Synthesis of New Seven-Membered Ring Cyclic Dipeptides From Functionalized β-Amino Acids

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A short synthesis of new, functionalized seven-membered ring cyclic dipeptides is described. After the coupling of *N*-protected β-amino acids to *N*-substituted α-amino *tert*-butyl esters, the protective groups of the terminal functions were removed and the cyclization took place diastereoselectively in the presence of the coupling agent BOP. Amide substitution was found to be effective in promoting the cyclization of linear dipeptides.

Introduction

Numerous cyclopeptides of natural origin containing non-proteinogenic β-amino acids display important biological activities.[1] Due to their restricted conformational flexibility, cyclic peptides often possess an improved resistance to enzymatic degradation and a better receptor site selectivity.[2] Such properties are valuable in the design and development of therapeutic molecules. In recent years interest has been focused increasingly on cyclic dipeptide derivatives, which are designed to substitute a dipeptide unit within a peptide chain, thus inducing certain conformational restrictions.[3] Several cyclic dipeptide templates have been prepared with markedly different ring sizes.[4] However, there are few literature reports concerning the synthesis of dipeptides containing the 1,4-diazepine-2,5-dione ring system.[5] This family of derivatives offers very useful structures for the discovery of new biologically active compounds. In the synthesis of such molecules the cyclization step is usually the most difficult. Peptide bonds possess strong π character and preferentially adopt a transoid conformation.[6] Short linear precursors with the terminal functions in remote positions do not easily undergo intramolecular coupling.

The aim of the present study was to develop an efficient and general approach to cyclic dipeptides from functionalized β-amino acids, which can be easily incorporated into peptide sequences. As shown in Scheme 1, whichever cyclization site was chosen the synthesis of these compounds required the *N*-substitution of the peptide bond in order to constrain the amide to the cisoid conformation and thus allow the dipeptides to cyclize easily.[7] Recent works also recognize this substitution effect in performing small-peptide cyclizations.[8]

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Results and Discussion

Coupling Reaction

Following the retrosynthetic approach depicted in Scheme 1, we initially prepared the functionalized β-amino acid **1** with methoxy carbonyl groups in the 2 and 3 positions (Scheme 2). Compound **1** was obtained in 72% yield by alkylation of methyl *N*-Boc bromoglycinate with the anion derived from benzyl methyl malonate, followed by hydrogenolysis.[7] As the projected dipeptides were to be functionalized, an orthogonal protecting group strategy was employed to allow the selective deprotection of the terminal functions. *N*-Substitution was directly introduced at the amide bond by using *N*-substituted α- amino esters. The coupling reaction were performed between β-amino acid **1** and the *N*-benzylated α-amino-*tert*-butyl esters **2a−c**, in the presence of BOP reagent (Scheme 2).

The yields at this coupling step depended on the steric hindrance imposed by the amino components. Attempts to couple to Bn−Phe−O*t*Bu were unsuccesful. We therefore chose to introduce two-electron donor methoxy groups on the benzyl substituent to increase the nucleophicity of the amino group of **2c** and to enhance the coupling efficiency.[9] The linear dipeptides **3a−c** were purified by column chromatography and isolated in 41−81% yield. HPLC analysis of compound **3a** showed the presence of two separable diastereoisomers in a 1:1 ratio. The dipeptides **3b−c** were obtained as a mixture of four diastereoisomers. It is worth noting here that the *N*-substituted amide bond is necessary not only for promoting the cyclization step but also to prevent the competitive formation of an intramolecular cyclization at the pyrrolidine.[10]

Once the dipeptides had been formed both the Boc and *tert*-butyl protecting groups were removed with 30% TFA at room temperature. The trifluoroacetate salts **4a−c** were obtained in quantitative yields (Scheme 2). Nevertheless the

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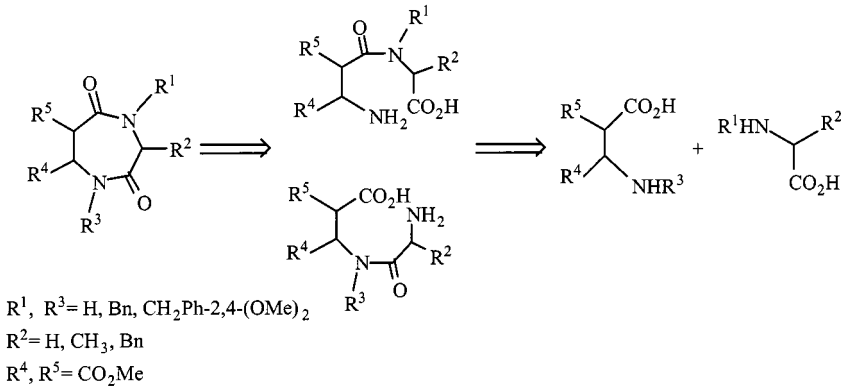
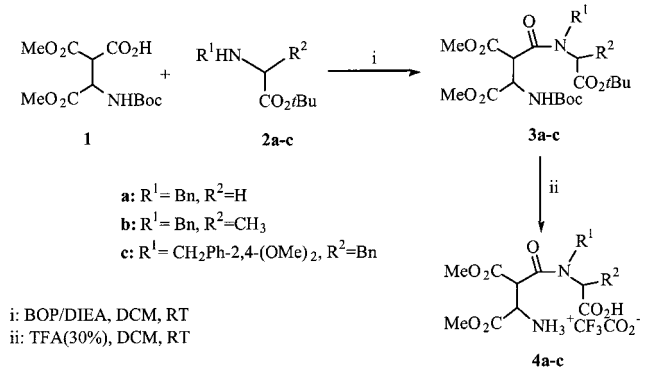


Scheme 1. Retrosynthetic scheme



Scheme 2. Coupling reaction between β-amino acid **1** and α-amino esters **2**

functionalized dipeptides **4a−c** were stable only as salts. They decomposed in basic conditions at room temperature as much as the Asa itself does.[11]

Cyclization Reaction

The linear precursors were cyclized upon mild activation of the carboxyl group in the presence of BOP/DIEA.[12] Cyclization was accomplished at −30°C in chloroform. This reaction was carried out initially on an equimolar mixture of diastereoisomers **4a**, and on the *threo* and *erythro* diastereoisomers **4a**$_1$/**a**$_2$ separately (Scheme 3). In all cases, only the *trans* stereoisomer **5a** was isolated as a racemic mixture in 68% yield. The analytical and spectral data obtained confirmed the proposed structure. The relative stereochemistry of the methoxycarbonyl groups at the C-5 and C-6 carbons was proven to be *trans* by X-ray crystallography.[7] Formation of the *cis* stereoisomer has never been observed. This *trans* stereochemistry implies epimerization of the C-6 carbon, this being further confirmed by D_2O exchange (Scheme 4). The doublet due to proton H-6 in compound **6a** was not observed in the ^{1}H NMR spectra. Satisfactory results were also obtained from the cyclization of dipeptides **4b−c** under the same conditions (Scheme 5).

A mixture of two *trans* isomers of the four possible stereoisomeric cyclic dipeptides was isolated and separated by column chromatography. Compounds **5b**$_1$−5c$_1$ were characterized by HPLC analysis and standard spectroscopic techniques. The structure of **5b**$_1$ was established by an X-ray crystallographic analysis (Figure 1).

The use of benzyl group derivatives for backbone amide protection and the BOP reagent allows the efficient ring closure to seven-membered cyclic dipeptides. The stereochemistry of the activated amino acid residue was not discussed.

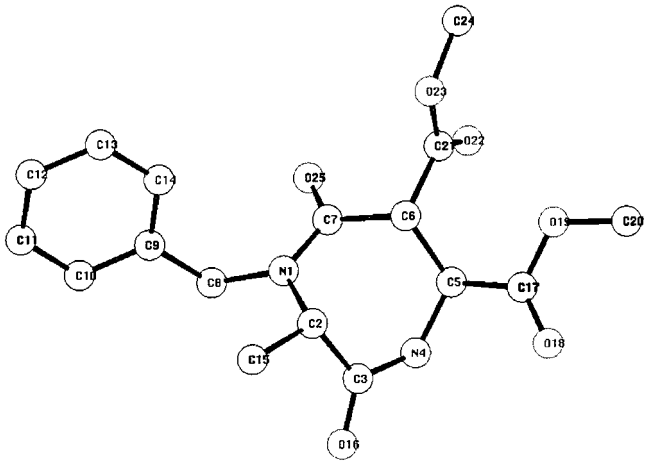
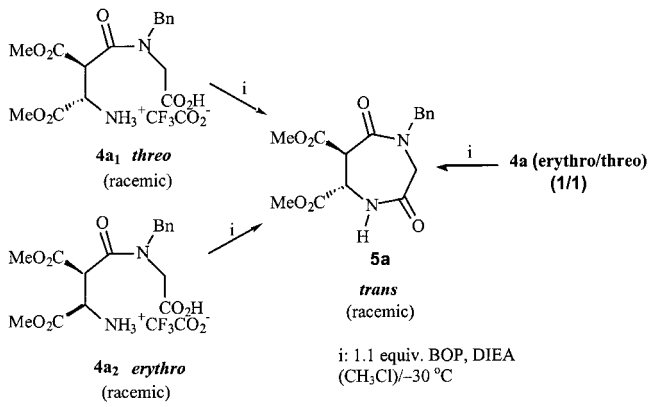


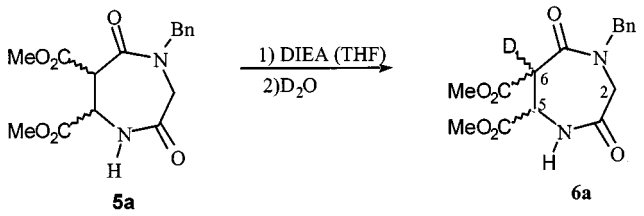
Figure 1. ORTEP projection of the X-ray structure of compound **5b**$_1$

Conclusions

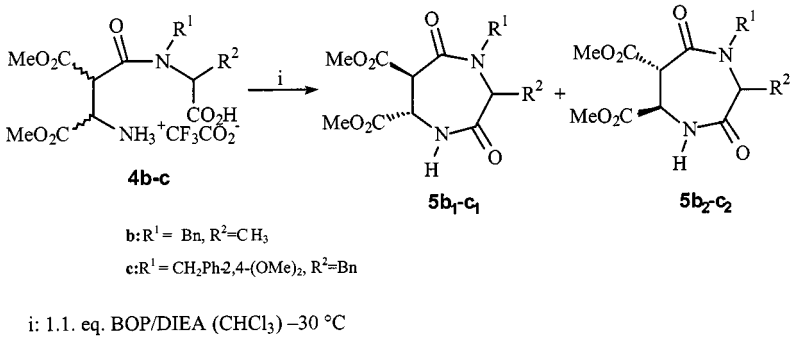
The present study has established an efficient synthesis of functionalized seven-membered ring cyclic dipeptides from suitably protected β-carboxyaspartic acid and *N*-substituted α-amino acids residues. Of particular interest in this synthesis is the stereocontrolled arrangement of functional groups at 5 and 6 positions of the cyclic system. The general nature of this approach will permit a large number of cyclic dipeptides to be prepared with various functional groups at the C-3, C-5 and C-6 carbons of diazepine. Ongoing efforts to apply this strategy to the preparation of multifunctional compounds with controlled stereochemistry and their incorporation into peptides are presently in progress.



Scheme 3. Cyclization reaction



Scheme 4. D_2O exchange



Scheme 5. Diastereoselective cyclisation of linear dipeptides **4**

Experimental Section

General: Reagents and solvents were purified in the usual way. Thin layer chromatography was performed on Merck precoated silica gel 60 F_{254} plates and spots were visualized by ultraviolet light or by iodine vapour. Column chromatography was performed on silica gel Merck 60. The purity of all products was checked by reverse phase HPLC on C-18 Nucleosyl. Spectra were recorded with the following instruments: IR spectra: Pekin-Elmer FT-IR Paragon 1000; ^{1}H NMR spectra: Brücker AC-250; ^{13}C NMR spectra: Brücker WP-20; Mass spectra: Jeol JMS DX 300. Uncorrected melting points were obtained on a Büchi 510 apparatus. Routine analyses agreed with calculated values within ± 0.3%.

Abbreviations: Asa: β−carboxyaspartic acid. Boc: *tert*-butoxycarbonyl. BOP: benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate. Dmb: 2,4-dimethoxybenzyl, DCM: dichloromethane. DIEA: *N,N*-diisopropylethylamine. TFA: trifluoroacetic acid.

Coupling Reaction. − General Procedure: To a stirred and cooled solution of **1** (4 mmol) in DCM (5 mL/mmol), were added the *N*-substituted α-amino esters (prepared by the *in situ* reduction of the Schiff's bases of the appropriate aldehydes and α-amino *tert*-butyl esters with $NaBH_4$ according to ref.[13]), **2a−c** (4 mmol), BOP reagent (4.4 mmol) and DIEA (8 mmol). The mixture was stirred for 16 h at room temperature. The solvent was concentrated in vacuo and ethyl acetate (20 mL) was added. The resulting solution was washed sequentially with 5% $KHSO_4$, water, 5% $NaHCO_3$ and saturated brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was then purified by chromatography on silica gel (hexane/EtOAc 9:1).

Boc−Asa[α,β-(OMe)]−(Bn)−Gly−O*tBu* (3a): Yield 1.65 g, 81% (oil). − R_f = 0.65 (EtOAc/hexane 3:7). − FAB$^+$/GT: *m/z* = 509 [M + H$^+$].

This compound was obtained as a mixture of two diastereoisomers (1:1) wich were separated by semi-preparative HPLC using Waters C_{18} DeltaPack 10 × 40 column. A gradient was formed from 10% H_2O to 100% CH_3CN over 40 min with a flow of 50 mL/min. These diastereoisomers are described as below:

3a$_1$: HPLC (CH_3CN/H_2O 10:90): t_R = 28.07 min. − ^{1}H NMR ($CDCl_3$): δ = 1.41 (s, 9 H, *t*Bu), 1.45 (s, 9 H, *t*Bu), 3.75 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 3.79 (s, 2 H, CH_2), 4.20 (d, 1 H, *J* = 4.5 Hz, H-5), 4.42−4.59 (m, 2 H, CH_2Ph), 5.20 (dd, 1 H, H-6, J_1 = 4.6 Hz, J_2 = 8.0 Hz), 5.55 (d, 1 H, *J* = 8.1 Hz, NH), 7.22−7.39 (m, 5 H, H_{arom}).

3a$_2$: HPLC (CH_3CN/H_2O 10:90): t_R = 28.71 min. − ^{1}H NMR ($CDCl_3$): δ = 1.41 (s, 9 H, *t*Bu),1.43 (s, 9 H, *t*Bu), 3.70 (s, 3 H, OMe), 3.74 (s, 2 H, CH_2), 3.76 (s, 3 H, OMe), 4.37 (d, 1 H, *J* = 5.0 Hz, H-5), 4.54−4.74 (m, 2 H, CH_2Ph), 5.10 (dd, 1 H, J_1 = 4.4 Hz, J_2 = 10.0 Hz, H-6), 6.24 (d, 1 H, *J* = 10 Hz, NH), 7.10−7.40 (m, 5 H, H_{arom}).

Boc−Asa[α,β-(OMe)$_2$]−(Bn)−Ala−O*t*Bu (3b): Yield 1.33 g, 64% (oil). − R_f = 0.32 (EtOAc/hexane: 3:7). − FAB$^+$/NBA: *m/z* = 523 [M + H$^+$]. − ^{1}H NMR ($CDCl_3$) (one identifiable diastereoisomer): δ = 1.35 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.40 (s, 9 H, *t*Bu), 1.41 (s, 9 H, *t*Bu), 3.70 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.82 (q, *J* = 6.9 Hz, 1 H, H-2), 4.30 (d, *J* = 17.0 Hz, 1 H, CH_2Ph), 4.38 (d, *J* = 4.1 Hz, 1 H, H-5), 4.55 (d, *J* = 17.0 Hz, 1 H, CH_2Ph), 4.97 (dd, J_1 = 4.1 Hz, J_2 = 10.3 Hz, 1 H, H-6), 6.25 (d, *J* = 10.3 Hz, 1 H, NH), 7.20−7.41 (m, 5 H, H_{arom}).

Boc−Asa[α,β-(OMe)$_2$]−(Dmb)−Phe−O*t*Bu (3c): Yield 1.08 g, 41% (oil). − R_f = 0.24 (EtOAc/hexane 1:4). − FAB$^+$/NBA: *m/z* = 659 [M + H$^+$]. − ^{1}H NMR spectroscopy at 250 MHz did not allow an unambiguous identification of the signals of compound **3c**.

Cleavage of the Boc and *t*Bu Groups: The protected dipeptides **3a−c** (2 mmol), were treated with trifluoroacetic acid (30%) in DCM (10 mL/mmol) at room temperature for 4−24 h. The mixture was concentrated in vacuo and the corresponding trifluoroacetate salts **4a−c** were dried in high vacuum to constant weight.

H−Asa[α,β-(OMe)$_2$]−(Bn)−Gly−OH.CF$_3$CO$_2$H (4a$_1$/a$_2$): Yield 0.91 g, 98% (oil). − FAB$^+$/NBA: *m/z* = 353 [M + H$^+$]. − ^{1}H NMR(CDCl$_3$): δ = 3.60 (s, 2 H, CH$_2$), 3.73 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 4.89−4.32 (m, 4 H, H-5, CH$_2$Ph, H-6), 7.20−7.42 (m, 5 H, H$_{arom}$).

H−Asa[α,β-(OMe)$_2$]−(Bn)−Ala−OH·CF$_3$CO$_2$H (4b): Yield 0.93 g, 97% (oil). − FAB$^+$/NBA: *m/z* = 367 [M + H$^+$]. − ^{1}H NMR (CDCl$_3$) (one identifiable diastereoisomer): δ = 1.38 (d, *J* = 7 Hz, 3 H, CH$_3$), 3.71 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.79 (q, *J* = 7.1 Hz, 1 H, CH), 4.23−4.56 (m, 3 H, CH + CH$_2$Ph), 4.90−5.01 (m, 1 H, CH), 7.19−7.43 (m, 5 H, H$_{arom}$), 10.11 (br, 1 H, OH).

H−Asa[α,β-(OMe)$_2$]−(Dmb)−Phe−OH·CF$_3$CO$_2$H (4c): Yield 1.21 g, 98% (oil). − FAB$^+$/NBA: *m/z* = 503 [M + H$^+$]. − ^{1}H NMR spectroscopy at 250 MHz did not allow an unambiguous identification of the signals of compound **4c**. However no signals corresponding to the *t*Bu group were observed in CDCl$_3$.

Cyclization Reaction. − General Procedure: A solution of a linear precursor **4a−c** in CHCl$_3$ (1.3 mmole/10 mL) was added over 5 h from a syringe pump to a stirred and cooled solution (−30°C) of BOP reagent (1.43 mmol) and DIEA (3.9 mmol). The final concentration was 10^{-2}M. Stirring was continued for 16 h at −30°C and then the reaction was left to warm slowly to −10°C. The solvent was then removed under reduced pressure and the residue was dissolved in ethyl acetate (10 mL) and washed with 5% KHSO$_4$, water, 5% NaHCO$_3$ and saturated brine. The organic phase was dried over anhydrous MgSO$_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc 1:1).

Diester 5a: Yield 0.293 g, 68% (white solid). − R_f = 0.42 (hexane/EtOAc 1:4). − HPLC (gradient from CH$_3$CN/H$_2$O 50:50) t_R = 5.8 min. − M.p. = 138−140°C (MeOH). − FAB$^+$/NBA: *m/z* = 335 [M + H$^+$]. − IR (KBr): ν$_{NH}$ = 3350 cm^{-1}, ν$_{CO}$ = 1738, 1667, 1650 cm^{-1}. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.53 (d, *J* = 16.5 Hz, 1 H, H-2), 3.68 (s, 3 H, OCH$_3$), 3.75 (s, 3 H, OCH$_3$), 4.45 (d, *J* = 15.1 Hz 1 H, CH$_2$Ph), 4.55 (d, *J* = 16.4 Hz, 1 H, H-2), 4.56 (dd, *J* = 9.1 Hz, *J* = 4.4 Hz, 1 H, H-5), 4.64 (d, *J* = 15.1 Hz, 1 H, CH$_2$Ph), 4.81 (d, *J* = 9.2 Hz, 1 H, H-6), 7.21−7.39 (m, 5 H, H$_{arom}$), 7.90 (d, *J* = 4.4 Hz, 1 H, NH). − ^{13}C NMR (CD$_3$COCD$_3$): δ = 51.42 (CH$_2$Ph), 52.39 (C-2), 52.98 (C-6), 53.07 (C-5), 53.37 (OCH$_3$), 54.73 (OCH$_3$), 128.39 (CH−Ar), 128.91 (CH−Ar), 129.43 (CH−Ar), 137.71 (C−Ar), 167.16 (C=O), 169.13 (C=O), 170.42 (C=O), 171.50 (C=O). − C$_{16}$H$_{18}$N$_2$O$_6$ (334.3): C 57.48, H 5.42, N 8.37; found C 57.57, H 5.61, N 8.24.

D$_2$O Exchange: To a solution of compound **5a** (42 mg, 0.12 mmol) in THF (3 mL) was added DIEA (44 μL, 2 equiv). The reaction mixture was stirred for 1 hour. Then, D$_2$O (0.5 mL) was added. After 30 minutes stirring the solvent was concentrated in vacuo and the residue dissolved in ethyl acetate. The organic layer was washed with a saturated ammonium solution, dried over MgSO$_4$ and the solvent was removed under vaccuo.

Diester 6a: Yield 98%. − ^{1}H NMR([D$_6$]DMSO): δ = 3.65 (d, *J* = 15.0 Hz, 1 H, H-2), 3.72 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 4.49 (d, *J* = 15.2 Hz, 1 H, CH$_2$Ph), 4.59 (d, *J* = 14.9 Hz, 1 H, H-2), 4.58 (d, *J* = 10.0 Hz, 1 H, H-5), 4.70 (d, *J* = 15.0 Hz, 1 H, CH$_2$Ph), 7.20−7.51 (m, 5 H, H$_{arom}$), 7.91 (br, 1 H, NH).

Diester 5b$_1$: This compound was obtained in 41% yield (0.185 g) as a mixture of two diastereoisomers (1:1) **5b$_1$**/b$_2$. Only **5b$_1$** was isolated in pure form after column chromatography (EtOAc/hexane 1:1). − R_f = 0.67 (EtOAc/hexane 4:1). − HPLC (gradient from CH$_3$CN/H$_2$O 40:60) t_R = 8.68 min. − White solid m.p. = 180−182°C (MeOH). − FAB$^+$/NBA: *m/z* = 349 [M + H$^+$]. − IR(KBr): ν$_{NH}$ = 3333 cm^{-1}, ν$_{CO}$ = 1743, 1679, 1660 cm^{-1}. − ^{1}H NMR ([D$_6$]DMSO): δ = 1.18 (d, *J* = 6.6 Hz, 3 H, CH$_3$), 3.70 (s, 3 H, OMe), 3.78 (s, 3 H, OMe), 4.32 (d, *J* = 16.1 Hz, 1 H, CH$_2$Ph), 4.61 (d, *J* = 15.9 Hz, 1 H, CH$_2$Ph), 4.63 (dd, *J*$_1$ = 8.4 Hz, *J*$_2$ = 5.8 Hz, 1 H, H-5), 5.0 (d, *J* = 8.5 Hz, 1 H, H-6), 4.75 (q, *J* = 6.7 Hz, 1 H, H-2), 7.15−7.34 (m, 5 H, H$_{arom}$), 7.80 (d, *J* = 5.8 Hz, 1 H, NH). − ^{13}C NMR (CD$_3$COCD$_3$): δ = 12.94 (CH$_3$), 45.44 (CH$_2$Ph), 53.07 (CH), 53.40 (CH), 53.52 (CH), 53.75 (OCH$_3$), 53.80 (OCH$_3$), 127.69 (CH−Ar), 127.88 (CH−Ar), 129.15 (CH−Ar), 139.67 (C−Ar), 168.61 (C=O), 169.84 (C=O), 172.30 (C=O), 173.40 (C=O). − C$_{17}$H$_{20}$N$_2$O$_6$ (348.4): C 58.61, H 5.78, N 8.04; found: C 58.60, H 5.94, N 8.04.

X-ray Crystal structure of 5b$_1$

Crystal data: C$_{17}$H$_{20}$N$_2$O$_6$, M_w = 348.3, orthorhombic, space group *P*bca, *Z* = 8, *a* = 8.907(3), *b* = 34.132 (10), *c* = 11.141(3) Å, V = 3387(2)Å^3, d$_{calcd}$ = 1.37 g·cm^{-3}, λ(Cu*K*$_α$) = 1.5418 Å, μ = 0.88 mm^{-1}. Intensity data were measured on a Enraf−Nonius CAD-4 diffractometer using graphite-monochromated Cu*K*$_α$ radiation and the (θ − 2θ) scan technique up to θ = 68°. 6138 collected reflexions, 3048 unique (R_{int} = 0.04) of which 2163 were considered as observed having $I \geq 2\,\sigma(I)$. Hydrogen atoms are in theoretical positions. Refinement (using *SHELXS*86, *SHELX*93) minimizing the function $\Sigma w(F_o^2 - |F_c|^2)^2$, R = 0.041 and wR_2 = 0.119 goodness of fit 1.03. The residual electron density in the final difference map was located between −0.20 and 0.25e·Å^3. Two centrosymmetric molecules form a dimer linked by two hydrogen bonds N4−H···O11(COOMe at C5) [2.963(2)Å].

Crystallographic data (excluding structure factors) for the structure included in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-118167. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Diester 5c: The cyclisation of **4c** afforded **5c$_1$**/c$_2$ (0.335 g) in 54% yield. Diastereoisomer **5c$_1$** was isolated in pure form after chromatography on a silica gel column (EtOAc/hexane 3:2). − R_f = 0.36 (EtOAc/hexane 3:2). − HPLC (gradient from CH$_3$CN/H$_2$O 1:1), 50% H$_2$O to 100% CH$_3$CN over 40 min, t_R = 10.21 min. − White solid m.p. = 196−197°C (CHCl$_3$). − FAB$^+$/NBA: *m/z* = 485 [M + H$^+$]. − IR(KBr): ν$_{NH}$ = 3341 cm^{-1}, ν$_{CO}$ = 1740, 1666, 1651 cm^{-1}. − ^{1}H NMR(CDCl$_3$): δ = 3.17 (dd, *J*$_1$ = 13.8 Hz, *J*$_2$ = 9.5 Hz, 1 H, CH$_2$Ph), 3.37 (dd, *J*$_1$ = 13.8 Hz, *J*$_2$ = 6.0 Hz, 1 H, CH$_2$Ph), 3.60 (d, *J* = 14.0 Hz, 1 H, CH$_2$Ar), 3.76 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 4.43 (d, *J* = 10.7 Hz, 1 H, H-6), 4.60−4.66 (m, 3 H, H-5 + H-2 + CH$_2$Ar), 5.98 (br, 1 H, NH), 6.34−6.37 (m, 2 H, H$_{arom}$), 6.96 (d, *J* = 7.9 Hz, 1 H, H$_{arom}$), 7.20−7.35 (m, 5 H, H$_{arom}$). − ^{13}C NMR (CD$_3$COCD$_3$): δ = 38.04 (CH$_2$), 46.87 (CH$_2$), 53.03 (C-5), 53.50 (C-6), 54.05 (OCH$_3$), 55.60 (OCH$_3$), 55.73 (OCH$_3$), 55.82 (OCH$_3$), 64.49(C-2), 99.02 (C−Ar), 105.51 (C−Ar), 117.82 (C−Ar), 127.82 (CH−Ar), 129.53 (CH−Ar), 130.17 (CH−Ar), 131.51 (CH−Ar), 138.20 (C−Ar), 159.35 (C−Ar), 161.69 (C−Ar), 166.76 (C=O), 168.89 (C=O), 170.85 (C=O), 171.10 (C=O). − C$_{25}$H$_{28}$N$_2$O$_8$ (484.5): C 61.97, H 5.78, N 5.82; found C 61.93, H 5.81, N 5.71.

[1] [1a] H. Sone, T. Nemoto, H. Ishiwata, M. Ojika, K. Yamada, *Tetrahedron Lett.* **1993**, 34, 8449−8452. − [1b] R. L. Valentekovich, S. L. Schreiber, *J. Am. Chem. Soc*. **1995**, 117, 9069−9072. − [1c] N. Sin, J. Kallmerten, *Tetrahedron Lett.* **1996**, 37, 5645−5648.

[2] [2a] D. D. Smith, J. Slaninova, V. J. Hruby, *J. Med. Chem.* **1992**, 35, 1558−1563. − [2b] R. S. Mc Dowell, T. R. Gadek, *J. Am. Chem. Soc.* **1992**, 114, 9245−9253.

[3] R. M. J. Liskamp, *Recl. Trav. Chim. Pays-Bas* **1994**, 113, 1−19.

[4] [4a] G. Asche, H. Kunz, H. Nar, H. Köppen, H. Briem, K. H. Pook, P. W. Schller, N. Chung, C. Lemieux, F. Esser, *J. Peptide Res.* **1998**, 51, 323−336. − [4b] J. A. Robl, M. P. Cimarusti, L. M. Simpks, B. Brown, D. E. Ryono, J. E. Bird, M. M. Asaad, T. R. Schaeffer, N. C. Trippodo, *J. Med. Chem.* **1996**, 39, 494−502. − [4c] F. Corelli, A. Crescenza, D. Dei, M. Taddei, M. Botta, *Tetrahedron: Asymmetry* **1994**, 5, 1469−1472. − [4d] M. Botta, A. Crescenza, W. Magara, F. Corelli, *Tetrahedron Lett.* **1997**, 38, 2775−2778.

[5] [5a] V. Krchnak, A. S. Weichesel, *Tetrahedron Lett.* **1997**, 38, 7299−7302. − [5b] T. P. Curran, P. M. Mc Enaney, *Tetrahedron Lett.* **1995**, 36, 191−194. − [5c] . Nefzi, J. M. Ostresh, R. A. Houghten, *Tetrahedron Lett.* **1997**, 38, 4943−4946.

[6] B. Calas, R. Michelot, J. P. Leacer, A. Cave, J. Parello, P. Potier, *Int. J. Pept. Protein Res.* **1987**, 29, 170−183.

[7] O. El Mahdi, J.-P. Lavergne, P. Viallefont, J. Martinez, C. Riche, *Synth. Commun*. **1997**, 27, 3539−3545.

[8] [8a] F. Cavelier-Frontin, S Achmad, J Verducci, R. Jacquier, G. Pepe, *J. Mol. Struct. (Theochem)*. **1993**, 286, 125−130. − [8b] M. Rothe, R. H. Mattern, K. Fahrenscon-Blum, T. Ruckle, *Peptides*, *Proc. 23rd Europ. Peptide Symp.* **1994**, 171−172. − [8c] A. Ehrlich, H.-U. Heyne, R. Winter, M. Beyermann, H. Haber, L. A. Carpino, M.Bienert, *J. Org. Chem.* **1996**, 61, 8831−8838.

[9] M. Narita, K. Ishikawa, J. Y. Chen, Y. Kim, *Int. J. Peptide Protein Res.* **1984**, 24, 580−587.

[10] [10a] M. Bodansky, J. Martinez, *The Peptides*, Academic press, **1983**, 5, 143−148. − [10b] S. Zimmer, E. Hoffmann, G. Gump, H. Kessler, *Interlaken 22*nd Europ. Pept. Symp. **1992**.

[11] R. M. Williams, P. J. Sinclair, W. Zhai, *J. Am. Chem. Soc.* **1988**, 110, 482−483.

[12] P. Jouin, J. Poncet, M. N. Dufour, A. Pantolini, B. Castro, *J. Org. Chem.* **1989**, 54, 617−627.

[13] F. Weygand, W. Steglich, J. Bjarnarsson, R. Akhtar, N. Chytill, *Chem. Ber.* **1968**, 101, 3623−3641.

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