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Chemoenzymatic Synthesis of Both Enantiomers of Cispentacin

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Dedicated to Prof. Dr. Hans Schick on the occasion of his 60th birthday

Abstract: Based on the lipase-catalysed kinetic resolution of the silyloxyalcohol (1*RS*,2*SR*)-**5** by transesterification with vinyl acetate in the presence of lipase from *Pseudomonas cepacia* a synthesis of both enantiomers of the β-amino acid cispentacin (1*R*,2*S*)-**1** and (1*S*,2*R*)-**1** using simple functional group interconversions is described. Copyright © 1996 Elsevier Science Ltd

The use of biotransformations for the synthesis of enantiomerically pure compounds has been established as an important tool in organic synthesis during the last decade.[1] Among the biocatalysts used in organic synthesis lipases have been applied most frequently because they are easy to handle, available from many sources and accept a broad range of substrates.[2]

The β-amino acid cispentacin, (1*R*,2*S*)-2-aminocyclopentane-1-carboxylic acid (1*R*,2*S*)-**1**, was isolated in 1989 as an antifungal antibiotic from the culture broth of the *Bacillus cereus* strain L450-B2 or from *Streptomyces setonii* No. 7562[3-5] exhibiting selective activity against some *Candida* species. Cispentacin has been used as a peptidomimetic for proline in the synthesis of biologically active oligopeptides.[6]

Chemical synthesis of enantiomerically pure cispentacin was achieved by addition of chlorosulfonyl isocyanate to cyclopentene yielding the *N*-chlorosulfonyl β-lactam which was subsequently transformed into racemic cispentacin which was resolved into its enantiomers by crystallization of diastereomerically salts.[3] Kinetic resolution of 6-azabicyclo[3.2.0]hept-3-en-7-one by enantiomer selective hydrolysis with a lactamase gave the corresponding unsaturated derivative which subsequently was hydrogenated to give the title compound.[7] The synthesis of (1*R*,2*S*)-cispentacin by S. G. Davies *et al.*[8] based on the addition of enantiomerically pure lithium (*S*)-(α-methylbenzyl)benzylamide to *tert*-butyl 1-cyclopentene-1-carboxylate. Very recently, the racemic ethyl ester of cispentacin was resolved by lipase-catalysed acylation.[9]

It was our aim to synthesize both enantiomers of cispentacin from the enantiomerically pure *trans*-2-(hydroxymethyl)cyclopentanols (1*R*,2*S*)-**2** and (1*S*,2*R*)-**2**, respectively, in which the carbon skeleton of the amino acid is preformed (Figure 1). We recently separated racemic *trans*-2-(hydroxymethyl)cyclopentanol (1*RS*,2*SR*)-**2** into its enantiomers by a stepwise lipase-catalysed transesterification with vinyl acetate in the presence of lipase from *Pseudomon cepacia* (Amano PS)[10] which should be the basis for the

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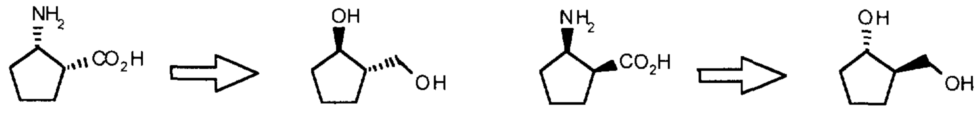
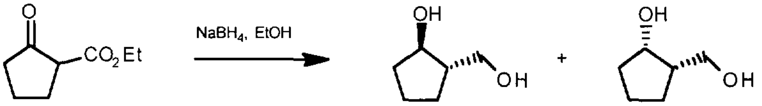
preparation of enantiomerically pure cispentacin (1*R*,2*S*)-**1** and its enantiomer (1*S*,2*R*)-**1**. Based on **2**, substitution of the secondary hydroxy group under inversion of configuration and oxidation of the hydroxymethyl moiety to a carboxylate group are the key steps of our synthesis in combination with simple protecting group variation.



(1*R*,2*S*)-**1** (1*R*,2*S*)-**2** (1*S*,2*R*)-**1** (1*S*,2*R*)-**2**

Figure 1

The mixture of *trans*- and *cis*-2-(hydroxymethyl)cyclopentanol can be prepared either in an one-step procedure by reduction of methyl or ethyl 2-oxocyclopentanecarboxylate with LAH[11] in a yield of about 20 % or alternatively by two-step procedures using two different reducing agents.[12,13] The insufficient access to the starting material prompted us to find a more efficient synthesis of (1*RS*,2*SR*)-**2**. This was achieved by reduction of ethyl 2-oxocyclopentanecarboxylate with 6 equivalents of $NaBH_4$[14] in ethanol to give 44 % of the *trans*-diol (1*RS*,2*SR*)-**2** and 20 % of the *cis*-diol (1*SR*,2*SR*)-**4** which could be separated by flash chromatography (Scheme 1).



(*RS*)-**3** (1*RS*,2*SR*)-**2** (1*SR*,2*SR*)-**4**

Scheme 1

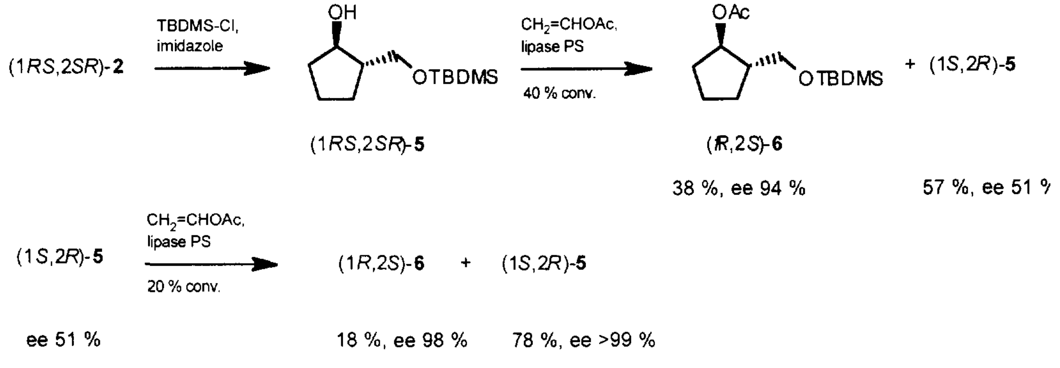
Lipase-catalysed acylation of (1*RS*,2*SR*)-**2** proceeds in two steps. The first step is a regioselective acetylation at the primary hydroxy group with very poor enantioselection to give after complete conversion the corresponding racemic primary monoacetate. The latter monoacetate reacts without isolation in an enantiomer selective manner by acylation of the free secondary hydroxy group.[10] In order to differentiate between the two hydroxy groups during the synthesis, it seemed reasonable to introduce an appropriate protecting group at the primary hydroxy function of (1*RS*,2*SR*)-**2** which is different from acetate. The resulting monoprotected racemic diol shoud be used as substrate for the kinetic resolution and the resulting non-racemic products as starting material for the target compound. Hence, the silyloxy alcohol (1*RS*,2*SR*)-**5** was chosen as substrate for the lipase-catalysed kinetic resolution and its enantiomers as precursors for the whole synthesis.

(1*RS*,2*SR*)-**2** was monosilylated with *tert*-butyldimethylsilyl chloride (TBDMS chloride) to afford the silyloxy alcohol (1*RS*,2*SR*)-**5** in high yield (Scheme 2). Lipase-catalysed enantiomer selective transesterification with vinyl acetate in the presence of lipase from *Pseudomonas cepacia* (Amano PS) or with the recombinant lipase from *Candida antarctica* B (Novo SP 435) proceeds with good selectivity in various organic solvents (Scheme 2, Table 1). The kinetic resolution on a preparative scale was carried out with lipase PS from Amano in *tert*-butyl methyl ether by monitoring of the conversion by HPLC. Termination of the reaction at 40 % conversion of the substrate (1*RS*,2*SR*)-**5** yielded the silyloxy acetate (1*R*,2*S*)-**6** with an ee of 94 %. The remaining enantiomerically enriched silyloxy alcohol (1*S*,2*R*)-**5** with an ee of 51 % was subjected to a second transesterification which was terminated at 20 % conversion (i.e. 60 % conversion from start) and yielded a further fraction of (1*R*,2*S*)-**6** with an ee of 98 % and the remaining almost enantiomerically pure alcohol (1*S*,2*R*)-**5** with an ee > 99%.

Table 1: Kinetic resolution of the silyloxy alcohol (1*RS*,2*SR*)-**5** by lipase-catalysed acetylation[a]

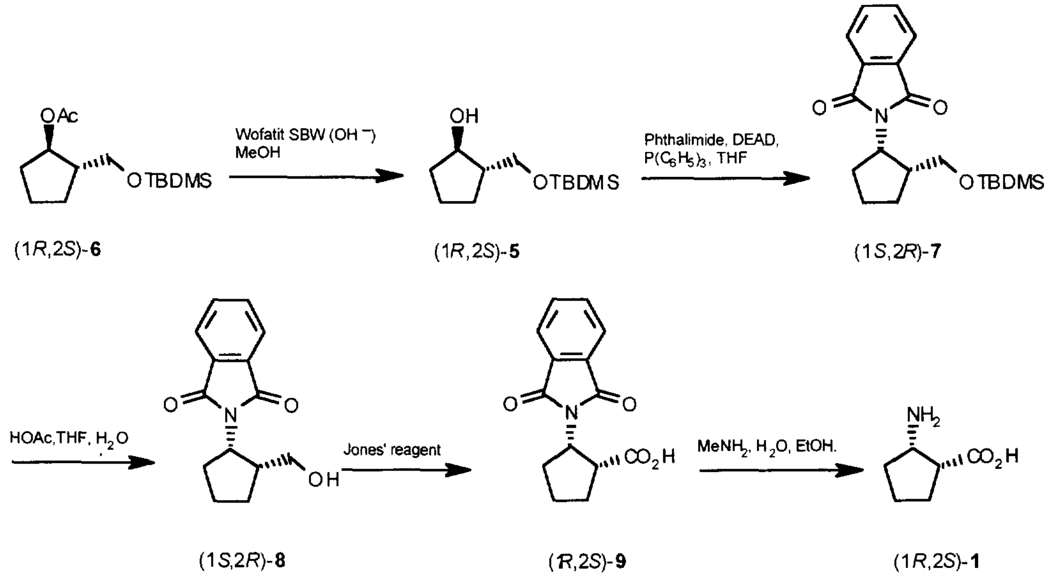
Lipase	Solvent	Time (h)	(1*R*,2*S*)-**6** ee (%)	(1*S*,2*R*)-**5** ee (%)	*c*[b]	*E*[b]
Amano PS	3-Methyl-3-pentanol	23	84.2	89.0	0.51	34
Amano PS	*n*-Hexane	16	88.2	88.4	0.50	47
Amano PS	*t*-BuOMe	16	90.0	89.4	0.50	57
Novo SP 435	THF	23	84.1	95.9	0.53	45
Novo SP 435	*t*-BuOMe	23	84.8	96.4	0.53	48

[a] 50 mg of (1*RS*,2*SR*)-**5**, 1.5 ml of solvent, 0.15 ml of vinyl acetate, 10 mg of lipase,
[b] *c*=conversion and *E*=enantiomeric ratio calculated according to[15].



Scheme 2

Transformation of (1*R*,2*S*)-**6** into the target molecule was carried out as depicted in Scheme 3. Deacetylation of the silyloxy acetate (1*R*,2*S*)-**6** with the strong basic ion-exchange resin Wofatit SBW (OH^-) afforded the silyloxy alcohol (1*R*,2*S*)-**5**. The introduction of a protected amino group in 1-position of the *trans*-silyloxy alcohol (1*R*,2*S*)-**5** was achieved by Mitsunobu reaction[16] with phthalimide, triphenylphosphine and diethyl azodicarboxylate (DEAD) to furnish under retention of configuration at C_1 the *trans*-configured phthalimido silyl ether (1*S*,2*R*)-**7** in a yield of 70 %. Subsequent desilylation of (1*S*,2*R*)-**7** with acetic acid in THF–H_2O afforded the phthalimido alcohol (1*S*,2*R*)-**8**. Desilylation with tetrabutylammonium fluoride in THF failed. Oxidation of (1*S*,2*R*)-**8** with Jones' reagent at the primary hydroxy group yielded the phthalimido carboxylic acid (1*R*,2*S*)-**9** in 92 % yield. (1*R*,2*S*)-**9** was deprotected with an aqueous solution of methyl amine[17] in EtOH to furnish the free amino acid (1*R*,2*S*)-**1** in enantiomerically pure form. The enhancement of the ee from 94 % of the starting material up to >99 % for the final product should be a result of the recrystallisation of (1*S*,2*R*)-**9**. The enantiomer (1*S*,2*R*)-**1** was prepared analogously starting from the silyloxy alcohol (1*S*,2*R*)-**5**.



Scheme 3

In conclusion, we have accomplished a chemoenzymatic synthesis of both enantiomers of cispentacin (1*R*,2*S*)-**1** and (1*S*,2*R*)-**1** in enantiomerically pure form based on an improved procedure for the preparation of (1*RS*,2*SR*)-**2** and a subsequent lipase-catalysed kinetic resolution of the racemic monoprotected silyloxy alcohol (1*RS*,2*SR*)-**5**. This synthesis demonstrates the usefulness of a lipase-catalysed resolution for the preparation of cispentacin and should be an alternative to previously reported procedures.

Experimental

All reactions, except those which were monitored by HPLC, were followed by TLC on glass plates coated with a 0.25 mm layer of silica gel. Compounds were visualized with a 3.5 % solution of molybdatophosphoric acid in ethanol and/or by UV light. The amino acid was visualized by ninhydrine in 2-propanol. HPLC was carried out on a Merck-Hitachi system consisting of L-6200A Pump, Differential Refractometer RI-71 and Chromato-Integrator D-2500. GC was performed on a Hewlett Packard 5890 instrument. Flash chromatography was performed with silica gel 60 (0.040–0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on the Varian instruments UNITYplus-500 or -300 at 500 or 300 and 125 or 75 MHz, respectively. Mass spectra were recorded on the Autospec VG. Optical rotations were measured on a Perkin-Elmer 241 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}.

(1*RS*,2*SR*)-2-(Hydroxymethyl)cyclopentanol (1*RS*,2*SR*)-2 and (1*SR*,2*SR*)-2-(hydroxymethyl)cyclopentanol (1*SR*,2*SR*)-4: Dry ethanol (150 mL) was cooled to −30 °C and treated with $NaBH_4$ (12.2 g, 0.32 mol). To this solution was added dropwise a solution of ethyl cyclopentanone-2-carboxylate (10.0 g, 0.064 mol) in ethanol (30 mL) that the temperature did not rise to more than −20 °C. After stirring for 1 h between −20 and −30 °C the cooling bath was removed and stirring was continued at r. t. for another 20 h. Thereafter the reaction mixture was treated dropwise with glacial acetic acid (50 mL). The resulting solution was concentrated under reduced pressure. The residue was treated with toluene (100 mL) and concentrated under reduced pressure to remove acetic acid by co-distillation. The residue was treated with brine (100 mL) and extracted with ethyl acetate (3×100 mL). The combined organic extracts were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The residue was subjected to flash chromatography on silica gel (1000 g, 6×70 cm) with ethyl acetate as eluent to give the *cis*-diol (1*SR*,2*SR*)-**4** as the first eluting compound and the *trans*-diol (1*RS*,2*SR*)-**2** as the second eluting compound. After Kugelrohr distillation (150 °C, 0.01 mbar) 1.48 g (20 %) of the *cis*-diol (1*SR*,2*SR*)-**4** and 3.26 g (44 %) of the *trans*-diol (1*RS*,2*SR*)-**2** were obtained. Spectral data were identical with those reported in the literature.[13]

(1*RS*,2*SR*)-2-(*tert*-Butyldimethylsilyloxymethyl)cyclopentanol (1*RS*,2*SR*)-5: A solution of (1*RS*,2*SR*)-**2** (2.80 g, 24 mmol) and imidazole (4.04 g, 57.6 mmol) in dry THF (40 mL) was treated dropwise under ice-cooling with a solution TBDMS chloride (4.35 g, 28.8 mmol) in THF (30 mL). The reaction mixture was stirred at r. t. for 4.5 h and subsequently concentrated under reduced pressure. The residue was dissolved in diethyl ether (100 mL) and washed with water (3×30 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. Thereafter the residue was treated twice with toluene (20 mL) and concentrated to dryness under reduced pressure. Kugelrohr distillation (125 °C, 0.01 mbar) of the residue yielded 4.90 g (89 %) of the silyloxy alcohol (1*RS*,2*SR*)-**5**. ^{1}H NMR($CDCl_3$): δ = 0.00 (s, 6 H), 0.83 (s, 9 H), 1.04–1.33 (m, 1 H), 1.42–1.56 (m, 2 H), 1.62–1.74 (m, 2 H), 1.83–1.92 (m, 2 H), 2.53 (d, *J* = 2 Hz, 1 H), 3.41 (t, *J* = 9.5, 1 H), 3.72 (dd, *J* = 9.5, 5.2 Hz, 1 H), 3.91 (dd, *J* = 7.4, 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$): δ = −5.56, −5.50, 18.17, 21.56, 25.87, 33.81, 49.24, 63.18, 66.86, 78.35; MS (EI): *m/z* = 229 (M^+ − H), 75 (100 %); calc. C 62.55, H 11.37, found C 62.59, H 11.61.

(1*R*,2*S*)-2-(*tert*-Butyldimethylsilyloxymethyl)cyclopentyl acetate (1*R*,2*S*)-6 and (1*S*,2*R*)-2-(*tert*-Butyldimethylsilyloxymethyl)cyclopentanol (1*S*,2*R*)-5: A solution of the silyloxy alcohol (1*RS*,2*SR*)-**5** (3.60 g, 15.6 mmol) in *tert*-butyl methyl ether (110 mL) was treated with vinyl acetate (10.80 mL, 117 mmol) and lipase PS (0.72 g). The conversion was monitored by HPLC on 7μm Lichrosorb Si-60 (4.6×250 mm) with *n*-heptane–*tert*-butyl methyl ether (5:1) by RI-detection and terminated after 4 h at 40 % conversion by filtration of the enzyme. The filter-cake was washed *tert*-butyl methyl ether (3×20 mL). The combined organic filtrates were concentrated under reduced pressure and subjected to flash chromatography on 100 g of silica gel (3.6×20 cm) with *n*-hexane–*tert*-butyl methyl ether (5:1) as eluent to give 1.60 g (38 %) of the silyloxy acetate (1*R*,2*S*)-**6** with an ee of 94 % as the first eluting compound and 2.06 g (57 %) of the silyloxy alcohol

(1*S*,2*R*)-**5** with an ee of 51 % as the second eluting compound. The enantiomerically enriched silyloxy alcohol (1*S*,2*R*)-**5** was subjected to a second lipase-catalysed transesterification: A solution (1*S*,2*R*)-**5** (2.00 g, 8.7 mmol) in *tert*-butyl methyl ether (60 mL) was treated with vinyl acetate (6.0 mL, 65 mmol) and lipase PS (0.575 g). The reaction mixture was stirred at room temperature under HPLC-monitoring for 24 h until a conversion of 20 % was reached. Work-up as described above and flash chromatography on 50 g of silica gel (2.2×20 cm) yielded 0.438 g (18 %) of the silyloxy acetate (1*R*,2*S*)-**6** with an ee of 98 % and 1.564 g (78 %) of the silyloxy alcohol (1*S*,2*R*)-**5** with an ee > 99 %. (1*R*,2*S*)-**6**: $[\alpha]_D^{20}$ −6.24 (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 0.02$ (s, 3 H), 0.03 (s, 3 H), 0.87 (s, 9 H), 1.32–1.44 (m, 1 H), 1.56–1.74 (m, 3 H), 1.76–1.95 (m, 2 H), 2.00 (s, 3 H), 2.03–2.16 (m, 1 H), 3.57 (dd, J = 6.0, 4.0 Hz, 1 H), 4.94 (dd, J = 6.7, 3.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$): $\delta = -5.46$, −5.45, 18.25, 21.35, 23.38, 25.87, 27.20, 32.68, 47.89, 64.29, 78.66, 170.87; (1*S*,2*R*)-**5**: $[\alpha]_D^{20}$ +2.0 (c = 1.0, $CHCl_3$); calc. C 61.71, H 10.36, found C 61.64, H 10.45. ^1H and ^{13}C NMR-spectra were identical with those of the racemic silyloxy alcohol (1*RS*,2*SR*)-**5**. The ee's of the products were determined by GC on FS-Lipodex E (25 m, Macherey-Nagel) after conversion of the products into the corresponding diols (1*R*,2*S*)-**2** and (1*S*,2*R*)-**2**, respectively, as follows: (1*R*,2*S*)-**6** was deacetylated with MeOH in the presence of the strong basic ion-exchange resin Wofatit SBW (OH^-). The silyloxy alcohols (1*R*,2*S*)-**5** and (1*S*,2*R*)-**5** were desilylated by hydrolysis with acetic acid–H_2O in THF.

(1*R*,2*S*)-2-(*tert*-Butyldimethylsilyloxymethyl)cyclopentanol (1*R*,2*S*)-5: A solution of the silyloxy acetate (1*R*,2*S*)-**6** (2.16 g, 7.94 mmol, ee 95 %) in MeOH (50 mL) was treated with the strong basic ion-exchange resin Wofatit SBW (OH^-) (5 g) and stirred at r. t. for 24 h. The ion-exchange resin was filtered off and washed with MeOH (3×30 mL). The combined filtrates were concentrated under reduced pressure and the remaining residue was distilled in the Kugelrohr (125 °C, 0.01 mbar) to yield 1.69 g (92 %) of the silyloxy alcohol (1*R*,2*S*)-**5**, $[\alpha]_D^{20}$ −2.0 (c = 1.0, $CHCl_3$). ^1H and ^{13}C NMR-spectra were identical with those of the racemic silyloxy alcohol (1*RS*,2*SR*)-**5**.

(1*S*,2*R*)-2-(*tert*-Butyldimethylsilyloxymethyl)-1-phthalimidocyclopentane (1*S*,2*R*)-7: A solution of phthalimide (2.048 g, 13.9 mmol), triphenyl phosphine (3.648 g, 13.9 mmol) and the silyloxy alcohol (1*R*,2*S*)-**5** (1.60 g, 6.9 mmol) in dry THF 50 mL) was treated under argon and ice-cooling with a solution of DEAD (2.42 g, 13.9 mmol) in THF (8 mL). After stirring overnight the solvent was removed under reduced pressure. The residue was filtered through a pad (3×5 cm) of silica gel 60 (0.040–0.063 mm) with *n*-hexane–ethyl acetate (5:1) to remove triphenylphosphine oxide. The filtrate was concentrated and subjected to flash chromatography (100 g, 3.6×20 cm) with *n*-hexane–ethyl acetate (20:1) to afford 1.745 g (70 %) of the phthalimido silyl ether (1*S*,2*R*)-**7**. $[\alpha]_D^{20}$ +10.63 (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = -0.34$ (s, 3 H), −0.27 (s, 3 H), 0.59 (s, 9 H), 1.48–1.60 (m, 1 H), 1.63–1.72 (m, 1 H), 1.76–1.83 (m, 1 H), 1.95–2.05 (m, 2 H), 2.32–2.41 (m, 1 H), 2.45–2.54 (m, 1 H), 3.51–3.60 (m, 2 H), 4.76 (dd, J = 8.6, 8.5 Hz, 1 H), 7.55–7.65 (m, 2 H), 7.69–7.77 (m, 2 H); ^{13}C NMR ($CDCl_3$): $\delta = -5.82$, −5.76, 18.13, 24.36, 25.66, 28.32, 28.73, 45.44, 52.24, 63.60, 122.88, 132.27, 133.57, 169.23; MS (FAB): m/z = 360 ($M^+ + H$), 358 ($M^+ - H$), 302 (100 %); calc. C 66.81, H 8.13, N 3.89, found C 66.82, H 8.31, N 3.85.

(1*R*,2*S*)-2-(*tert*-Butyldimethylsilyloxymethyl)-1-phthalimidocyclopentane (1*R*,2*S*)-7: Yield: 76 %; $[\alpha]_D^{20}$ −10.75 (c = 1.0, $CHCl_3$).

(1*S*,2*R*)-2-(Hydroxymethyl)-1-phthalimidocyclopentane (1*S*,2*R*)-8: A solution of the phthalimido silyl ether (1*S*,2*R*)-**7** (1.70 g, 4.7 mmol) in glacial acetic acid–H_2O–THF (3:1:1, 15 mL) was kept at r. t. overnight. The reaction mixture was concentrated under reduced pressure and traces of water and acetic acid were removed by co-distillation with toluene (2×20 mL) under reduced pressure. The residue was subjected to flash chromatography on silica gel (20 g, 20×1.6 cm) with *n*-hexane–ethyl acetate as eluent and yielded 1.11 g, (95 %) of analytically pure (1*S*,2*R*)-**8**. $[\alpha]_D^{20}$ +4.9 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 1.58–1.75 (m, 2 H), 1.81–1.88 (m, 1 H), 2.00–2.14 (m, 2 H), 2.30–2.38 (m, 1 H), 2.44–2.53 (m, 1 H), 3.42–3.49 (m, 1 H), 3.60 (dd, J = 11.5, 4.9 Hz, 1 H), 4.77 (dd, J = 13.3, 6.4 Hz, 1 H), 7.68–7.74 (m, 2 H), 7.79–7.84 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ = 23.79, 28.08, 46.59, 53.01, 62.78, 123.17, 131.76, 134.01, 169.58; MS (FAB): m/z = 246 (M^+ + H, 100 %); calc. C 68.55, H 6.16, N 5.71, found C 68.61, H 6.23, N 5.65.

(1*R*,2*S*)-2-(Hydroxymethyl)-1-phthalimidocyclopentane (1*R*,2*S*)-8: Yield: 78 %; $[\alpha]_D^{20}$ −5.0 (c = 1.0, $CHCl_3$).

(1*R*,2*S*)-2-Phthalimidocyclopentane-1-carboxylic acid (1*R*,2*S*)-9: A solution of the phthalimido alcohol (1*S*,2*R*)-**8** (1.22 g, 4.97 mmol) in acetone (16 mL) was treated under ice-cooling with Jones' reagent (4.5 mL, 18 mval) and stirred at r. t. for 30 min. The excess of the oxidant was destroyed by addition of 2-propanol. The solid residue was filtered off and washed with acetone (3×5 mL). The combined filtrates were diluted with water (20 mL) and concentrated to ~20 mL. The remaining aqueous residue was extracted with ethyl acetate (5×10 mL). The combined organic extracts were washed with 1 N $NaHCO_3$ (3×10 mL). The combined aqueous extracts were acidified with 1 N HCl and reextracted with diethyl ether (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give 1.044 g (80 %) of (1*R*,2*S*)-**9** as analytically pure crystals; mp 119–121 °C (ethyl acetate–*n*-hexane). $[\alpha]_D^{20}$ +20.11 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 1.54–1.62 (m, 1 H), 1.95–2.01 (m, 1 H), 2.03–2.15 (m, 2 H), 2.30–2.43 (m, 2 H), 3.05 (dd, J = 12.0, 7.7 Hz, 1 H), 4.88 (dd, J = 17.2, 8.0 Hz, 1 H), 7.64–7.71 (m, 2 H), 7.74–7.82 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ = 23.91, 28.30, 28.98, 46.93, 51.66, 123.20, 131.85, 133.87, 168.50, 175.99; MS (FAB): m/z = 260 (M^+ + H), 242 (100 %); calc. C 64. 86, H 5.05, N 5.40, found C 64.90, H 5.03, N 5.30.

(1*S*,2*R*)-2-Phthalimidocyclopentane-1-carboxylic acid (1*S*,2*R*)-9: Yield: 80 %; $[\alpha]_D^{20}$ −20.12 (c = 1.0, $CHCl_3$).

(1*R*,2*S*)-2-Aminocyclopentane-1-carboxylic acid (1*R*,2*S*)-1: A solution of the phthalimido carboxylic acid (1*R*,2*S*)-**9** (1.00 g, 3.8 mmol) in EtOH–H_2O (1:1, 50 mL) was treated with a 28 % aqueous solution of methyl amine (2.08 mL, 19 mmol) and stirred at r. t. for 1.5 h. The reaction mixture was concentrated under reduced pressure, dissolved in water (50 mL) and acidified with 0.1 N HCl to pH ~2.5. The aqueous solution was adjusted to pH 7.0 by addition of the strong basic ion-exchange resin Wofatit SBW (OH^-). The neutral solution was concentrated to dryness and subjected to flash chromatography on silica gel (50 g, 2.2×20 cm) with EtOH–H_2O (95:5) as eluent to afford 0.447 g (91 %) of cispentacin (1*R*,2*S*)-**1**. $[\alpha]_D^{20}$ −7.5 (c = 1.0, H_2O); {ref.[3] $[\alpha]_D^{25}$ −10.7; ref.[5] $[\alpha]_D^{20}$ −9.8; ref.[8] $[\alpha]_D^{23}$ −8.8 (c = 1.0, H_2O)}. The ee of the product was > 99 % as determined by HPLC on Crownpak CR (+) (4.0×150 mm) at 0 °C with aqueous $HClO_4$ of pH 1.5 as eluent.

^{1}H NMR (D_2O): δ = 1.64–1.90 (m, 4 H), 2.02–2.16 (m, 2 H), 2.85 (ddd, *J* = 10.2, 6.3, 6.1 Hz, 1 H), 3.70 (ddd, *J* = 13.0, 6.5, 4.4 Hz, 1 H); ^{13}C NMR (D_2O): δ = 23.84, 30.60, 32.07, 50.22, 55.61, 183.63.

(1*S*,2*R*)-2-Aminocyclopentane-1-carboxylic acid (1*S*,2*R*)-1: Yield: 90 %, $[\alpha]_D^{20}$ +8.5 (*c* = 1.0, H_2O). The ee of the product was > 99 % as determined by HPLC on Crownpak CR (+) (4.0×150 mm) at 0 °C with aqueous $HClO_4$ of pH 1.5 as eluent.

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