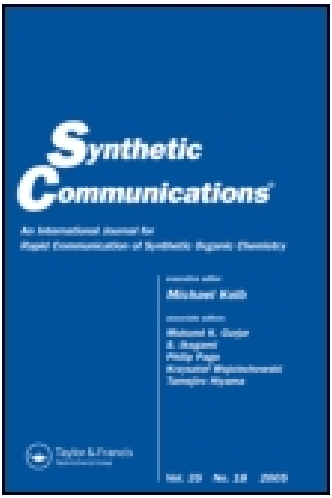

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2,5-IMIDAZOLIDINEDIONE FORMATION FROM SEVEN MEMBERED CYCLODIPEPTIDE REARRANGEMENT

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2,5-IMIDAZOLIDINEDIONE FORMATION FROM SEVEN MEMBERED CYCLODIPEPTIDE REARRANGEMENT

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ABSTRACT

Cyclization of the linear peptide **5** prepared by coupling a suitably β-amino acid **1** with N-protected L-Ala yielded 2,5-imidazolidinedione **6**.

Cyclopeptides constitute an important class of compounds in view of their wide spectrum of biological activity.[1] Several cyclic dipeptides of different sizes including diketopiperazines have been prepared.[2]

The synthesis of seven-membered cyclopeptides of type **A** was envisioned by two ways from the linear precursors **B** (Scheme 1). We have previously described the results using the first strategy (pathway **a**).[3] The cyclic diazepinedione, presenting two carbomethoxy groups in position trans, was obtained in good yields but without control of chirality at C-2 carbon.

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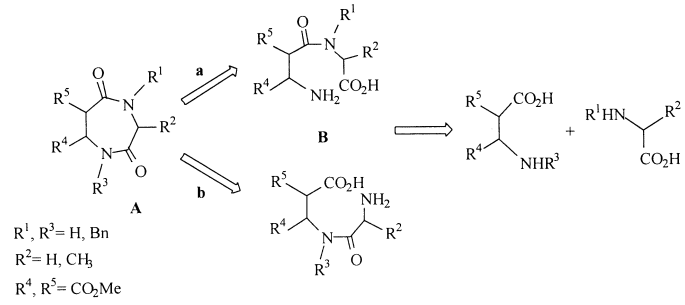


Scheme 1.

We report here the synthesis and the cyclization of peptide **5** (type **B**), following the second strategy (pathway **b**) which includes activation of the C-terminal of the β-amino acid. This compound was prepared in three steps (Scheme 2) from the β-amino acid **1** and diBoc-L-Ala.[4] Compound **1** was obtained in 65% yield through alkylation of N-benzyloxycarbonyl-2-chloroglycine methyl ester[5] by the anion derived from t-butyl methylmalonate followed by hydrogenolysis of the benzyloxycarbonyl groups.

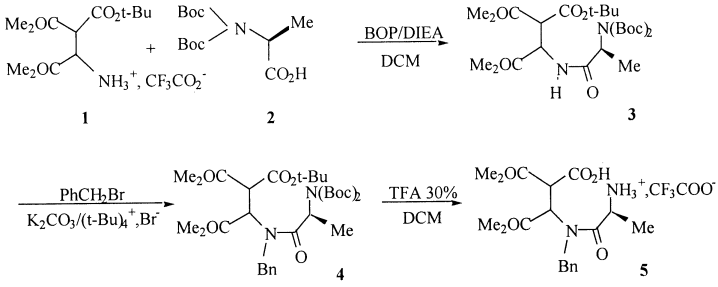
Coupling of the two amino acids using BOP/DIEA in dichloromethane,[6] afforded peptide **3** in 70% yield. In the following step the amide bond was benzylated with benzyl bromide using phase transfer catalysis. It was shown that alkylation of the amide nitrogen was essential to allow cyclization.[7] Compound **4** was deprotected by 30% TFA to afford the linear peptide **5** (Scheme 2). Cyclization of this peptide was achieved using the method previously described[3] in the presence of BOP/DIEA in DMF. The isolated compound (in 50% yield) was not the expected diazepinedione but the imidazolidinedione **6** (mixture of four diastereomers: **$6a_1$**/**$6a_2$**, **$6b_1$**/**$6b_2$**), (Scheme 3).

The structure of compound **6** was established from the spectral data and from X-ray crystallographic analysis (Figure 1). Formation of **6** can be explained by a transannular reaction of the initially formed, but not isolated, seven-membered cyclodipeptide, followed by migration of the benzyl group like in the Stevens rearrangement (Scheme 3).

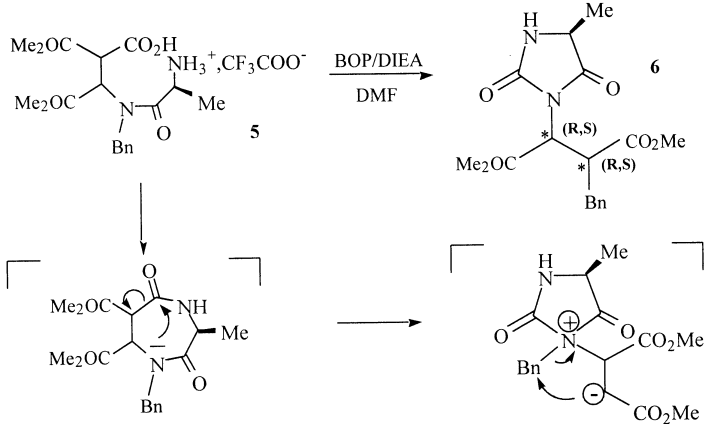
EXPERIMENTAL

General

Reagents and solvents were purified in the usual way. Thin layer chromatography was performed on Merck precoated silica gel $60F_{254}$



Scheme 2.



Scheme 3.

plates and spots were visualized by ultraviolet light or by iodine vapour. Column chromatography was performed on silica gel Merck 60. Spectra were recorded with the following instruments: IR spectra: Perkin-Elmer FT-IR Parangon 1000, ^{1}H NMR spectra: Brücker AC-250, ^{13}C NMR spectra: Brücker WP-200, Mass spectra: Jeol JMS DX 300. Melting points are reported uncorrected and were obtained on a Büchi 510 apparatus. Routine analyse agreed with calculated values within +/− 0.3%.

Synthesis of the β-Amino Ester 1

NaH (0.19 g, 8 mmoles, 1.1 equiv.) was added to a stirred solution of t-butyl methylmalonate (1.39 g, 8 mmoles, 1.1 equiv.) in dry THF (20 ml), at −10°C. The mixture was stirred at −10°C (15 mn) and then a solution of

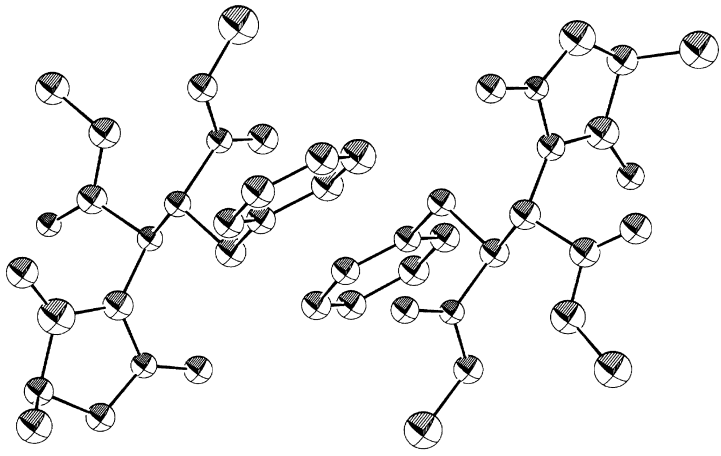


Figure 1. X-Ray structure of $6a_1$ (S,S,S,), $6a_2$ (R,R,S).

N-benzyloxycarbonyl-2-chloroglycine methyl ester (1.85 g, 7,2 mmoles, 1 equiv.) in THF (3 ml) was added using a syringe at −78°C. After the mixture had been stirred at −78°C for 2 h, it was washed with a saturated solution of NH_4Cl and the aqueous phase was then extracted with ethyl acetate (3 × 20 ml). The organic layer was dried ($MgSO_4$) and then concentrated under reduced pressure and purified by chromatography on silica gel (EtOAc/hexane: 1/9). Yield: 1.66 g (69%), colourless oil. Rf = 0.70 (hexane/EtOAc: 7/3).

^{1}H-NMR ($CDCl_3$), δ ppm: 7.29 (s, 5H, Ar), 5.94 (d, 1H, NH, J = 9.5 Hz), 5.11 (s, 2H, CH_2Ph), 5.02 (dd, 1H, CHα, J = 9.5 Hz, J = 4.2 Hz), 4.07 (d, 1H, CHβ, J = 4.2 Hz), 3.73 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 1.43 (s, 9H, t-Bu). $[M+H^+] = 396$ (FAB^+/GT). IR (NaCl, film): $\nu NH = 3390\ cm^{-1}$, $\nu CO = 1750, 1728, 1716, 1688\ cm^{-1}$.

Hydrogenolysis

20% palladium hydroxyde (0.05 g) was added to a solution of the protected β-aminoester (1 g, 2.53 mmoles) in EtOH/HCl 0.03 N (50 ml). The mixture was stirred at room temperature under H_2. After stirring (2 h), the mixture was filtered on celite and the solvent was concentrated in vacuo to yield **1**. Yield: 0.43 g (85%).

^{1}H-NMR ($CDCl_3$), δ ppm: 4.68 (d, 1H, CHα, J = 5.6 Hz), 4.32 (d, 1H, CHβ, J = 5.6 Hz), 3.78 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 1.41 (s, 9H,

t-Bu). $[M+H^+]=262$ (FAB^+/GT). IR (NaCl, film):$\nu CO=1745$, 1730, 1710, 1694 cm^{-1}.

Coupling Reaction, Synthesis of Compound 3

To a stirred and cooled solution of **1** (1.04 g, 4 mmoles) in DCM (10 ml), were added $(Boc)_2$-Gly-OH (0.88 g, 4 mmoles), BOP reagent (1.94 g, 4.4 mmoles) and DIEA (1.53 ml, 8 mmoles). The mixture was stirred for 16 h at $-10^{\circ}C$. The solvent was evaporated and ethyl acetate (20 ml) was added. The organic fraction was washed with $KHSO_4$, water, $NaHCO_3$ and saturated brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was then purified by chromatography on silica gel (hexane/EtOAc : 4/1) to give **3**. Yield: 1.45 g (68%). Rf = 0.36 (hexane/EtOAc: 4/1).

^{1}H-NMR ($CDCl_3$), δ ppm: 6.96 (br, 1H, NH), 5.17 (m, 1H, C5-H), 4.76 (m, 1H, C2-H), 3.98 (m, 1H, C6-H), 3.69 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 1.43 (s, 27H, 2Boc, tBu), 1.38 (d, 3H, CH_3, J = 7.0 Hz). $[M+H^+]=533$ (ES). IR (NaCl, film): $\nu NH=3438\ cm^{-1}$, $\nu CO=1746$, 1731, 1698 cm^{-1}.

N-Benzylation of Compound 3

To a solution of **3** (2.13 g, 4 mmoles) in dry toluene (80 ml) were added pulverized K_2CO_3, tetrabutylammonium bromide (0.8 g) and benzyl bromide (0.64 ml). The mixture was stirred at room temperature for 48 h. The reaction mixture was then filtered, concentrated in vacuo, purified on silica gel (hexane/EtOAc: 4/1) to give **4**. Yield: 1.12 g (45%). Rf = 0.36 (hexane/EtOAc: 4/1).

^{1}H-NMR ($CDCl_3$), δ ppm: 7.12 (m, 5H, Ar), 5.16 (m, 1H, C5-H), 4.75 (m, 1H, C6-H), 3.98 (m, 1H, C6-H), 3.69 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.41 (q, 1H, C2-H, J = 7.0 Hz), 3.21 (m, 2H, CH_2Ph), 1.43 (s, 27H, 2Boc, tBu), 1.13 (d, 3H, CH_3, J = 7.0 Hz). $[M+H^+]=533$ (ES). IR (NaCl, film): $\nu NH=3438\ cm^{-1}$, $\nu CO=1746$, 1731, 1698 cm^{-1}.

Cleavage of the Boc and tBu Groups, Synthesis of Compound 5

Compound **4** (1 g, 1.88 mmole), was treated with trifluoroacetic acid (30%) in DCM for 4 h at room temperature. The mixture was concentrated in vacuo and the corresponding trifluoroacetic salt **5**, was dried under high vacuum to constant weight. Yield: 0.90 g (100%).

^{1}H-NMR (CD_3COCD_3), δ ppm: 7.35 (m, 5H, Ar), 4.42–5.35 (m, 4H, C5-H, CH_2Ph, C6-H), 3.70 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.60 (m, 1H, C2-H), 1.58 (d, 3H, CH_3, J = 7.0 Hz). $[M+H^+] = 366$ (ES).

Cyclisation Reaction Synthesis of Compound 6

The linear precursor **5** (0.5 g, 1.4 mmole) was added over 5 h from a syringe pump to a stirred and cooled solution (−30°C) of BOP reagent (0.63 g, 1.43 mmole) and DIEA (0.68 ml, 3.9 mmoles) in DMF (10 ml). The mixture was stirred 24 h at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (10 ml) and washed with $KHSO_4$, water, $NaHCO_3$ and saturated brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/EtOAc: 1/1). Yield: 0.23 g (49%).

Dimethyl 3-Benzyl-2-(4-methyl-2,5-dioxoimidazolidin-1-yl) butanedioate: **6**

Mixture of Four Diastereoisomers

$6a_1/a_2$ (16%): mp = 134°C (EtOAc). Rf = 0.25 (hexane/EtOAc: 1/4), HPLC (CH_3CN/H_2O: 70/30), Rt: 20.42 mn. Anal. Calcd. for $C_{17}H_{20}N_2O_6$: C, 58,61; H, 5,78; N, 7,82. Found: C, 58,68; H, 5,75; N, 7,85.

Crystal Structure of $6a_1/6a_2$: $C_{17}H_{20}N_2O_6$, $M_W = 348.355$, Monoclinic, space group P 21, Z = 4, a = 11.0323(7), b = 11.7742(4), c = 14.1121(9) Å, b = 99.380(2)° V = 1808.6(2)Å3, d calc = 1.23 g cm^{-3}, λ(MoKα) = 1.5418 Å, μ = 0.88 mm^{-1}. Intensity data were measured on a Enraf-Nonius KappaCCD diffractometer using graphite-monochromated Mo Kα radiation and the φ-scan technique. 12894 collected reflexions, 3708 unique (Rint = 0.055) of which 2890 were considered as observed having $I > 3\sigma(I)$. Hydrogen are in theoretical position. Refinement of F2, $R[F2 > 3\sigma(F2)] = 0.059$ and $wR(F2) = 0.059$ $w = 1/[\sigma 2(Fo2)+0.030+Fo2]$ goodness of fit > 1.51. The residual electron density in the final difference map was located between −0.20 and 0.311 e Å3. Two independent molecules form a dimer. Computer-programs: *MaXus*.

$6b_1/b_2$ (33%) : mp = 141°C (EtOAc). Rf = 0.28 (hexane/EtOAc: 1/4), HPLC (CH_3CN/H_2O: 70/30), Rt: 20.31 mn. $[M+H^+] = 349$ (FAB^+/GT). Anal. Calcd. for $C_{17}H_{20}N_2O_6$: C, 58,61; H, 5,78; N, 7,82. Found:C, 58,65; H, 5,77; N, 7,87.

^{1}H-NMR (CD_3COCD_3): δ ppm

$6a_1/a_2$: 7.02 (m, 5H, Ar), 4.88 (d, 1H, J = 10.6 Hz, CH-COOMe), 3.92 (qd, 1H, C4-H, J = 6.9, 1.3 Hz), 3.54 (s, 3H, OCH_3), 3.46 (m, 1H, CH-COOMe), 3.35 (s, 3H, OCH_3), 2.68 (m, 1H, CH_2Ph), 2.55 (m, 1H, CH_2Ph), 1.21 (d, 3H, CH_3, J = 7.2 Hz).

$6b_1/6b_2$: 7.11 (m, 5H, Ar), 4.69 (d, 1H, J = 9.6 Hz, CH-COOMe), 4.03 (qd, 1H, C4-H, J = 6.5, 1.3 Hz), 3.60 (s, 3H, OCH_3), 3.56 (m, 1H, CH-COOMe), 3.35 (s, 3H, OCH_3), 3.01 (m, 1H, CH_2Ph), 2.85 (m, 1H, CH_2Ph), 1.20 (d, 3H, CH_3, J = 7.2 Hz).

^{13}C-NMR (CD_3COCD_3): δ ppm

$6a_1/6a_2$: 174.8, 173.3, 168.6, 155.9 (C = O), 138.3, 129.0, 128.7, 128.6, 126.9, 126.8 (C-Ar), 53.4, 53.3, 53.1, 52.7, 52.6, 51.6, 51.4, 46.5 (OCH_3, CH-2, CH-3, CH-CH_3), 36.1 (CH_2Ph), 17.2 (CH_3).

$6b_1/6b_2$: 174.3, 174.2, 171.9, 168.5, 155.6 (C = O), 139.3, 129.1, 128.8, 128.4, 126.9, 126.8 (C-Ar), 54.4, 52.9, 52.8, 52.7, 52.6, 52.5, 51.5, 48.1 (OCH_3, CH-2, CH-3, CH-CH_3), 36.2, 36.1 (CH_2Ph), 17.3, 17.2 (CH_3).

ABBREVIATIONS

Boc : *tert*-butyloxycarbonyl
BOP : benzotriazol-1-yloxy-tris (dimethylamino)phosphonium hexafluorophosphate
DMF : dimethylformamide
DCM : dichloromethane
DIEA : diisopropylethylamine
TFA : trifluoroacetic acid

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