The First Synthesis of a β^2 -Homoaminoacid by Enantioselective Catalysis

Audrius Rimkus and Norbert Sewald*

University of Bielefeld, Faculty of Chemistry, PO Box 10 01 31, D-33501 Bielefeld, Germany

norbert.sewald@uni-bielefeld.de

Supporting Information

Experimental Section

General:

All reactions were performed in flame-dried glassware under an inert atmosphere (argon or nitrogen). Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled from sodium benzophenone ketyl immediately prior to use. Toluene was distilled over calcium hydride and then over sodium, triethylamine was distilled over calcium hydride. Petrol ether (PE, 30-60 °C boiling point fraction) and ethyl acetate (EtOAc) were used for flash chromatography and were distilled over calcium chloride. All other reagents were used as received.

Analytical TLC was performed on silica gel plates 60 F₂₅₄ on aluminum foil (Merck). The compounds were visualized by illumination with UV light, staining with iodine or cerium sulfate/ammonium molybdate solution.

Flash column chromatography was carried out with silica gel 60 (40-63 μ m) from Merck. Melting points were determined using a melting point apparatus B-540 (Büchi) and are uncorrected.

¹H NMR spectra were recorded at 200 MHz, 250 MHz, or 500 MHz; ¹³C NMR spectra were recorded at 50 MHz, 63 MHz, or 126 MHz; ³¹P NMR spectra were recorded at 81 MHz or 202 MHz. TMS was used as an internal standard (¹H, ¹³C) and 85 % phosphoric acid (H₃PO₄) as an external standard (³¹P). Shift values are reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

IR spectra were collected on a FT/IR-410 (Jasco) spectrometer from the neat oil film (sodium chloride plates) or from a solid in a potassium bromide pellet. Peaks are reported in cm⁻¹ with the following abbreviations for signal intensity: s, strong; m, medium; w, weak; br., broad.

Capillary gas chromatography was performed on a GC-17A (Shimadzu) gas chromatograph using a HP-5MS (25 m, 0.25 mm ID, 0.33 μ m, Hewlett Packard) column. Enantiomer separations were performed on FS-Lipodex D (50 m, 0.25 mm ID, Macherey-Nagel) and FS-Lipodex E (50 m, 0.25 mm ID, Macherey-Nagel) columns, resp.

EI mass spectra (70 eV) were recorded using GC-MS on a HP 5890 gas chromatograph (Hewlett Packard) with an HP 5972 A integrated mass detector unit (Hewlett Packard) or a GCMS-QP5050A (Shimadzu) on HP-5MS (30 m, 0.25 mm ID, 0.25 μ m, Hewlett Packard) columns.

MALDI-ToF mass spectra were recorded on Voyager-DETM (PerSeptive Biosystems) using 2,5-dihydroxybenzoic acid (DHB) as matrix.

Elemental analyses were performed on CHNS-932 (Leco), CHN-O-Rapid (Heraeus) and Vario EL (Heraeus) apparatus.

General procedure for synthesis of phosphoramidites:

A solution of bis(1-phenylethyl)amine (2.06 g, 9.16 mmol) and triethylamine (1.05 g, 10.38 mmol) in toluene (8 mL) was added dropwise under argon to the solution of phosphorus trichloride (1.25 g, 9.16 mmol) in toluene (120 mL). The mixture was stirred at 70 °C for 6 h and allowed to cool to r.t. Triethylamine (2.10 g, 20.76 mmol) was added dropwise under argon. The reaction mixture was cooled to –78 °C and a solution of BINOL (9.17 mmol) or its 3,3'-dimethyl derivative, resp., in a mixture of toluene (24 mL) and THF (4 mL) was added dropwise. The mixture was allowed to warm up slowly to r.t. and was stirred for additional 12 h. The mixture was filtered and the solvents were removed under reduced pressure. The diastereomers were purified and separated by column chromatography.

((*M*)-Bis-naphthaleno[1,2-f;2,1-d]-1,3-dioxo-2-phosphacycloheptan-2-yl)-(S,S)-bis(1-phenylethyl)amine ((*M,S,S*)-L1)

Colorless crystals; yield: 46 % (1.15 g); m.p. 102-104 °C; R_f =0.29 (PE : dichloromethane = 3 : 1); ^1H NMR (200 MHz, CDCl_3): δ =1.76 (6H, d, J =7.2 Hz), 4.55 (2H, dq, J =11.5 Hz, 7.2 Hz), 7.03-7.71 (18H, m), 7.85-8.07 (4H, m); ^{13}C NMR (50 MHz, CDCl_3): δ =22.6 (d, J =8.2 Hz), 52.7 (d, J =12.2 Hz), 122.3, 122.4, 123.0, 124.6, 122.7, 125.1, 125.3, 126.6, 127.2, 127.7, 127.8, 128.3, 128.5, 128.6, 128.7, 128.9, 130.0, 130.8, 131.0, 132.0, 133.4, 143.4, 150.2, 150.6, 150.8; ^{31}P NMR (81 MHz, CDCl_3): 146.5 (t, 3J =11.5 Hz); IR (KBr): $\tilde{\nu}$ =3057 (w), 2970 (w), 2927 (w), 1590 (m), 1460 (m), 1327 (m), 1231 (s), 1204 (m), 947 (s); MS (EI): m/z (%): 434 (100), 105 (77), 268 (21), 79 (16), 77 (13), 239 (9), 315 (7), 252 (6), 391 (5); microanalysis calcd (%) for $\text{C}_{36}\text{H}_{30}\text{NO}_2\text{P}$ (539.62): C 80.13, H 5.60, N 2.60, O 5.93; found: C 80.24, H 5.75, N 2.48, O 5.52.

((*P*)-Bis-naphthaleno[1,2-f;2,1-d]-1,3-dioxo-2-phosphacycloheptan-2-yl)-(S,S)-bis(1-phenylethyl)amine ((*P,S,S*)-L1)

Colorless crystals; yield: 54 % (1.35 g); m.p. 87-89 °C; R_f =0.35 (PE : dichloromethane = 3 : 1); ^1H NMR (200 MHz, CDCl_3): δ =1.74 (6H, d, J =7.1 Hz), 4.47 (2H, dq, J =11.0 Hz, 7.1 Hz), 7.12-7.68 (18H, m), 7.75-8.09 (4H, m); ^{13}C NMR (50 MHz, CDCl_3): δ =23.5 (d, J =11.8 Hz), 55.0 (d, J =11.1 Hz), 121.7, 121.8, 123.0, 123.1, 124.7, 124.7, 125.0, 125.1, 126.4, 126.6, 127.3, 127.7, 127.9, 128.3, 128.5, 128.6, 128.7, 128.9, 130.2, 130.9, 131.0, 131.9, 133.4, 133.4, 143.7, 150.4, 151.0, 151.2; ^{31}P NMR (81 MHz, CDCl_3): 151.6 (t, 3J =11.0 Hz); IR (KBr): $\tilde{\nu}$ =3057 (w), 2970 (w), 2927 (w), 1590 (m), 1460 (m), 1327 (m),

1231 (s), 1204 (m), 947 (s); MS (EI): m/z (%): 434 (100), 105 (77), 268 (21), 79 (16), 77 (13), 239 (9), 315 (7), 252 (6), 391 (5).

((*P*)-Bis-3,3'-dimethyl-naphthaleno[1,2-f;2,1-d]-1,3-dioxo-2-phosphacycloheptan-2-yl)-(*R,R*)-bis(1-phenylethyl)amine ((*P,R,R*)-L2)

Colorless crystals; yield: 49 % (0.39 g); m.p. 116-123 °C; $[\alpha]_D^{29}$: +467.9 ($c=2.96$, CHCl_3); $R_f=0.28$ (PE : dichloromethane/5: 1); ^1H NMR (500 MHz, CDCl_3): $\delta=1.48\text{--}1.80$ (6H, m, br.), 2.40 (3H, s), 2.72 (3H, s), 4.55 (2H, s, br.), 6.96-7.20 (13H, m), 7.28-7.37 (3H, m), 7.74-7.82 (4H, m); ^{13}C NMR (126 MHz, CDCl_3): $\delta=17.7$, 18.9, 23.3, 23.3, 52.6 (d, $J=12.2$ Hz), 122.5, 122.5, 124.3, 124.3, 124.8, 125.0, 125.4, 125.5, 127.0, 127.3, 127.5, 127.7, 127.9, 129.8, 130.1, 130.4, 130.7, 130.8, 131.7, 132.1, 132.3, 149.3, 149.5, 149.6; ^{31}P NMR (202 MHz, CDCl_3): 143.9 (s); IR (KBr): $\tilde{\nu}=3056$ (w), 2962 (m), 2921 (m), 1498 (m), 1448 (m), 1411 (m), 1240 (m), 1205 (m), 1141 (m), 1085 (m), 900 (s), 773 (s), 746 (s), 696 (m); MALDI-ToF-MS calcd: 568.66 $[\text{M}+\text{H}]^+$; found: 569.00 $[\text{M}+\text{H}]^+$; microanalysis calcd (%) for $\text{C}_{38}\text{H}_{34}\text{NO}_2\text{P}$ (567.66): C 80.40, H 6.04, N 2.47; found: C 80.35, H 6.74, N 2.36.

((*M*)-Bis-3,3'-dimethyl-naphthaleno[1,2-f;2,1-d]-1,3-dioxo-2-phosphacycloheptan-2-yl)-(*R,R*)-bis(1-phenylethyl)amine ((*M,R,R*)-L2)

Colorless crystals; yield: 49 % (0.39 g); m.p. 171-173 °C; $[\alpha]_D^{29}$: -92.0 ($c=2.98$, CHCl_3); $R_f=0.32$ (PE : dichloromethane = 5 : 1); ^1H NMR (500 MHz, CDCl_3): $\delta=1.62$ (6H, d, $J=7.0$ Hz), 1.91 (3H, s), 2.67 (3H, s), 4.54 (2H, m), 6.98-7.04 (4H, m), 7.06-7.36 (12H,

m), 7.67-7.86 (4H, m); ^{13}C NMR (126 MHz, CDCl_3): δ =17.5, 17.5, 23.1 (br.), 54.8 (d, J =10.9 Hz), 121.6, 121.7, 124.0, 124.1, 124.3, 124.6, 124.8, 125.0, 126.9, 126.9, 127.0, 127.3, 127.5, 127.9, 128.1, 129.1, 129.7, 130.1, 130.3, 131.2, 131.2, 131.7, 131.8, 143.2, 149.0, 149.2, 149.2; ^{31}P NMR (202 MHz, CDCl_3): 147.8 (s); IR (KBr): $\tilde{\nu}$ =3019 (w), 2958 (m), 2917 (m), 2850 (m), 1596 (m), 1498 (m), 1465 (m), 1409 (m), 1236 (m), 1130 (m), 1093 (s), 900 (s), 775 (s), 748 (s), 692 (s); MALDI-ToF-MS calcd: 606.75 $[\text{M}+\text{K}]^+$, 568.66 $[\text{M}+\text{H}]^+$; found: 606.79 $[\text{M}+\text{K}]^+$, 568.88 $[\text{M}+\text{H}]^+$; microanalysis calcd (%) for $\text{C}_{38}\text{H}_{34}\text{NO}_2\text{P}$ (567.66): C 80.40, H 6.04, N 2.47; found: C 80.39, H 6.04, N 2.54.

Methyl 2-(nitromethyl)butanoate (3)

Copper(II) triflate (0.5-2.0 mol % referring to nitroolefin) and the corresponding phosphoramidite (1.0-4.1 mol %) were dissolved in a dry solvent (catalyst concentration: ca. 5 mM) and stirred for 1 h at r.t. under argon. The clear solution was cooled to the appropriate temperature and the solution of diethylzinc (1.5 eq.; 1 M in hexane) was added dropwise followed by a solution of methyl 3-nitropropenoate (ca. 1 M in the corresponding solvent). Dodecane was used as an inner standard for GC analysis. The reaction progress was monitored by GC analysis. The reaction was quenched by addition of saturated aqueous ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine, dried (over sodium sulfate or magnesium sulfate, resp.) and filtered. The solvents were removed under reduced pressure and the resulting oil was purified by column chromatography to afford the product.

entry	ligand	solvent	T, °C	ee, %	isomer
1	(<i>M,S,S</i>)- L1	toluene	−50	10	(+)
2	(<i>M,S,S</i>)- L1	toluene	−30	28	(+)
3	(<i>P,S,S</i>)- L1	toluene	−30	12	(−)
4	(<i>M,S,S</i>)- L1	ether	−30	68	(+)
5	(<i>M,S,S</i>)- L1	ether	−78	77	(+)
6	(<i>M,S,S</i>)- L1	THF	−30	16	(−)
7	(<i>P,R,R</i>)- L2	toluene	−30	67	(+)
8	(<i>M,R,R</i>)- L2	toluene	−30	52	(+)
9	(<i>P,R,R</i>)- L2	ether	−30	73	(+)
10	(<i>M,R,R</i>)- L2	ether	−30	12	(−)
11 ^b	(<i>P,R,R</i>)- L2	ether	−78	92	(+)
12 ^b	(<i>M,R,R</i>)- L2	ether	−78	15	(+)

Colorless oil; yield: 94 % (2.89 g); R_f =0.51 (PE : EtOAc = 6 : 1); ^1H NMR (200 MHz, CDCl_3): δ =0.98 (3H, t, J =7.5 Hz); 1.71 (2H, m); 3.17 (1H, m); 3.75 (3H, s); 4.43 (1H, dd, J =14.3 Hz, 4.4 Hz); 4.75 (1H, dd, J =14.3 Hz, 9.2 Hz); ^{13}C NMR (50 MHz, CDCl_3): δ =11.5, 23.0, 44.6, 52.8, 75.4, 173.1; IR (neat): $\tilde{\nu}$ =2971 (m), 2881 (w), 1737 (s), 1556 (s), 1438 (m), 1380 (s), 1257 (s), 1205 (s), 1182 (s), 971 (w), 848 (w); MS (EI): m/z (%): 130 (15), 87 (22), 83 (48), 73 (25), 59 (91), 56 (13), 55 (100), 45 (16), 41 (29), 39 (22), 30 (19), 29 (31), 27 (34), 15 (30); microanalysis calcd (%) for $\text{C}_6\text{H}_{11}\text{NO}_4$ (161.16): C 44.72, H 6.88, N 8.69; found: C 45.00, H 6.94, N 8.55.

Separation of enantiomers: retention time (t_R , min): 9.9 (–) and 10.9 (+); column: FS-Lipodex E; carrier gas: hydrogen; temperature: 140 °C, isothermic; head pressure: 1.25 bar; injector temperature: 250 °C; detector temperature: 250 °C; split ratio: 1: 100.

Methyl 2-[(*tert*-Butoxycarbonyl)-aminomethyl]-butanoate

Dried ammonium formate (296 mg, 4.69 mmol) and palladium (56 mg, 10 % on charcoal) are added under argon atmosphere to a solution of the nitro compound (0.86 mmol) in abs. methanol (2.0 mL). While the mixture is stirred for 30 min, gas evolution is observed. The solution is then filtered through a plug of Celite®. The Celite® plug is washed with abs. methanol (8 mL). Dry triethylamine (0.25 mL, 1.80 mmol) and di-*tert*.-butyl-dicarbonate (Boc_2O , 242 mg, 1.11 mmol) are added to the filtrate and the mixture is stirred under argon atmosphere for 12 h at r.t. Then water (8 mL) is added, the solution is cooled to 0 °C, and acidified to pH~3 with 1 N KHSO_4 solution. The mixture is extracted with ethyl acetate (5×15 mL). The combined organic layers are dried over MgSO_4 , filtered, and evaporated *in vacuo*. The Boc protected β^2 -homoaminoacid ester is purified by flash chromatography.

Colorless oil; yield for 2 steps: 79 % (395 mg); $[\alpha]_D^{26}$: –23.9 (c 1.0, CHCl_3); R_f : 0.53 (PE : EtOAc = 4 : 1); ^1H NMR (250 MHz, CDCl_3): 0.94 (3H, t, 3J =7.5 Hz); 1.43 (9H, s);

1.60 (2H, m); 2.53 (1H, m); 3.28 (2H, m); 3.70 (3H, s); 4.86 (br., s); ^{13}C NMR (126 MHz, CDCl_3): 11.5; 22.9; 28.4; 41.4; 47.2; 51.7; 79.4; 155.9; 175.4; IR (Film): 3379 (m); 2973 (s); 1718 (s); 1520 (s); 1457 (w); 1438 (w); 1366 (m); 1272 (s); 1252 (s); 1173 (s); MS (CI): m/z (%): 184 (32); 176 (92); 158 (79); 144 (33); 133 (15); 132 (100); 126 (63); 100 (20); microanalysis calcd. (%) for $\text{C}_{11}\text{H}_{21}\text{NO}_4$ (231.29): C 57.12; H 9.15; N 6.06; found: C 57.43; H 9.10; N 5.80.

2-[(*tert*-Butoxycarbonyl)-aminomethyl]-butanoic acid (**4**)

Lithium hydroxide monohydrate (629 mg, 15.00 mmol) is added at 0 °C to a solution of methyl 2-[(*tert*-butoxycarbonyl)-aminomethyl]-butanoate (360 mg, 1.56 mmol) in THF (35 mL). The mixture is stirred at 0 °C for 6 h and then allowed to warm up to r.t. Stirring is continued for further 18 h. Water (5 mL) is added and the mixture is acidified with 1N HCl to pH~3. The solution is extracted with ethyl acetate (4×30 mL) and the combined organic layers are dried over MgSO_4 , filtered, and evaporated *in vacuo* to afford 2-[(*tert*-butoxycarbonyl)-aminomethyl]-butanoic acid **4**.

Off-white powder; yield: 95 % (322 mg); m.p.: 51-53 °C; $[\alpha]_D^{26}$: -17.3 (c 1.3, MeOH); ^1H -NMR (250 MHz, CDCl_3): 1.03 (3H, t, $^3J=7.5$ Hz); 1.46 (9H, s); 1.75 (2H, m); 3.18 (1H, m); 4.44 (1H, dd, $^2J=14.4$ Hz, $^3J=5.0$ Hz); 4.75 (1H, dd, $^2J=14.4$ Hz, $^3J=8.9$ Hz); 5.20 (br., s); 9.57 (br., s); ^{13}C -NMR (126 MHz, CDCl_3): 11.0; 22.4; 28.3; 44.1; 74.7; 80.8; 158.4; 176.9; IR (KBr): 3385 (m); 2972 (m); 1686 (s); 1528 (s); 1270 (s); 1171 (s); microanalysis calcd. (%) for $\text{C}_{10}\text{H}_{19}\text{NO}_4$ (217.26): C 55.28; H 8.81; N 6.45; found: C 55.24; H 8.69; N 6.00.