (d, $J = 6.8$ Hz), 62.9 (d, $J = 6.8$ Hz), 44.5 (d, $J = 159.8$ Hz), 38.3, 16.5, 16.4, 16.3; IR 3436, 3247, 3055, 2981, 1738, 1635, 1581, 1541, 1438, 1394, 1367, 1229, 1146, 1082, 979, 819, 730, 549 cm^{-1} ; Chiral HPLC, Daicel Chiralcel AD, hexane/ i PrOH = 9/1, flow rate = 1.0 mL/min; $t_R = 15.7$ min (R), $t_R = 29.7$ min (S); Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{Cl}_3\text{NO}_6\text{P}$ C: 32.76 H: 3.44 N: 2.39. Found C: 32.60 H: 3.58 N: 2.49.

(1S)-[3-(4-Methoxy-phenyl)-3-oxo-1-(2,2,2-trichloro-ethoxycarbonylamino)-propyl]-phosphonic acid diethyl ester (4f): $[\alpha]_D^{26} -6.47$ (68% ee, c 2.09, CHCl₃); ¹H NMR (CDCl₃) δ = 7.94 (2H, m), 6.94 (2H, m), 6.1-5.8 (1H, m), 4.81 (1H, d, *J* = 12.2 Hz), 4.65 (1H, d, *J* = 12.2 Hz), 4.8-4.7 (1H, m), 4.2-4.1 (4H, m), 3.55-3.32 (2H, m), 1.32 (3H, t, *J* = 7.1 Hz), 1.29 (3H, t, *J* = 7.1 Hz); ¹³C NMR (CDCl₃) δ = 194.6, 163.9, 154.0, 135.6, 129.4, 129.7, 113.9, 95.4, 74.7, 63.2 (d, *J* = 6.6 Hz), 62.8 (d, *J* = 6.6 Hz), 55.5, 44.7 (d, *J* = 159.7 Hz), 37.8, 16.5 (d, *J* = 4.9 Hz), 16.3 (d, *J* = 5.7 Hz); IR 3473, 1680, 1547, 1449, 1398, 1362, 1227, 1150, 1029, 967, 810, 729, 689, 547 cm⁻¹; HRMS (FAB); Exact mass calcd for C₁₇H₂₄Cl₃NO₇P [M+H]⁺, 490.0356. Found 490.0374; Chiral HPLC, Daicel Chiralcel AD, hexane/ⁱPrOH = 9/1, flow rate = 1.0 mL/min; t_R = 31.0 min (*R*), t_R = 47.0 min (*S*).

(1S)-[3-(3,4-Dichloro-phenyl)-3-oxo-1-(2,2,2-trichloro-ethoxycarbonylamino)-propyl]-phosphonic acid diethyl ester (4g): $[\alpha]_D^{27} -5.88$ (89% ee, c 4.05, CHCl₃); ¹H NMR (CDCl₃) δ = 7.90 (2H, m), 7.46 (2H, m), 5.74 (1H, d, *J* = 9.8 Hz), 4.80 (1H, d, *J* = 12.0 Hz), 4.67 (1H, d, *J* = 12.0 Hz), 4.9-4.7 (1H, m), 4.2-4.1 (4H, m), 3.6-3.35 (2H, m), 1.32 (3H, t, *J* = 7.0 Hz), 1.29 (3H, t, *J* = 7.4 Hz); ¹³C NMR (CDCl₃) δ = 195.1, 154.0, 135.0, 132.1, 129.7, 128.9, 95.3, 74.8, 63.3 (d, *J* = 7.5 Hz), 62.9 (d, *J* = 7.4 Hz), 44.5 (d, *J* = 160.5 Hz), 38.3, 16.5 (d, *J* = 5.8 Hz), 16.3 (d, *J* = 5.8 Hz); IR 3235, 3050, 2981, 1739, 1687, 1590, 1570, 1540, 1444, 1400, 1367, 1228,

1146, 1094, 1032, 975, 823, 738, 557, 526, 461 cm^{-1} ; HRMS (FAB); Exact mass calcd for $\text{C}_{16}\text{H}_{20}\text{Cl}_5\text{NO}_6\text{P}$ $[\text{M}+\text{H}]^+$, 527.9471. Found 527.9496; Chiral HPLC, Daicel Chiralcel AD, hexane/ i PrOH = 9/1, flow rate = 1.0 mL/min; t_R = 14.4 min (*R*), t_R = 26.6 min (*S*).

(1S)-[3-Naphthalen-1-yl-3-oxo-1-(2,2,2-trichloro-

ethoxycarbonylamino)-propyl]-phosphonic acid diethyl ester (**4h**): $[\alpha]_D^{27}$ -6.33 (92% ee, c 0.99, CHCl_3); ^1H NMR (CDCl_3) δ = 8.65 (1H, m), 8.02-7.85 (3H, m), 7.64-7.46 (3H, m), 6.20-5.75 (1H, m), 4.77 (1H, d, J = 12.1 Hz), 4.67 (1H, d, J = 12.1 Hz), 4.85-4.70 (1H, m), 4.25-4.10 (4H, m), 3.64-3.52 (2H, m), 1.33 (3H, t, J = 7.1 Hz), 1.29 (3H, t, J = 7.1 Hz); ^{13}C NMR (CDCl_3) δ = 199.7, 154.0, 134.7, 134.0, 133.4, 130.1, 128.4, 128.3, 128.2, 126.6, 125.8, 124.3, 95.4, 74.7, 63.3 (d, J = 7.4 Hz), 62.9 (d, J = 6.8 Hz), 44.9 (d, J = 158.9 Hz), 38.3, 16.5, 16.4, 16.3; IR 3430, 3240, 3052, 2987, 1744, 1691, 1541, 1508, 1438, 1394, 1370, 1254, 1146, 1099, 1029, 968, 802, 777, 738, 541 cm^{-1} ; HRMS (FAB); Exact mass calcd for $\text{C}_{20}\text{H}_{23}\text{Cl}_5\text{NO}_6\text{P}$ $[\text{M}+\text{H}]^+$, 510.0407. Found 510.0422; Chiral HPLC, Daicel Chiralcel AD, hexane/ i PrOH = 9/1, flow rate = 1.0 mL/min; t_R = 14.3 min (*R*), t_R = 21.6 min (*S*).

(1S)-[3-Naphthalen-2-yl-3-oxo-1-(2,2,2-trichloro-

ethoxycarbonylamino)-propyl]-phosphonic acid diethyl ester (**4i**): $[\alpha]_D^{25}$ -16.4 (87% ee, c 1.41, CHCl_3); ^1H NMR (CDCl_3) δ = 8.49 (1H, m), 8.02-7.84 (2H, m), 7.65-7.50 (2H,

m), 6.2-6.0 (1H, m), 4.82 (1H, d, $J = 12.1$ Hz), 4.67 (1H, d, $J = 11.9$ Hz), 5.0-4.8 (1H, m), 4.25-4.10 (4H, m), 3.75-3.50 (2H, m), 1.37 (3H, t, $J = 7.1$ Hz), 1.29 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (CDCl_3) δ = 196.0, 154.1, 135.7, 133.6, 132.4, 130.2, 129.6, 128.8, 128.6, 127.8, 126.9, 123.7, 95.4, 74.7, 63.3 (d, $J = 7.4$ Hz), 62.9 (d, $J = 6.8$ Hz), 44.7 (d, $J = 160.4$ Hz), 38.3, 16.5, 16.4, 16.3; IR 3852, 3237, 3056, 2986, 1737, 1685, 1628, 1596, 1542, 1469, 1438, 1392, 1369, 1226, 1146, 1124, 1030, 969, 859, 821, 735, 546, 476 cm^{-1} ; Chiral HPLC, Daicel Chiralcel AD, hexane/ i PrOH = 9/1, flow rate = 1.0 mL/min; t_R = 20.0 min (R), t_R = 32.1 min (S); Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{Cl}_3\text{NO}_6\text{P}$ C: 47.03, H:4.54, N:2.74 Found C:47.33, H:4.74, N:2.73.

(1S)-[3-(3-Nitro-phenyl)-3-oxo-1-(2,2,2-trichloro-ethoxycarbonylamino)-propyl]-phosphonic acid diethyl ester (4j): $[\alpha]_D^{27} -8.46$ (94% ee, c 2.12, CHCl_3); ^1H NMR (CDCl_3) δ = 8.78 (1H, m), 8.46 (1H, m), 8.29 (1H, m), 7.71 (1H, m), 5.75-5.65 (1H, m), 4.80 (1H, d, $J = 11.9$ Hz), 4.69 (1H, d, $J = 11.9$ Hz), 4.85-4.70 (1H, m), 4.25-4.10 (4H, m), 3.60-3.45 (2H, m), 1.36 (3H, t, $J = 7.1$ Hz), 1.32 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (CDCl_3) δ = 194.1, 154.0, 148.5, 137.4, 133.7, 130.1, 127.8, 123.1, 95.2, 74.8, 63.5 (d, $J = 6.6$ Hz), 63.0 (d, $J = 6.6$ Hz), 44.4 (d, $J = 160.4$ Hz), 38.8, 16.4 (d, $J = 5.8$ Hz), 16.3 (d, $J = 5.8$ Hz); IR 3233, 3049, 2987, 1739, 1698, 1614, 1531, 1478, 1440, 1392, 1352, 1228, 1147, 1093, 1031, 970, 887, 819, 735, 545 cm^{-1} ; HRMS (FAB); Exact mass calcd for $\text{C}_{16}\text{H}_{21}\text{Cl}_5\text{N}_2\text{O}_8\text{P}$ $[\text{M}+\text{H}]^+$, 505.0101. Found 505.0123; Chiral HPLC, Daicel Chiralcel AD, hexane/ i PrOH = 9/1, flow rate = 1.0 mL/min; t_R = 28.3 min (R), t_R = 53.0 min (S).

(1S)-[3-Oxo-1-(2,2,2-trichloro-ethoxycarbonylamino)-butyl]-

phosphonic acid diethyl ester (4k): $[\alpha]_D^{23} -3.61$ (89% ee, c 1.16, CHCl_3); ^1H NMR (CDCl_3) δ = 6.2-5.4 (1H, m), 4.80 (1H, d, J = 11.9 Hz), 4.69 (1H, d, J = 11.9 Hz), 4.6-4.4 (1H, m), 4.3-4.0 (4H, m), 2.94 (1H, d, J = 7.0 Hz), 2.90 (1H, d, J = 6.4 Hz), 2.22 (3H, s), 1.332 (3H, t, J = 7.0 Hz), 1.326 (3H, t, J = 7.0 Hz); ^{13}C NMR (CDCl_3) δ = 204.7, 154.0, 95.3, 74.9, 63.2 (d, J = 6.8 Hz), 62.8 (d, J = 6.8 Hz), 44.3 (d, J = 159.2 Hz), 42.9, 42.8, 30.1, 16.4, 16.3, 16.2; IR 3437, 3053, 2988, 1735, 1643, 1542, 1400, 1369, 1226, 1149, 1095, 1032, 968, 819, 729, 544 cm^{-1} ; HRMS (FAB); Exact mass calcd for $\text{C}_{11}\text{H}_{20}\text{Cl}_3\text{NO}_6\text{P}$ $[\text{M}+\text{H}]^+$, 398.0094. Found 398.0087.

(3S)-3-(Diethoxy-phosphoryl)-3-(2,2,2-trichloro-

ethoxycarbonylamino)-thiopropionic acid S-tert-butyl ester (4l): $[\alpha]_D^{28} -10.68$ (90% ee, c 2.83, CHCl_3); ^1H NMR (CDCl_3) δ = 5.90-5.75 (1H, m), 4.77 (1H, d, J = 12.0 Hz), 4.72 (1H, d, J = 12.2 Hz), 4.65-4.50 (1H, m), 4.25-4.05 (4H, m), 3.10-2.75 (2H, m), 1.45 (3H, s), 1.332 (3H, t, J = 7.1 Hz), 1.329 (3H, t, J = 7.1 Hz); ^{13}C NMR (CDCl_3) δ = 196.0 (d, J = 18.9 Hz), 153.9 (d, J = 7.4 Hz), 95.3, 74.7, 63.2 (d, J = 9.0 Hz), 62.9 (d, J = 8.2 Hz), 48.7, 46.2, 44.1, 43.6, 43.5, 29.6, 16.4, 16.4, 16.3; IR 3433, 3236, 3047, 2964, 1741, 1685, 1543, 1477, 1454, 1392, 1367, 1302, 1261, 1244, 1227, 1155, 1092, 1028, 976, 816, 735, 553, 525 cm^{-1} ; Chiral HPLC, Daicel Chiralcel AD, hexane/ i PrOH = 19/1, flow

rate = 0.5 mL/min; t_R = 34.1 min (*R*), t_R = 38.3 min (*S*); Anal. Calcd for $C_{14}H_{25}Cl_3NO_6PS$

C: 35.57 H: 5.33 N: 2.96, Found C: 35.30 H: 5.08 N: 3.02.

(1*S*)-[2-(3-Methyl-1,5-dihydro-benzo[*e*][1,3]dithiepin-3-yl)-1-(2,2,2-

trichloro-ethoxycarbonylamino)-ethyl]-phosphonic acid diethyl ester (**13**): $[\alpha]_D^{28}$

−18.03 (89% ee, c 0.92, $CHCl_3$); 1H NMR ($CDCl_3$) δ = 7.2–7.1 (4H, m), 6.10–5.85 (1H, m), 4.82 (1H, d, J = 12.2 Hz), 4.73 (1H, d, J = 12.2 Hz), 4.6–4.5 (H, m), 4.25–4.10 (4H, m), 3.77–3.65 (2H, m), 2.9–2.8 (1H, m), 2.4–2.3 (1H, m), 1.62 (3H, s), 1.33 (3H, t, J = 7.1 Hz), 1.32 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ = 153.8, 139.0, 128.8, 127.6, 95.4, 74.7, 63.2 (d, J = 6.6 Hz), 62.8 (d, J = 7.1 Hz), 55.6 (d, J = 18.1 Hz), 45.6 (d, J = 158.8 Hz), 40.1, 32.9 (d, J = 23.9 Hz), 27.4, 16.5, 16.448, 16.366; IR 3410, 2939, 2362, 2347, 2341, 1741, 1543, 1444, 1236, 1041, 993, 742 cm^{-1} ; HRMS (FAB); Exact mass calcd for $C_{19}H_{27}Cl_3NO_5PS_2$ $[M+H]^+$, 550.0212, Found 550.0236; Chiral HPLC, Daicel Chiralcel AD, hexane/*i*PrOH = 19/1, flow rate = 2.0 mL/min; t_R = 27.8 min (*R*), t_R = 31.5 min (*S*)

(*S*)-1-amino-3-(3,4-dichlorophenyl)-3-oxopropylphosphonic

acid (**8g**): 1H NMR (20% DCl in D_2O , H_2O was served as internal standard (δ = 4.79)) δ

= 5.59 (1H, m), 5.35 (1H, m), 5.17 (1H, m), 1.80–1.65 (1H, m), 1.35–1.10 (2H, m); Chiral

HPLC, Daicel Crownpak CR(+), HClO₄aq (pH = 1.205)/MeOH = 85/15, flow rate = 1.0 mL/min; t_R = 21.5 min (*R*), t_R = 28.3 min (*S*)

(*S*)-1-amino-3-(3-nitrophenyl)-3-oxopropylphosphonic acid

(8j): ¹H NMR (20% DCl in D₂O, H₂O was served as internal standard (δ = 4.79)) δ = 6.22 (1H, m), 5.98 (1H, m), 5.85 (1H, m), 5.27 (1H, m), 1.85-1.70 (1H, m), 1.45-1.15 (2H, m); Chiral HPLC, Daicel Crownpak CR(+), HClO₄aq (pH = 1.205), flow rate = 0.2 mL/min; t_R = 22.4 min (*R*), t_R = 30.9 min (*S*)

References

- ¹ Colvin, E.W. *Silicon Reagents in Organic Synthesis*; Academic: New York, 1988; Chapter 15.1.
- ² Gennari, C.; Beretta, M. G.; Bernarde, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893.
- ³ Walshe, N. D. A.; Goodwin, G. B. T.; Smith, G. C.; Woodward, F. E. *Org. Synth.* **1987**, *65*, 1.
- ⁴ Schrader, T.; Kober, R.; Steglich, W. *Synthesis* **1986**, 372.
- ⁵ Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507.

⁶ Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.;

Ranganathan, S.; Vorbrüggen, H. *J. Am. Chem. Soc.* **1966**, 88, 852.

⁷ Shahak, I.; Bergmann, E. D. *J. Chem. Soc. C* **1966**, 1005.