Efficient Asymmetric Synthesis of β-Amino Acid BAY 10-8888/PLD-118, a Novel Antifungal for the Treatment of Yeast Infections

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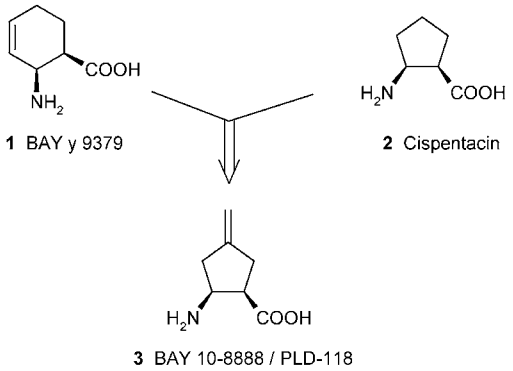
Abstract: The β-amino acid BAY 10-8888/PLD-118 is currently being investigated in phase II clinical studies as a novel antifungal for the treatment of yeast infections. An efficient asymmetric synthesis of this compound is described. The key step employed a highly enantioselective, quinine-mediated alcoholysis of a *meso*-anhydride intermediate.

Key words: amino acids, antifungal agents, asymmetric synthesis, desymmetrization, quinine

Major increases in the incidence of systemic fungal infections caused by the yeast *Candida albicans* have been observed during the last two decades, particularly in immunocompromised patients.[1] A critical need exists for new antifungal agents to treat these life-threatening infections.[2] BAY y 9379 (**1**) and other 1-aminocyclohexane-2-carboxylic acids, which were originally designed at Bayer AG as pyridoxal phosphate suicide inhibitors, turned out to also have activity against *C. albicans*[3] (Scheme 1). In addition, the reported antifungal activity of the natural β-amino acid cispentacin **2**[4] prompted us to initiate a derivatization program to identify cyclic β-amino acids with superior efficacy and tolerability. Among more than a thousand derivatives, BAY 10-8888 (**3**) exhibited the most favourable activity–tolerability profile and was selected for further development. BAY 10-8888 acts by a unique dual mode of action.[5] It was licensed to PLIVA d.d. and is currently in phase II clinical studies as PLD-118.

For this purpose, multikilogram quantities of enantiomerically pure BAY 10-8888 (**3**) were required. The other stereoisomers showed significantly lower antifungal activity. Our initial laboratory synthesis[6] of β-amino acid **3** did not allow for the preparation of kilogram amounts due to a lengthy 13 step sequence including reagents undesirable for large-scale work, hazardous reaction conditions and a low yield classical resolution. Here we describe a shorter and more efficient large-scale asymmetric synthesis of BAY 10-8888 (**3**).

Encouraged by previously published results[7,8] the asymmetric synthesis of β-amino acid **3** centered around the



Scheme 1

enantioselective alcoholysis of *meso*-anhydride **7**,[9] followed by a subsequent Curtius rearrangement.[10] Other published methods for the enantioselective synthesis of cyclic β-amino acids[11] appeared less feasible. This can be mainly attributed to the *exo*-methylene group, which showed a distinct tendency to isomerize under acidic conditions and was potentially unstable under a variety of other reaction conditions.

The preparation of *meso*-anydride **7** started from commercially available butanetetracarboxylic acid (**4**) (Scheme 2). A four-step sequence involving esterification, Dieckmann cyclization, hydrolysis, decarboxylation and again esterification afforded cyclopentanone diester **5** as a mixture of diastereomers (*trans*/*cis* = 5:1) in 75% yield. A two-step, one-pot sequence consisting of Wittig methylenation and subsequent ester hydrolysis provided dicarboxylic acid **6** mainly as the *trans*-diastereomer (71% yield, *trans*/*cis* >50:1). Conversion of diacid **6** under complete *trans–cis* isomerization to *meso*-anhydride **7** was accomplished by treatment with propionic anhydride at 135 °C. Following a distillative work-up and recrystallization from diisopropyl ether, anhydride **7** was obtained in 75% yield.

Several other routes for the construction of 4-methylene-1,2-cyclopentanedicarboxylate derivatives have been described.[12] Among these routes, only Binger's palladium-catalyzed [3 + 2] cycloaddition[12a] of methylenecyclopropane to diethyl fumarate offered a valuable alternative for us and will be considered for further technical scale synthesis. All other routes were regarded as less suitable for

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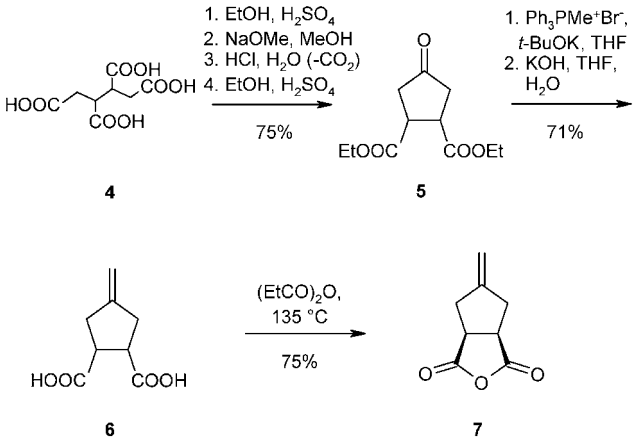
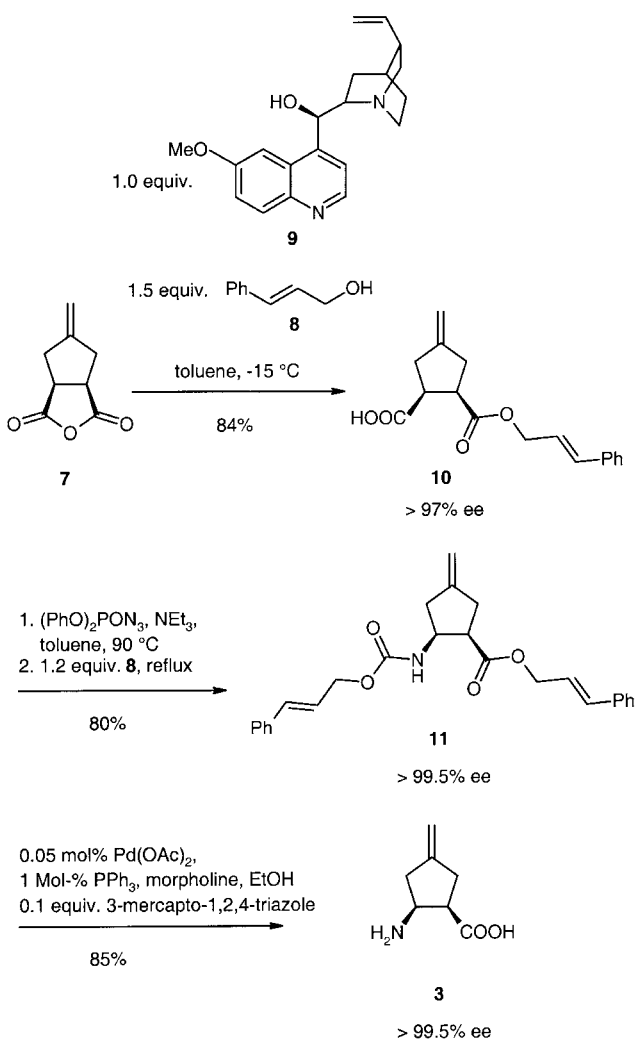


Scheme 2 Synthesis of *meso*-anhydride **7**



Scheme 3

large-scale work mainly due to low yields and undesirable reagents in terms of availability or safety.

Following the published conditions[8] (3 equiv of MeOH in toluene, 0.5 equiv quinine at 25 °C), methanolysis of anhydride **7** provided the corresponding methyl hemiester with low enantiomeric excess (max. 35% ee). After investigating various reaction conditions, it was found that the enantiomeric excess of the quinine-mediated alcoholysis of anhydride **7** could be significantly improved by lowering the temperature and by using stoichiometric amounts of the chiral auxiliary. While screening different alcohols for the ring-opening step, *trans*-cinnamyl alcohol (**8**) proved to be the best choice with regard to yield, enantiomeric excess, crystallization properties of products in subsequent steps and ester cleavage conditions. Alcoholysis of anhydride **7** with cinnamyl alcohol (**8**) in the presence of stoichiometric amounts of quinine (**9**) in toluene at –15 °C afforded crude hemiester **10** with 85% ee. When this material was stirred with a small amount of toluene, approx. 10% of crystalline racemic hemiester ***rac*-10** precipitated. The filtrate contained cinnamyl ester **10** (84% yield) with > 97% ee and was used without further purification in the next step (Scheme 3). The racemic hemiester **10**, as well as the chiral auxiliary **9**, could be easily recovered making this process highly efficient and economical.

Recently, Deng and coworkers[13] described an enantioselective methanolysis of various cyclic *meso*-anhydrides catalyzed by modified bis-cinchona alkaloids. Following this protocol the anhydride **7** was treated with 5 mol% of the dihydroquinidine-based $(DHQD)_2AQN$[14] and 10 equivalents of cinnamyl alcohol (**8**) in diethyl ether at r.t. for 72 h. Extractive work-up and chromatographic separation of excess **8** afforded hemiester ***ent*-10** in 54% yield and with 89% ee. As the reaction was still not complete after 72 h, this method appeared less attractive for a large-scale production of cinnamyl ester **10**.

The next step was a Curtius rearrangement using diphenyl phosphoryl azide–triethylamine in toluene. Subsequent reaction of the intermediate isocyanate with cinnamyl alcohol (**8**) gave the protected β-amino acid ester **11**, which after cooling precipitated from the reaction mixture in pure form with >99.5% ee (80% yield). This reaction was successfully carried out in a controlled manner on a pilot plant scale to produce 26 kg of protected β-amino acid **11**.[15]

In the final step the ester and carbamate protecting groups of **11** were removed by treatment with palladium acetate (0.05 mol%)–triphenyl phosphine and morpholine in refluxing ethanol. The crude product **3** crystallized from the reaction mixture and was further purified by recrystallization from aqueous ethanol (Scheme 3). 3-Mercapto-1,2,4-triazole was added prior to each crystallization to reduce the Pd-content of the product. β-Amino acid **3** was obtained in 85% yield with >99.5% ee and with a Pd-content of <0.5 ppm. The (1*R*,2*S*)- configuration of **3** could be determined by a single crystal X-ray structure determination using $Cu_{K\alpha}$-radiation as X-ray source (Figure 1).[16]

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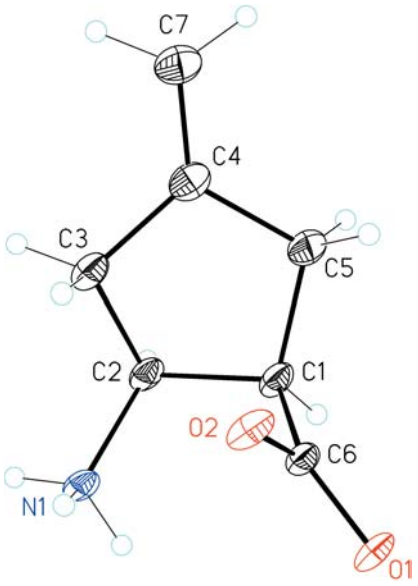

Figure 1 Ortep plot of β-amino acid **3**

In conclusion, we have developed a short and efficient asymmetric synthesis of the antifungal clinical candidate BAY 10-8888/PLD-118 (**3**) in a 23% overall yield, starting from commercially available butanetetracarboxylic acid (**4**). The described process was successfully used on a pilot plant scale.

In recent years, there has been an increasing interest in β-amino acids also for other applications.[11,16] Our process offers an attractive approach for the synthesis of further conformationally restricted β-amino acids.[10,17]

Mps were determined on a Büchi capillary mp apparatus and are uncorrected. Optical rotations were determined using a Perkin–Elmer 241 MC polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM 250, AM 300 and AV 500C spectrometers in either $CDCl_3$, DMSO-d_6, or D_2O solution using TMS ($CDCl_3$, DMSO-d_6), sodium 3-(trimethylsilyl)proponoate (^{1}H NMR in D_2O) and 1,4-dioxane (^{13}C NMR in D_2O) as an internal standard. Microanalyses were obtained using a Perkin–Elmer 240 element analyser. Mass spectra were obtained on the following mass spectrometers: electron ionization (EI) and desorption chemical ionisation (DCI) on a Finnigan MAT 95; high resolution mass spectra (HRMS) on a Finnigan MAT 90 under FAB conditions. Chemical purities were determined by HPLC quantitative and qualitative methods with a HP 1090 series instrument. Enantiomeric excesses of compounds **10**, **11**, and **3** were determined by chiral HPLC on HP 1050 and HP 1090 series instruments. All reactions were performed under a positive atmosphere of argon or nitrogen. The Pd-content of **3** was determined by ICP-MS following wet decomposition at Central Analytics, Bayer AG, Leverkusen. Reactions were monitored by analytical TLC using 5 × 10 cm plates: silica gel 60 F-254, layer thickness 0.25 mm (E. Merck). All chemicals were purchased from commercial sources and were used without further purification.

Diethyl 4-Oxo-1,2-cyclopentanedicarboxylate (5)

To a solution of 1,2,3,4-butanetetracarboxylic acid (**4**) (2.34 kg, 10.0 mol) in EtOH (7.5 L) and toluene (5.0 L) in a 20 L reactor, concd H_2SO_4 (553 g) was added over a period of 15 min. The mixture was heated to reflux and stirred for 2 h. The solvent (approx. 8.2 L) was removed by distillation until the temperature reached 110 °C. Toluene (5.0 L) was added and the mixture was heated to reflux for 5 h. During this period H_2O (approx. 480 mL) was removed using a Dean–Stark trap. After cooling to 80 °C, EtOH (5.0 L) was added and the mixture was stirred at reflux for 1.5 h. The solvent (approx. 8.0 L) was distilled off until the temperature reached 105 °C. Toluene (6.0 L) was added and the mixture was heated to reflux for 0.5 h. During this period H_2O (approx. 30 mL) was removed. The reaction mixture was cooled to r.t. and washed with H_2O (0.5 L). The H_2O layer was extracted with toluene (0.5 L) and the combined toluene layers were washed with aq Na_2CO_3 (15%; 3.75 L). The solvent was removed in vacuo and the remaining crude tetraethyl 1,2,3,4-butanetetracarboxylate was dissolved in MeOH (3.2 L) in a 20 L reactor. A solution of sodium methylate (30%) in MeOH (5.19 kg, 28.8 mol) was added at r.t. over a period of 15 min. After stirring at r.t. for 1 h, aq HCl (50%; 5.95 L) was added whereby the temperature raised to 57 °C. After addition of concd aq HCl (1.6 L) the reaction mixture was heated to reflux and the solvent (approx. 12.4 L) was distilled off until the temperature reached 100 °C. The mixture was stirred at 100 °C for 5 h and cooled to r.t. Toluene (7.0 L) was added and the mixture was heated to reflux. H_2O (approx. 4.3 L) was removed using a Dean–Stark trap until the temperature reached 110 °C (approx. 5.5 h). Toluene (2 L) was removed by distillation and the mixture cooled to 80 °C. EtOH (9.0 L) was added and the slurry cooled to r.t. Precipitated salts were removed by filtration and washed with EtOH (5 L). The filtrate was transferred into the 20 L reactor and concd sulfuric acid (626 g) was added at r.t. The mixture was heated to reflux and solvent (7.5 L) was distilled off. After stirring for 2 h at reflux further solvent (8.5 L) was removed until the temperature reached 105 °C. Toluene (5.0 L) was added and the mixture was heated to reflux for 2 h. During this period H_2O (approx. 165 mL) was removed using a Dean–Stark trap. The reaction mixture was cooled to r.t. and washed with H_2O (1 L). The H_2O layer was extracted with toluene (0.5 L) and the combined toluene layers were washed successively with aq Na_2CO_3 (15%; 3.75 L) and H_2O (2.2 L). The solvent was removed in vacuo and the remaining crude product (2.02 kg) was purified by distillation using a thin film evaporator (1.4 mbar, bath temp. 178 °C) to afford diester **5**.

Yield: 1.72 kg (75%); colorless oil; *trans*–*cis*, 5: 1 [HPLC, Nucleosil C 8, 250 mm × 3 mm, 5 m, detection at 210 nm, 45 °C, flow rate 0.5 mL /min, gradient 100–20% of aq phosphoric acid (0.2%)– 0 – 80% MeCn, t_R *trans*-**5**, 15.10 min; *cis*-**5**, 14.40 min; the *cis*-configuration of the minor diastereomer could be confirmed by comparison with material obtained following the procedure of Gais et al.[12c]].

^{1}H NMR ($CDCl_3$, 250 MHz; cf. lit.[18]): δ = 1.21–1.33 (m, 3 H, CH_3), 2.42–2.82 (m, 4 H, CH_2COCH_2), 3.31–3.48 (m, 2 H, CHCH), 4.11–4.26 (m, 4 H, OCH_2).

MS (EI): *m*/*z* (%) = 228 (M^+, 15), 183 (20), 154 (35), 128 (100), 100 (65), 55 (60).

HRMS: *m*/*z* calcd for $C_{11}H_{20}NO_5$ [M + NH_4]: 246.1346; found: 246.1341.

4-Methylene-1,2-cyclopentanedicarboxylic Acid (6)

To a solution of methyl(triphenyl)phosphonium bromide (493 g, 1.38 mol) in THF (1.7 L), *t*-BuOK (151 g, 1.35 mol) was added at r.t. After stirring for 2 h at r.t., the mixture was cooled to –12 to –15 °C. Diethyl 4-oxo-1,2-cyclopentanedicarboxylate (**5**) (274 kg, 1.20 mol) was added dropwise over a period of 1 h, while maintaining the temperature of the reaction mixture at –12 to –15 °C. After further stirring for 1 h at this temperature, the reaction mixture was allowed to warm to 10 °C over 1 h. A solution of KOH (168 g, 3.00 mol) in H_2O (840 mL) was then added, while keeping the temperature below 30 °C. The reaction mixture was stirred at r.t. overnight. THF was evaporated in vacuo, precipitated solids were removed by filtration and washed with H_2O (100 mL). The combined aq solutions were washed with EtOAc (2 × 1000 mL) and a small amount

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of organic solvent was removed in vacuo. The aq solution was acidified under ice cooling to pH 2.0 with concd hydrochloric acid (approx. 250 mL). Precipitated product was collected by filtration, washed with H_2O (3 × 140 mL) and dried in vacuo at 50 °C to afford diacid **6**.

Yield: 145 g (71%); colorless crystals; mp 178 °C (lit.[19] mp 178–179 °C);

Trans– *cis* > 50: 1 [HPLC, Nucleosil C 8, 250 mm × 3 mm, 5 m, detection at 210 nm, 45 °C, flow rate 0.5 mL/min, gradient 100–20% phophoric acid (0.2%)→0–80% MeCN, t_R *trans*-**6**, 11.80 min; *cis*-**6**, 10.10 min].

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 2.34–2.48 (m, 2 H, CH_2), 2.49–2.73 (m, 2 H, CH_2), 2.92–3.04 (m, 2 H, CHCH), 4.84–4.88 (m, 2 H, =CH_2), 12.33 (br s, 2 H, COOH).

Anal. Calcd for $C_8H_{10}O_4$ (170.16): C, 56.5; H, 5.9; O, 37.6. Found: C, 56.8; H, 5.8; O, 37.8.

5-Methylenetetrahydrocyclopenta[c]furan-1,3-dione (7)

A mixture of 4-methylene-1,2-cyclopentanedicarboxylic acid (**6**) (649 g, 3.81 mol) and propanoic anhydride (1.5 L) was stirred at 135 °C for 8 h. Excess propanoic anhydride and propanoic acid were removed by thin film evaporation (1 mbar, bath temperature 84 °C). Subsequent distillation using a thin film evaporator (1 mbar, bath temp. 165 °C) afforded crude anhydride **7** (595 g), which was dissolved in diisopropyl ether (500 mL) at r.t. The mixture was cooled to –20 °C and stirred for 30 min at this temperature. The crystals were collected by filtration, washed with cold diisopropyl ether (250 mL) and dried in vacuo at r.t. to afford anhydride **7**.

Yield: 437 g (75%); colorless crystals; mp 50–52 °C (lit.[19] mp 50–51 °C).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.70–2.90 (m, 4 H, CH_2), 3.48–3.60 (m, 2 H, CH), 5.02 (s, 2 H, =CH_2).

Anal. Calcd for C_8H_8O3 (152.15): C, 63.2; H, 5.3; O, 31.1. Found: C, 63.6; H, 5.5; O, 31.6.

(+)-(1*S*,2*R*)-4-Methylene-2-[(2*E*)-3-phenyl-2-propenyloxycarbonyl]cyclopentanecarboxylic Acid (10)

A mixture of quinine (**9**) (960 g, 2.96 mol, contains 8% dihydroquinine) in toluene (12 L) was cooled to –15 °C. 5-Methylenetetrahydrocyclopenta[*c*]furan-1,3-dione (**7**) (450 g, 2.96 mol) was added and the mixture stirred for 10 min at –15 °C. Then (2*E*)-3-phenyl-2-propan-1-ol (**8**) (595 g, 4.44 mol) was added and the reaction mixture stirred overnight at –15 °C. The mixture was allowed to warm to r.t. and washed with aq HCl (1 N; 2 × 4.5 L) and H_2O (4.5 L). The organic layer was extracted with aq K_2CO_3 (2%) (22.5 L + 7.5 L). After washing of the combined aqueous solutions with EtOAc (2 × 5 L), toluene (5 L) was added and the mixture was acidified under vigorous stirring to pH 2.0 with aq HCl (10%; approx. 3.4 L). The aq layer was separated and extracted with toluene (5 L). The combined toluene solutions were washed with H_2O (2 × 2.5 L) and evaporated in vacuo at (20 mbar, bath 55 °C). The oily residue (889 g, 85% ee) was stirred with toluene (1.0 L) at r.t. for 1 h. The precipitated solid was collected by filtration, washed with toluene (300 mL) and dried in vacuo to afford almost racemic **10**.

Yield: 84.3 g (10%); (1*S*, 2*R*)-**10**–(1*R*, 2*S*)-**10** = 55: 45; colorless crystals; mp 101 °C.

The filtrate was evaporated in vacuo to afford (+)-(1*S*, 2*R*)-**10**. The product was stored as a 35% solution in toluene.

Yield: 714.6 g (84%); slightly yellow oil, which slowly crystallizes upon standing; mp 50–51 °C; $[\alpha]_D^{20}$ +6.8 (*c* 1.0, EtOAc); 97.3% ee [HPLC, Chiracel OD-H, 250 mm × 2 mm, 8 m, detection at 215 nm, 45 °C, flow rate 0.3 mL/min, 97% *n*-heptane containing TFA (0.2 mL/L)– 3% EtOH, t_R (1*S*,2*R*)-**10**, 6.90 min; (1*R*,2*S*)-**10**, 9.10 min].

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.58–2.88 (m, 4 H, 3-CH_2, 5-CH_2), 3.05–3.25 (m, 2 H, CHCH), 4.71 (d, 2 H, *J* = 6.4 Hz, OCH_2), 4.91–4.97 (m, 2 H, =CH_2), 6.23 (dt, 1 H, *J* = 15.9 Hz, 6.4 Hz, *CH*=CHPh), 6.62 (dd, 1 H, *J* = 15.9 Hz, 1 Hz, CH=*CH*Ph), 7.20–7.42 (m, 5 H, $CH_{arom.}$), 11.1 (br s, 1 H, COOH).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 34.82 (3-CH_2), 35.38 (5-CH_2), 46.11 (1-CH, 2-CH), 65.40 (OCH_2), 107.76 (C=*C*H_2), 122.86 (*CH*=CHPh), 126.64, 127.98, 128.53 (arom. CH), 134.07 (CH=*C*HPh), 136.17 (arom. C), 146.98 (*C*=CH_2), 172.95 (*C*$OOCH_2$), 179.92 (COOH).

MS (DCI/NH_3): *m*/*z* (%) = 304 (M + NH_4, 100), 188 (15), 151 (10).

Anal. Calcd for $C_{17}H_{18}O_4$ (286.33): C, 71.3; H, 6.3; O, 22.4. Found: C, 71.5; H, 6.3; O, 22.5.

(2*E*)-3-Phenyl-2-propenyl (1*R*,2*S*)-4-Methylene-2-{[(2*E*)-3-phenyl-2-propenyloxycarbonyl]amino}cyclopentanecarboxylate (11)

To a solution of (1*S*,2*R*)-4-methylene-2-[(2*E*)-3-phenyl-2-propenyloxycarbonyl]cyclopentanecarboxylic acid (**10**) (53.3 g, 186 mmol) in toluene (370 mL) was added Et_3N (26.0 mL, 18.8 g, 186 mmol). Diphenyl azidophosphate (51.2 g, 186 mmol) was added dropwise at r.t. over a period of 10 min and the mixture was heated to 90 °C until no further nitrogen escaped (approx. 30 min). (2*E*)-3-Phenyl-2-propan-1-ol (**8**) (30.0 g, 223 mmol) was added and the mixture was heated at reflux overnight. The reaction mixture was allowed to cool to r.t., while stirring, and was then cooled to 3 °C and stirred for 30 min. Precipitated crystals were collected by filtration, washed with cold toluene (250 mL) and dried in vacuo at 50 °C to afford title compound **11**.

Yield: 62.0 g, 80%; colourless crystals; mp 137 °C; $[\alpha]_D^{20}$ – 6.6 (*c* 1.0, CH_2Cl_2); > 99.5% ee [HPLC, Chiracel OD-H, 250 mm × 2 mm, 8 m, detection at 215 nm, 45 °C, flow rate 0.2 mL/min, *n*-heptane–EtOH (95:5), t_R (1*R*,2*S*)-**11**, 7.58 min; (1*S*,2*R*)-**11**, 9.22min].

^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.35–2.75 (m, 4 H, 3-CH_2, 5-CH_2), 3.16 (dd, 1 H, *J* = 7.3, 7.2 Hz, 1-CH), 4.27 (dd, 1 H, *J* = 7.2, 7.1 Hz, 2-CH), 4.50, 4.60 (AB of ABX, J_{AB} = 13 Hz, J_{AX} = 5.8 Hz, 2 H, $COOCH_2$), 4.63, 4.69 (AB of ABX, J_{AB} = 13.5 Hz, J_{AX} = 5.8 Hz, 2 H, $NHCOOCH_2$), 4.86–4.93 (m, 2 H, =CH_2), 6.20–6.40 (m, 2 H, *CH*=CHPh), 6.58, 6.62 (2 d, 2 H, *J* = 16, 16 Hz, CH=*CH*Ph), 7.20–7.54 (m, 11 H, NH, $CH_{arom.}$).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 33.19 (5-CH_2), 37.71 (3-CH_2), 47.13 (*CH*CO), 53.38 (CHNH), 64.08, 64.24 (OCH_2), 106.89 (C=*C*H_2), 123.87, 124.61 (CH=CHPh), 126.23, 126.33, 127.74, 127.80, 128.54, 128.56 (arom. CH), 131.98, 132.31 (CH=*CH*Ph), 135.96 (arom. C), 147.37 (C=CH_2), 155.50 (NHCO), 171.85 (CH*CO*).

MS (FAB): *m*/*z* (%) = 440 (M + Na, 20), 418 (M + H, 15), 307 (5), 154 (30), 117 (100).

Anal. Calcd for $C_{26}H_{27}NO_4$ (417.50): C, 74.8; H, 6.5; N, 3.4; O, 15.3. Found: C, 74.8; H, 6.7; N, 3.4; O, 15.3.

(–)-(1*R*,2*S*)-2-Amino-4-methylenecyclopentanecarboxylic Acid (3)

To a suspension of (2*E*)-3-phenyl-2-propenyl (1*R*,2*S*)-4-methylene-2-{[(2*E*)-3-phenyl-2-propenyloxycarbonyl]amino}cyclopentanecarboxylate (**11**) (352 g, 843 mmol) in EtOH (970 mL) was added Ph_3P (2.21 g, 8.43 mmol) and the mixture was stirred for 30 min at r.t., while N_2 was bubbled through. Morpholine (147 mL, 147 g, 1.69 mol) was added and the mixture was stirred at r.t. for 10 min, while N_2 was bubbled through. Palladium(II)acetate (95 mg, 42 mmol) was added and the mixture was heated at reflux for 2 h. 3-Mercapto-1,2,4-triazole (8.50 g, 84.3 mmol) was added, the mixture heated at reflux for 1 h and then allowed to cool to r.t., while stirring. It was then further cooled to 3 °C and stirred for 30 min. Pre-

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cipitated crystals were collected by filtration, washed with cold EtOH (320 mL) and dried in vacuo at 45 °C to afford crude β-amino acid **3** (109 g). The crude product was recrystallized from hot EtOH (915 mL)–H_2O (160 mL) in the presence of 3-mercapto-1,2,4-triazole (3.81 g, 37.7 mmol) to afford β-amino acid **3**.

Yield: 102 g (85%); colourless crystals; mp 219 °C (decomp.); $[\alpha]_D^{20}$ – 31.6 (*c* 1.0, H_2O); > 99.5% ee [HPLC, Chiracel OD-H, 250 mm × 2 mm, 5 m, detection at 210 nm, 40 °C, flow rate 2 mL/min, *n*-heptane–EtOH (9:1) containing camphersulfonic acid (20 g/L), t_R (1*R*,2*S*)-**3**, 13.3 min; (1*S*,2*R*)-**3**, 14.5 min].

^{1}H NMR (D_2O, 300 MHz): δ = 2.41–2.59, 2.64–2.71 (2 m, 4 H, 3-CH_2, 5-CH_2), 2.93–3.05 (m, 1 H, 1-CH), 3.72–3.82 (m, 1 H, 2-CH), 4.95–5.08 (m, 2 H, =CH_2).

^{13}C NMR (D_2O, 125 MHz): δ = 34.84 (5-CH_2), 37.39 (3-CH_2), 47.84 (*C*HCO), 53.27 ($CHNH_2$), 109.94 (C=*C*H_2), 146.19 (*C*=CH_2), 180.70 (CO).

MS (DCI/NH_3): *m*/*z* (%) = 159 (M + NH_4, 55), 14 (M + H, 100).

ICP-MS: Pd < 0.5 ppm.

Anal. Calcd for $C_7H_{11}NO_2$ (141.17): C, 59.6; H, 7.9; N, 9.9; O, 22.7. Found: C, 59.4; H, 7.7; N, 10.0; O, 23.0.

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