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Synthesis of enantiomerically pure *cis* and *trans* 2-aminocyclopentanecarboxylic acids. Use of proline replacements in potential HIV-protease inhibitors.

Daniel Nöteberg,[a] Jonas Brånalt,[a] Ingemar Kvarnström,[a] Björn Classon,[b] Bertil Samuelsson,*[,b,e] Ulrika Nillroth,[c] U. Helena Danielson,[c] Anders Karlén[d] and Anders Hallberg[d]

[a]Department of Chemistry, Linköping University, S-581 83 Linköping, Sweden.

[b]Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden.

[c]Department of Biochemistry, Uppsala University, BMC, S-751 23 Uppsala, Sweden.

[d]Department of Organic Pharmaceutical Chemistry, Uppsala University, BMC, S-751 23 Uppsala, Sweden.

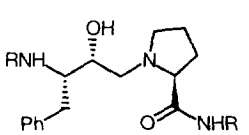
[e]Additional address: Astra Hässle AB, S-431 83 Mölndal, Sweden.

Abstract: The synthesis of the four diastereomeric 2-aminocyclopentanecarboxylic acids, their use as replacements for proline in potential HIV protease inhibitors containing a hydroxyethylamine dipeptide isostere and the evaluation of the biological activity of these is described. © 1997 Elsevier Science Ltd.

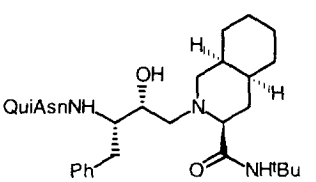
INTRODUCTION

The human immunodeficiency virus (HIV) protease has become one of the major targets for chemotherapeutic intervention in AIDS and in patients infected with HIV.[1] This proteolytic enzyme cleaves specific amide bonds in precursor *gag* and *gagpol* polyproteins into functional enzymes and structural proteins which are essential for the formation of mature, infectious virus.[2] The HIV protease is unusual in that it cleaves peptide bonds having a P1' proline (i.e. Phe-Pro). This fact has been the basis for the development of inhibitors containing a noncleavable Phe-Pro hydroxyethylamine dipeptide isostere[3] (Figure 1). A structurally related compound, Saquinavir,[4] **1** which was the first HIV protease inhibitor to enter clinical trials has recently been approved for the treatment of AIDS. In order to improve the pharmacokinetic properties of **1**, several analogues of this compound have been prepared.[5]

Recently we reported that compound **2** (Figure 1), containing anthranilic acid as replacement for proline, is approximately equipotent with **1** against HIV protease although the antiviral activity in cell culture was lower.[6]



Phe-Pro-hydroxyethylamine isostere



Saquinavir **1**

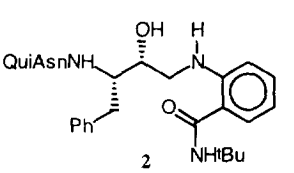


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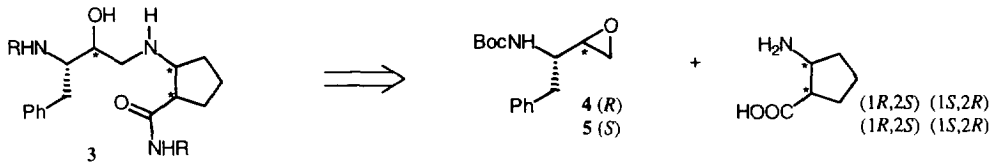
Figure 1

We have now synthesized hydroxyethylamine dipeptide isosteres containing 2-aminocyclopentanecarboxylic acids as novel proline replacements. As depicted in scheme 1, these compounds should be accessible by a convergent approach involving opening of chiral α-aminoalkyl epoxides **4**[7] and **5**[6,8] with each of the enantiomers of *cis* and *trans* 2-aminocyclopentanecarboxylic acids.



Scheme 1

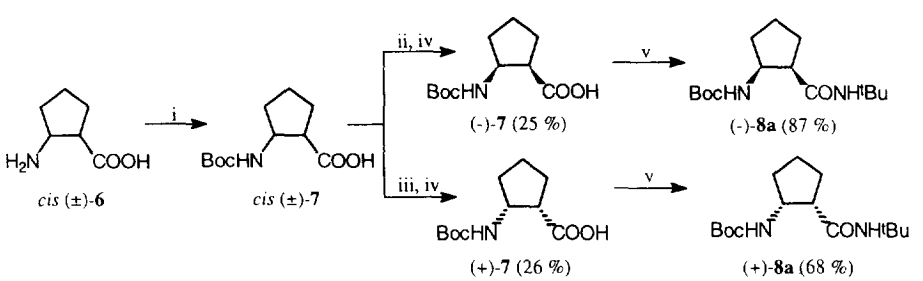
2-Aminocyclopentanecarboxylic acids and derivatives thereof have shown a variety of interesting biological activities. For example the 1*R*,2*S* isomer (cispentacin) displays potent antifungal activity in vivo.[9, 10] One of the *cis*-isomers also form part of the antibiotic amipurimicin.[11] The L-aspartyl dipeptides of all four stereoisomers were used to probe a molecular model of taste.[12] On this basis, the synthesis of homochiral cis and trans 2-aminocyclopentanecarboxylic acids have been the subject of several recent investigations which include traditional resolution,[9, 12] enzymatic resolution[13] and asymmetric synthesis.[14]

Herein we report the synthesis of Phe-Pro hydroxyethylamine dipeptide isosteres containing all four isomers of 2-aminocyclopentanecarboxylic acid as novel replacements for proline in potential HIV-protease inhibitors. The *cis*-compounds were prepared by resolution, for the *trans* isomers, we have developed a new synthetic route from readily available chiral diesters.

RESULTS AND DISCUSSION

Racemic *cis*-2-aminocyclopentanecarboxylic acid (±)-**6** was synthesized according to the method of Nativ and Rona.[15] Boc protection of the amine and resolution with (+) and (–)-ephedrine[12] gave (+)-**7** and (–)-**7** in high enantiomeric excess ((+)-**7**: $[\alpha]^{22}_D$ +64.9 . (–)-**7** : $[\alpha]^{22}_D$ –69.7 [lit.[12], (+)-**7**: $[\alpha]^{22}_D$ +46.7]) (Scheme 2).

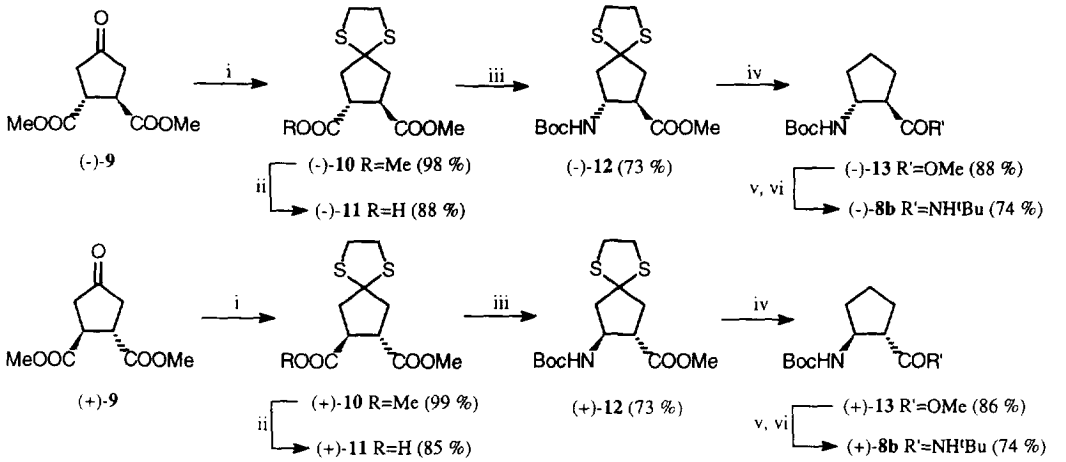
The carboxylic acid moiety was coupled with *tert*-butylamine using HOBt and EDC to give (–)-**8a** and (+)-**8a** in 87 % and 68 % yield, respectively.



Reagents and conditions : **i**, Boc-anhydride, $NaHCO_3$, THF-H_2O 3:1, rt; **ii**, (+)-ephedrine, EtOAc, crystallization; **iii**, (-)-ephedrine, EtOAc, crystallization; **iv**, 1M $NaHSO_4$; **v**, *tert*-butylamine, HOBt, EDC, THF, rt.

Scheme 2

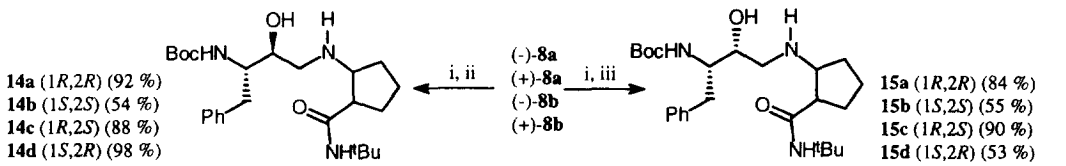
For the synthesis of the *trans* isomers the chiral ketones (–)-**9** and (+)-**9** were used as starting materials, which are readily available in high enantiomeric purity by enzymatic resolution.[16] The ketone moiety was protected as a thioketal by treatment with ethanedithiol and $SnCl_4$ in 98 % yield (Scheme 3). Monohydrolysis of (–)-**10** using 1.1 eq. of NaOH gave the monoacid (–)-**11** in 88 % yield as a single diastereomer. Curtius rearrangement of (–)-**11** using diphenylphosphorylazide (DPPA) and triethylamine in *tert*-butanol gave the Boc protected amine (–)-**12** in 73 % yield. Desulfurization of (–)-**12** by treatment with Raney Nickel in refluxing methanol gave 2-aminocyclopentanecarboxylic ester (–)-**13** in 88 % yield. The (+) enantiomer (+)-**13** was prepared from (+)-**9** using the same procedures in comparable yields. For both enantiomers hydrolysis of the methyl ester, followed by coupling with *tert*-butylamine in a similar manner as for the corresponding *cis*-isomers (*vide supra*) gave (–)-**8b** and (+)-**8b** in 74 % yield, respectively.



Reagents and conditions : **i**, $HSCH_2CH_2SH$, $SnCl_4$, CH_2Cl_2, rt; **ii**, NaOH, H_2O-dioxan (1:1), rt; **iii**, DPPA, Et_3N, *tert*-butanol, 80°C; **iv**, Raney-Nickel, methanol, reflux; **v**, NaOH, H_2O-dioxan (1:1), rt; **vi**, *tert*-butylamine, HOBt, EDC, THF, rt.

Scheme 3

Compounds (–)-**8a**, (+)-**8a**, (–)-**8b** and (+)-**8b** were treated with trifluoroacetic acid to hydrolyze off the boc group and without further purification allowed to react with epoxides **4** and **5** in 2-butanol at neutral pH (neutalization with triethylamine) to give compounds **14a-d** and **15a-d** in 53-98 % yield (Scheme 4). The reactions were conducted at room temperature and required several days for completion. Heating the reaction gave faster reaction, but as epoxides **4** and **5** decomposed under these conditions lower yields of the target compounds were obtained. This method of epoxide opening was found to give the highest yields. Other reaction conditions examined, i.e. using Al_2O_3 catalyst in diethyl ether[17] or $Mg(ClO_4)_2$ and $LiClO_4$ as catalysts in acetonitrile[18] gave low yields at room temperature.



Reagents and conditions : **i**, TFA-CH_2Cl_2 (1:1), rt; **ii**, epoxide **4**, 2-propanol, Et_3N, rt; **iii**, epoxide **5**, 2-propanol, Et_3N, rt.

Scheme 4

Compounds **14a-d** and **15a-d** were tested for HIV-protease inhibition.[19] None of the compounds showed significant activity at 10 μM.

EXPERIMENTAL SECTION

General methods. ^1H and ^{13}C NMR spectra were recorded on a Bruker 250 instrument using $CDCl_3$ or methanol-d_4 with TMS as an internal standard. The shifts are reported in ppm (δ scale) and all *J* values are in Hz. TLC was performed on Merck precoated 60 F_{254} plates. The spots were visualised with ethanol / sulphuric acid / acetic acid / *p*-anisaldehyde, 90:3:1:2 or ethanol / acetic acid / collidine / ninhydrine, 500:150:20:1. Column chromatography was performed using silica gel 60 (0.040-0.063 mm, Merck). Optical rotations were measured in $CHCl_3$ or methanol solutions at room temperature using a Perkin-Elmer 141 instrument. Organic phases were dried over anhydrous $MgSO_4$.

Optical resolution of *N*-(*tert*-Butyloxycarbonyl)-*cis*-2-aminocyclopentanecarboxylic acids [(+)-**7**, (-)-**7**] Compound (±)-**7** was prepared from (±)-**6** according to earlier publications.[12] To a hot solution of EtOAc (20 mL) were added (±)-**7** (1.821 g, 7.94 mmol) and (−)-ephedrine. The solution was diluted with 200 mL of diethyl ether and allowed to stand for 24 h at 0 °C. The white precipitate was collected by filtration and recrystallized from hot acetonitrile / diethyl ether. These procedures were repeated until optical rotation of the precipitate became constant. The precipitate was then dissolved in 40 mL of ethyl acetate and 1 M $NaHSO_4$ was added until the pH of the water layer became ~ 3. The organic layer was dried, filtered and concentrated to give (+)-**7** (0.47 g, 26%) as a colorless syrup that solidified on standing. The mother liquor was concentrated, redissolved in 30 mL of EtOAc and 1 M $NaHSO_4$ was added until pH of the water layer became ~ 3. The organic layer was dried, filtered and concentrated and treated with (+)-ephedrine as described above to give (−)-**7** (0.45 g, 25%) as a colorless syrup that solidified on standing. (+)-**7** : $[\alpha]^{22}_D$ +64.9 (*c* 1.3, methanol), (-)-**7** : $[\alpha]^{22}_D$ −69.7 (*c* 0.9, methanol). [lit.[12], (+)-**7**: $[\alpha]^{22}_D$ +46.7 (*c* 1.5, methanol)].

***N*-(*tert*-Butyloxycarbonyl)-*cis*-(1*R*,2*S*)-2-aminocyclopentanecarbonyl-*tert*-butylamide** [(−)-**8a**]. To a solution of (−)-**7** (0.406 g, 1.77 mmol) in dry THF (20 mL) were added *tert*-butylamine (0.789 mL, 3.54 mmol) and hydroxybenzotriazole (HOBt) (0.761 g, 2.66 mmol). The mixture was cooled to 0 °C and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) (0.506 g, 2.66 mmol) was added. After 1 h the icebath was removed and the solution was stirred at room temperature overnight. After evaporation of the solvent, the residue was dissolved in EtOAc, washed with saturated $NaHCO_3$, dried, filtered and evaporated.

Crystallization from EtOAc afforded compound (–)-**8a** (0.436 g, 87%) as a white solid. (–)-**8a**: $[\alpha]^{22}_D$ –71.4 (*c* 1.4, $CHCl_3$), mp 133-134 °C, ^1H NMR ($CDCl_3$, 250 MHz) δ 1.29 (9H, s, 3 CH_3), 1.43 (9H, s, 3 CH_3), 1.48-2.10 (6H, m, 3 CH_2), 2.61-2.80 (1H, dd, *J* = 7.8, 14.6 Hz, CH), 4.00-4.19 (1H, dt, *J* = 8.1 15.3 Hz, CH), 4.95-5.11 (1H, d, *J* = 8.1 Hz, NH), 5.56 (1H, s, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 22.7, 27.9 (2 CH_2), 28.5, 28.8 (6 CH_3), 32.9 (CH_2), 48.4, 51.1, 54.3 (2 CH, C), 79.1 (C), 155.8, 173.1 (2 C=O). Anal. calcd. for $C_{15}H_{28}N_2O_3$: C, 63.35; H, 9.92; N, 9.85. Found: C, 63.26; H, 9.75; N, 9.79.

***N*-(*tert*-Butyloxycarbonyl)-*cis*-(1*S*,2*R*)-2-aminocyclopentanecarbonyl-tert-butylamide [(+)-8a].** Compound (+)-**8a** (0.23 g, 68 %) was prepared from (+)-**7** (0.275 g, 1.20 mmol) according to the method for the preparation of (–)-**8a**. (+)-**8a**: $[\alpha]^{22}_D$ +74.5 (*c* 0.8, $CHCl_3$), mp 139-140 °C. Anal. calcd. for $C_{15}H_{28}N_2O_3$: C, 63.35; H, 9.92; N, 9.85. Found: C, 63.27; H, 10.05; N, 9.85.

***trans*-(7*R*,8*R*)-1,4-Dithiaspiro[4.4]nonane-7,8-dicarboxylic acid bis(methyl ester) [(–)-10].** A catalytic amount of $SnCl_4$ in dichloromethane was added to an ice cold stirred solution of *trans*-(3*R*,4*R*)-Bis(methoxycarbonyl)cyclopentanone [(–)-**9**] (6.02 g, 10.1 mmol) and ethanedithiol (1.5 mL, 18.3 mmol) in dichloromethane (150 mL). The mixture was stirred at room temperature for 24 h, diluted with dichloromethane (50 mL), washed with saturated $NaHCO_3$, dried, filtered, concentrated and purified by column chromatography (toluene-EtOAc 7:1) to give the thioketal [(–)-**10**] (8.10 g, 98 %) as a colorless liquid. (–)-**10**: $[\alpha]^{22}_D$ –21.3 (*c* 1.0, $CHCl_3$), ^1H NMR (250 MHz, $CDCl_3$): δ 2.42-2.71 (4H, m, 2 CH_2), 3.33 (4H, s, 2 CH_2), 3.35-3.52 (2H, m, 2 CH), 3.72 (6H, s, 2 OCH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 39.7 (2 CH_2), 46.2 and 46.9 (2 CH_2 and 2 CH), 52.3 (2 OCH_3), 69.2 (C), 173.6 (2 C=O). Anal. calcd. for $C_{11}H_{16}O_4S_2$: C, 47.80; H, 5.84; S, 23.20. Found: C, 48.16; H, 5.86; S, 22.97.

***trans*-(7*S*,8*S*)-1,4-Dithiaspiro[4.4]nonane-7,8-dicarboxylic acid bis(methyl ester) [(+)-10].** Compound (+)-**10** (1.48 g, 99 %) was prepared from (+)-**9** (1.09 g, 5.44 mmol) according to the method for the preparation of (–)-**10**. (+)-**10**: $[\alpha]^{22}_D$ +20.3 (*c* 1.1, $CHCl_3$). Anal. calcd. for $C_{11}H_{16}O_4S_2$: C, 47.80; H, 5.84; S, 23.20. Found: C, 47.95; H, 6.00; S, 23.03.

***trans*-(7*R*,8*R*)-1,4-Dithiaspiro[4.4]nonane-7-carboxylic acid-8-carboxylic acid methyl ester [(–)-11].** To a solution of [(–)-**10**] (8.10 g, 29.3 mmol) in dioxan-water (1:1) (300 mL) was added aqueous NaOH (1.0 M, 32.2 mL) dropwise during 30 min at room temperature. After 2 h the reaction mixture was acidified with conc. HCl to pH ~ 2-3 and extracted 5 times with dichloromethane. The combined organic phases were dried, filtered, concentrated, purified by column chromatography (toluene-EtOAc-AcOH 70:10:1) and recrystallized from diethylether / hexane to give (–)-**11** (6.78 g, 88 %) as a white solid. (–)-**11**: $[\alpha]^{22}_D$ –25.7 (*c* 0.6, $CHCl_3$), mp 79-80 °C, ^1H NMR (250 MHz, $CDCl_3$): δ 2.41-2.71 (4H, m, 2 CH_2), 3.35 (4H, s, 2 CH_2), 3.38-3.55 (2H, m, 2 CH), 3.72 (3H, s, OCH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 39.8 (2 CH_2), 45.8, 46.0, 46.6 and 46.8 (2 CH_2 and 2 CH), 52.4 (OCH_3), 69.2 (C), 173.9 and 176.2 (2 C=O). Anal. calcd. for $C_{10}H_{14}O_4S_2 \cdot 0.1$ EtOAc: C, 46.06; H, 5.50; S, 23.64. Found: C, 46.44; H, 5.45; S, 23.98.

***trans*-(7S,8S)-1,4-Dithiaspiro[4.4]nonane-7-carboxylic acid-8-carboxylic acid methyl ester [(+)-11].** Compound (+)-**11** (3.24 g, 85 %) was prepared from (+)-**10** (4.01 g, 14.5 mmol) according to the method for the

preparation of (–)-**11**. (+)-**11**: $[\alpha]^{22}_D$ +21.6 (*c* 1.0, $CHCl_3$), mp 74-75 °C. Anal. calcd. for $C_{10}H_{14}O_4S_2$: C, 45.78; H, 5.38; S, 24.42. Found: C, 45.73; H, 5.42; S, 24.50.

***N*-(*tert*-Butyloxycarbonyl)-*trans*-(7*R*,8*R*)-1,4-dithiaspiro[4.4]nonane-7-amino-8-carboxylic acid methyl ester** [(–)-**12**]. To a solution of (–)-**11** (0.433 g, 1.65 mmol) in *tert*-butanol (25mL) was added diphenylphosphorylazide (DPPA) (0.41 mL, 1.81 mmol) and triethylamine (0.26 mL, 1.81 mmol). After 18 h at 80 °C the mixture was concentrated, dissolved in EtOAc, washed with saturated $NaHCO_3$, dried, filtered, concentrated and purified by flash column chromatography (toluene-EtOAc 7:1) to give compound (–)-**12** (0.383 g, 73 %) as a colorless liquid. (–)-**12**: $[\alpha]^{22}_D$ –48.4 (*c* 0.7, $CHCl_3$), ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.41 (9H, s, 3 CH_3), 2.11-2.29 (1H, dd, *J* = 6.0, 14.2 Hz, CH_2), 2.40-2.62 (2H, m, CH_2), 2.63-2.78 (1H, dd, *J* = 8.6, 14.2 Hz, CH_2), 2.78-2.91 (1H, dt, *J* = 7.9, 9.6 Hz, CH), 3.44 (4H, s, CH_2), 3.72 (3H, s, OCH_3), 4.27-4.46 (1H, m, CH), 4.94 (1H, s, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 26.3 (3 CH_3), 39.7 and 39.9 (2 CH_2), 46.3, 50.3 and 51.3 (2 CH_2 and CH), 52.1 (OCH_3), 54.4 (CH), 67.6 (C), 80.1 (C), 155.0 and 173.6 (2 C=O). Anal. calcd. for $C_{14}H_{23}NO_4S_2$: C, 50.42; H, 6.95; N, 4.20; S, 19.23. Found: C, 50.23; H, 6.88; N, 4.07; S, 19.25.

***N*-(*tert*-Butyloxycarbonyl)-*trans*-(7*S*,8*S*)-1,4-dithiaspiro[4.4]nonane-7-amino-8-carboxylic acid methyl ester** [(+)-**12**]. Compound (+)-**12** (0.199 g, 73 %) was prepared from (+)-**11** (0.213 g, 0.81 mmol) according to the method for the preparation of (–)-**12**. (+)-**12**: $[\alpha]^{22}_D$ +44.3 (*c* 1.2, $CHCl_3$). Anal. calcd. for $C_{14}H_{23}NO_4S_2$: C, 50.42; H, 6.95; N, 4.20; S, 19.23. Found: C, 50.41; H, 6.80; N, 4.06; S, 19.33.

***N*-(*tert*-Butyloxycarbonyl)-*trans*-(1*R*,2*R*)-2-aminocyclopentanecarboxylic acid methyl ester [(–)-13]**. A suspension of Raney-Nickel was filtered, washed ten times with water, five times with aqueous acetic acid (1 %) and three times with methanol and added to a solution of (–)-**12** (338 mg, 1.06 mmol) in methanol (15 mL). After refluxing the mixture for 4 h, it was cooled, filtered, concentrated, purified by column chromatography (toluene-EtOAc 7:1) and recrystallized from diethylether / hexane to give (–)-**13** (204 mg, 88 %) as a white solid. (–)-**13**: $[\alpha]^{22}_D$ –48.2 (*c* 1.2, $CHCl_3$), mp 73-74 °C, ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.44 (9H, s, 3 CH_3), 1.62-2.20 (6H, m, 3 CH_2), 2.51-2.68 (1H, m, CH), 3.71 (3H, s, OCH_3), 4.06-4.20 (1H, m, CH) 4.62 (1H, s, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 22.9 (CH_2), 28.3 (3 CH_3), 33.0 (CH_2), 50.8 (CH), 51.6 (OCH_3), 56.1 (CH), 79.1 (C), 155.3 and 175.2 (2 C=O). Anal. calcd. for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.39; H, 8.54; N, 5.62.

***N*-(*tert*-Butyloxycarbonyl)-*trans*-(1*S*,2*S*)-2-aminocyclopentanecarboxylic acid methyl ester** [(+)-**13**]. Compound (+)-**13** (0.89 g, 81 %) was prepared from (+)-**12** (1.50 g, 4.50 mmol) according to the method for the preparation of (–)-**13**. (+)-**13**: $[\alpha]^{22}_D$ +44.6 (*c* 1.3, $CHCl_3$), mp 66-67 °C. Anal. calcd. for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.47; H, 8.73; N, 5.63.

***N*-(*tert*-Butyloxycarbonyl)-*trans*-(1*R*,2*R*)-2-aminocyclopentanecarbonyl-tert-butylamide [(–)-8b]**. Compound (–)-**13** (0.454 g, 1.86 mmol) was stirred in an ice cold mixture of dioxan-water (1:1) (20 mL) and NaOH (1M, 5.0 mL) was added dropwise during 30 min. The mixture was stirred for an additional hour, acidified to pH ~ 2 with conc. HCl, and extracted several times with dichloromethane. The combined organic phases were dried, filtered and concentrated. The crude carboxylic acid was without any further purification

redissolved in dry THF (5 mL) containing *tert*-butylamine (0.17 mL, 0.82 mmol) and hydroxybenzotriazole (HOBt) (0.161 g, 0.61 mmol). The mixture was cooled to 0 °C and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) (0.107 g, 0.1 mmol) was added. After 1 h the icebath was removed and the solution was stirred at room temperature overnight. After evaporation of the solvent, the residue was dissolved in EtOAc, washed with saturated $NaHCO_3$, dried and evaporated. Crystallization from EtOAc afforded compound (–)-**8b** (0.39 g, 74 %) as white crystals. (–)-**8b**: $[\alpha]^{22}_D$ –9.2 (*c* 0.9, $CHCl_3$), mp 199-200 °C, ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.30 (9H, s, 3 CH_3), 1.41 (9H, s, 3 CH_3), 1.51-2.05 (6H, m, 3 CH_2), 2.40-2.54 (1H, m, CHN), 3.82-3.97 (1 H, dt, J = 6.8, 12.3 Hz, CH), 4.70-4.82 (1H, d, J = 5.7 Hz, NH), 7.03 (1H, s, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 23.9, 27.2 (2 CH_2), 28.4, 28.7 (6 CH_3), 33.4 (CH_2), 50.8, 53.7, 56.7 (2 CH, C), 79.7 (C), 156.1, 173.0 (2 C=O). Anal. calcd. for $C_{15}H_{28}N_2O_3 \cdot 0.2$ EtOAc: C, 62.81; H, 9.87; N, 9.27. Found: C, 62.76; H, 9.63; N, 9.27.

***N*-(*tert*-Butyloxycarbonyl)-*trans*-(1*S*,2*S*)-2-aminocyclopentanecarbonyl-tert-butylamide** [(+)-**8b**]. Compound (+)-**8b** (0.86 g, 74 %) was prepared from (+)-**13** (0.100 g, 0.41 mmol) according to the method for the preparation of (–)-**8b**. (+)-**8b**: $[\alpha]^{22}_D$ +9.8 (*c* 0.8, $CHCl_3$), mp 179-180 °C. Anal. calcd. for $C_{15}H_{28}N_2O_3 \cdot 0.3$ EtOAc: C, 62.57; H, 9.85; N, 9.08. Found: C, 62.23; H, 9.80; N, 9.20.

***N*-[1'-Phenyl-2'(*R*)-[(*tert*-Butyloxycarbonyl)amino]-3'(*R*)-hydroxybutane]-*trans*-(1*R*,2*R*)-2-aminocyclopentanecarbonyl-*tert*-butylamide (14a)**. A solution of (–)-**8b** (0.228 g, 0.802 mmol) in dichloromethane-trifluoroacetic acid (1:1, 5 mL) was stirred at room temperature for 1 h. After evaporation of the solvent *in vacuo* the crude amine was redissolved in 2-butanol (10 mL) and epoxide **4** (0.199 g, 0.802 mmol) was added. The mixture was neutralized with triethylamine to pH ~ 7-8 and then stirred at room temperature for 14 days. The solvent was evaporated and the residue was purified by silica gel chromatography (EtOAc-methanol-triethylamine, 80:20:1) to give **14a** (0.391 mg, 92 %) as a white solid. **14a**: $[\alpha]^{22}_D$ –14.5 (*c* 0.7, methanol), ^{1}H NMR (methanol-d_4, 250 MHz) δ 1.31 (9H, s, 3 CH_3), 1.33 (9H, s, 3 CH_3), 1.60-1.90 (4H, m, 2 CH_2), 2.07-2.26 (2H, m, CH_2), 2.68-2.99 (5H, m, CH and 2 CH_2), 3.69-3.96 (3H, m, 3 CH), 7.12-7.30 (5H, m, 5 Ar-H); ^{13}C NMR (methanol-d_4, 62.9 MHz) δ 24.7 (CH_2), 28.7, 28.9 (6 CH_3), 31.3, 32.3, 38.5 (3 CH_2), 50.5, 50.7, 52.2 (C, CH, CH_2), 55.9 (CH), 61.8 (CH), 69.0 (CH), 80.5 (C), 127.4, 129.4, 130.4, 139.5 (6 Ar-C), 158.4, 174.6 (2 C=O). Anal. calcd. for $C_{25}H_{41}N_3O_4 \cdot 1.2$ CF_3COOH: C, 56.31; H, 7.28; N, 7.19. Found: C, 56.33; H, 7.36; N, 7.06.

***N*-[1'-Phenyl-2'(*R*)-[(*tert*-Butyloxycarbonyl)amino]-3'(*R*)-hydroxybutane]-*trans*-(1*S*,2*S*)-2-aminocyclopentanecarbonyl-*tert*-butylamide (14b)**. Compound **14b** (0.090 g, 54 %) was prepared from (+)-**8b** (0.089 g, 0.313 mmol) according to the method for the preparation of **14a**. **14b**: $[\alpha]^{22}_D$ +4.4 (*c* 1.2, methanol), ^{1}H NMR (methanol-d_4, 250 MHz) δ 1.32 (9H, s, 3 CH_3), 1.35 (9H, s, 3 CH_3), 1.52-1.81 (4H, m, 2 CH_2), 1.98-2.19 (2H, m, CH_2), 2.51-2.62 (1H, m, CH), 2.71-2.95 (4H, m, 2 CH_2), 3.52-3.61 (1H, m, CH), 3.71-3.85 (2H, m, 2 CH), 7.12-7.31 (5H, m, 5 Ar-H); ^{13}C NMR (methanol-d_4, 62.9 MHz) δ 24.5 (CH_2), 28.7, 29.0 (6 CH_3), 31.6, 32.3, 38.7 (3 CH_2), 51.2, 51.9, 52.0 (C, CH, CH_2), 55.8 (CH), 62.7 (CH), 70.2 (CH), 80.3 (C), 127.4, 129.4, 130.4, 139.8 (6 Ar-C), 158.3, 175.7 (2 C=O). Anal. calcd. for $C_{25}H_{41}N_3O_4 \cdot 1.0$ CF_3COOH: C, 57.75; H, 7.53; N, 7.48. Found: C, 57.92; H, 7.63; N, 7.42.

***N*-[1'-Phenyl-2'(*R*)-[(*tert*-Butyloxycarbonyl)amino]-3'(*R*)-hydroxybutane]-*cis*-(1*R*,2*S*)-2-aminocyclopentanecarbonyl-*tert*-butylamide (14c).** Compound **14c** (0.348 g, 88 %) was prepared from (–)-**8a** (0.212 g, 0.745 mmol) according to the method for the preparation of **14a**. **14c**: $[\alpha]^{22}_D$ +37.2 (*c* 2.1, methanol), ^{1}H NMR (methanol-d_4, 250 MHz) δ 1.32 (9H, s, 3 CH_3), 1.39 (9H, s, 3 CH_3), 1.48-1.71 (2H, m, CH_2), 1.71-2.94 (4H, m, 2 CH_2), 2.58-2.93 (5H, m, CH and 2 CH_2), 3.09-3.20 (1H, m, CH), 3.63-3.80 (2H, m, 2 CH), 7.12-7.29 (5H, m, Ar-H); ^{13}C NMR (methanol-d_4, 62.9 MHz) δ 22.9 (CH_2), 28.7, 29.1 (6 CH_3), 29.4, 32.6, 39.1 (3 CH_2), 48.9, 51.8, 52.6 (C, CH, CH_2), 55.9 (CH), 63.5 (CH), 71.6 (CH), 80.1 (C), 127.2, 129.4, 130.4, 140.1 (6 Ar-C), 158.1, 175.9 (2 C=O). Anal. calcd. for $C_{25}H_{41}N_3O_4 \cdot 0.15\ CF_3COOH$: C, 65.39; H, 8.89; N, 9.04. Found: C, 65.45; H, 9.02; N, 8.94.

***N*-[1'-Phenyl-2'(*R*)-[(*tert*-Butyloxycarbonyl)amino]-3'(*R*)-hydroxybutane]-*cis*-(1*S*,2*R*)-2-aminocyclopentanecarbonyl-*tert*-butylamide (14d).** Compound **14d** (0.098 g, 95 %) was prepared from (+)-**8a** (0.055 g, 0.193 mmol) according to the method for the preparation of **14a**. **14d**: $[\alpha]^{22}_D$ –14.9 (*c* 1.0, methanol), ^{1}H NMR (methanol-d_4, 250 MHz) δ 1.32 (9H, s, 3 CH_3), 1.38 (9H, s, 3 CH_3), 1.55-1.95 (4H, m, 2 CH_2), 2.00-2.14 (2H, m, CH_2), 2.71-3.03 (5H, m, CH and 2 CH_2), 3.50-3.62 (1H, m, CH),3.71-3.90 (2H, m, 2 CH), 7.14-7.32 (5H, m, 5 Ar-H); ^{13}C NMR (methanol-d_4, 62.9 MHz) δ 23.2 (CH_2), 28.7, 28.9 (6 CH_3), 30.7, 31.2, 38.6 (3 CH_2), 46.3, 51.1, 52.2 (C, CH, CH_2), 56.1 (CH), 61.9 (CH), 69.5 (CH), 80.4 (C), 127.4, 129.4, 130.4, 139.7 (6 Ar-C), 158.3, 175.4 (2 C=O). Anal. calcd. for $C_{25}H_{41}N_3O_4 \cdot 0.14\ CF_3COOH$: C, 65.50; H, 8.92; N, 9.06. Found: C, 65.86; H, 9.24; N, 8.67.

***N*-[1'-Phenyl-2'(*R*)-[(*tert*-Butyloxycarbonyl)amino]-3'(*S*)-hydroxybutane]-*trans*-(1*R*,2*R*)-2-aminocyclopentanecarbonyl-*tert*-butylamide (15a).** Compound **15a** (0.053 g, 84 %) was prepared from (–)-**8b** (0.053 g, 0.186 mmol) according to the method for the preparation of **14a** using epoxide **5** instead of **4**. **15a**: $[\alpha]^{22}_D$ –25.3 (*c* 1.6, methanol), ^{1}H NMR (methanol-d_4, 250 MHz) δ 1.29 (9H, s, 3 CH_3), 1.35 (9H, s, 3 CH_3), 1.58-1.86 (4H, m, 2 CH_2), 2.00-2.21 (2H, m, CH_2), 2.53-2.75 (2H, m, CH_2), 2.76-2.92 (1H, m, CH), 2.98-3.21 (2H, m, CH_2), 3.60-3.81 (3H, m, 3 CH), 7.15-7.30 (5H, m, 5 Ar-H); ^{13}C NMR (methanol-d_4, 62.9 MHz) δ 24.5 (CH_2), 28.7, 28.9 (6 CH_3), 31.8, 32.1, 37.7 (3 CH_2), 51.3, 51.3, 52.0 (C, CH, CH_2), 56.8 (CH), 62.8 (CH), 71.8 (CH), 80.2 (C), 127.2, 129.2, 130.4, 139.7 (6 Ar-C), 156.1, 175.4 (2 C=O). Anal. calcd. for $C_{25}H_{41}N_3O_4 \cdot 0.5\ CF_3COOH \cdot 1.0$ EtOAc: C, 60.79; H, 8.42; N, 7.08. Found: C, 60.39; H, 8.59; N, 7.22.

***N*-[1'-Phenyl-2'(*R*)-[(*tert*-Butyloxycarbonyl)amino]-3'(*S*)-hydroxybutane]-*trans*-(1*S*,2*S*)-2-aminocyclopentanecarbonyl-*tert*-butylamide (15b).** Compound **15b** (0.042 g, 55 %) was prepared from (+)-**8b** (0.065 g, 0.286 mmol) according to the method for the preparation of **14a** using epoxide **5** instead of **4**. **15b**: $[\alpha]^{22}_D$ –17.6 (*c* 0.6, methanol), ^{1}H NMR (methanol-d_4, 250 MHz) δ 1.38 (9H, s, 3 CH_3), 1.45 (9H, s, 3 CH_3), 1.65-1.82 (4H, m, 2 CH_2), 1.94-2.13 (2H, m, CH_2), 2.43-2.76 (4H, m, 2 CH_2), 2.83-2.96 (1H, m, CH), 3.38-3.50 (1H, m, CH), 3.60-3.70 (2H, m, 2 CH), 7.13-7.30 (5H, m, 5 Ar-H); ^{13}C NMR (methanol-d_4, 62.9 MHz) δ 24.4 (CH_2), 28.7, 28.9 (6 CH_3), 31.4, 33.0, 37.9 (3 CH_2), 51.9, 52.7, 57.0 (C, CH, CH_2), 60.2 (CH), 63.5 (CH), 72.9 (CH), 80.1 (C), 127.2, 129.2, 130.5, 140.0 (6 Ar-C), 158.2, 176.3 (2 C=O). Anal. calcd. for $C_{25}H_{41}N_3O_4 \cdot 0.3\ CF_3COOH \cdot 1.5$ EtOAc: C, 61.81; H, 8.75; N, 6.84. Found: C, 61.87; H, 9.05; N, 7.22.

***N*-[1'-Phenyl-2'(*R*)-[(*tert*-Butyloxycarbonyl)amino]-3'(*S*)-hydroxybutane]-*cis*-(1*R*,2*S*)-2-aminocyclopentanecarbonyl-*tert*-butylamide (15c).** Compound **15c** (0.087 g, 90 %) was prepared from (−)-**8a** (0.081 g, 0.285 mmol) according to the method for the preparation of **14a** using epoxide **5** instead of **4**. **15c**: $[\alpha]^{22}_D$ −14.2 (*c* 1.1 , methanol), ^{1}H NMR (methanol-d_4, 250 MHz) δ 1.30 (9H, s, 3 CH_3), 1.36 (9H, s, 3 CH_3), 1.69-2.10 (6H, m, 3 CH_2), 2.51-2.67 (1H, m, CH), 2.76-2.98 (2H, m, CH_2), 3.08-3.21 (2H, m, CH_2), 3.40-3.52 (1H, m, CH), 3.62-3.72 (2H, m, 2 CH), 7.12-7.30 (5H, m, 5 Ar-H); ^{13}C NMR (methanol-d_4, 62.9 MHz) δ 22.9 (CH_2), 28.7, 28.9 (6 CH_3), 30.5, 30.9, 37.8 (3 CH_2), 47.3, 51.3, 52.1 (C, CH, CH_2), 57.2 (CH), 62.5 (CH), 72.0 (CH), 80.3 (C), 127.2, 129.2, 130.3, 139.9 (6 Ar-C), 158.4, 175.7 (2 C=O). Anal. calcd. for $C_{25}H_{41}N_3O_4 \cdot 0.3CF_3COOH \cdot 1.0$ EtOAc·1.0 MeOH: C, 61.06; H, 8.92; N, 6.98. Found: C, 61.09; H, 8.96; N, 6.95.

***N*-[1'-Phenyl-2'(*R*)-[(*tert*-Butyloxycarbonyl)amino]-3'(*S*)-hydroxybutane]-*cis*-(1*S*,2*R*)-2-aminocyclopentanecarbonyl-*tert*-butylamide (15d).** Compound **15d** (0.060 g, 53 %) was prepared from (+)-**8a** (0.094 g, 0.330 mmol) according to the method for the preparation of **14a** using epoxide **5** instead of **4**. **15d**: $[\alpha]^{22}_D$ +8.8 (*c* 1.5, methanol), ^{1}H NMR (methanol-d_4, 250 MHz) δ 1.29 (9H, s, 3 CH_3), 1.38 (9H, s, 3 CH_3), 1.78-2.10 (6H, m, 3 CH_2), 2.52-2.97 (3H, m, CH_2 and CH), 3.04-3.19 (2H, m, CH_2), 3.41-3.52 (1H, m, CH), 3.62-3.81 (2H, m, 2 CH), 7.12-7.28 (5H, m, 5 Ar-H); ^{13}C NMR (methanol-d_4, 62.9 MHz) δ 23.0 (CH_2), 28.6, 28.9 (6 CH_3), 30.4, 31.3, 37.6 (3 CH_2), 47.1, 51.7, 52.2 (C, CH, CH_2), 56.9 (CH), 63.0 (CH), 72.1 (CH), 80.1 (C), 127.1, 129.2, 130.3, 139.8 (6 Ar-C), 158.1, 175.5 (2 C=O). Anal. calcd. for $C_{25}H_{41}N_3O_4 \cdot 0.7$ $CF_3COOH \cdot 1.0$ EtOAc·1.7 MeOH: C, 57.54; H, 8.49; N, 6.26. Found: C, 57.22; H, 8.59; N, 6.20.

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