Pergamon

Tetrahedron 54 (1998) 5325–5336

TETRAHEDRON

Stereoselective synthesis of 6,5-bicyclic reverse-turn peptidomimetics

Lino Colombo,[a]* Marcello Di Giacomo,[a] Gloria Brusotti,[a] Nicola Sardone,[b] Mauro Angiolini,[c] Laura Belvisi,[c] Sonia Maffioli,[c] Leonardo Manzoni,[c] Carlo Scolastico[c]*

[a]*Pharmaceutical Chemistry Department, University of Pavia, via Taramelli 12, 27100 Pavia, Italy*

[b]*C.G.S. (Centro Grandi Strumenti), University of Pavia, 27100 Pavia, Italy*

[c]*Organic and Industrial Chemistry Department, C.N.R. (National Research Council) Centre for the Study of Organic and Natural Compounds, University of Milano, via Venezian 21, 20133 Milano, Italy*

Received 19 January 1998; accepted 5 March 1998

Abstract

A flexible stereoselective synthetic scheme was developed to prepare 6,5-fused bicyclic lactams, that molecular mechanics calculations revealed to have a potential as reverse-turn mimetics. The convergence of the synthetic sequence was achieved by attachment of a properly substituted malonate unit to the (2*S*)-*cis*-5-(2-hydroxyethyl)proline *tert*-butyl ester. Stereoselective intramolecular alkylation of the malonate afforded the 6-membered lactam fused to the 2-carbalkoxy pyrrolidine nucleus. X-ray diffraction analysis of a more advanced synthetic derivative allowed the unequivocal assignment of the configuration at the newly created quaternary stereocenter as *R*.
© 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Peptide mimetics; Lactams; Bicyclic aliphatic compounds; Conformation

Introduction

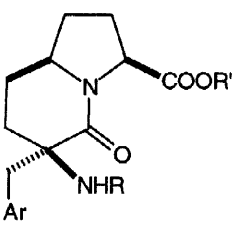
In the early stages of drug discovery processes, especially when targetting compounds that should bind to receptors or enzymes, small peptides are commonly used as initial lead compounds. The relevance of this strategy has been markedly enhanced by the advent of

0040-4020/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(98)00207-5

combinatorial organic synthesis, whose impressive expansion grew from its ability to synthesize, and screen, large random libraries of peptides [1,2].

However, peptides are not ideal drug candidates due to their low metabolic stability toward endogenous proteases and their poor bioavailability. An attractive alternative lies in peptide analogues or de novo designed molecules that mimic the action of the native peptides at the receptor level (peptidomimetics) [3,4]. Since β-turn motifs are secondary structural features implicated as recognition elements in a variety of biological interactions, the design of small constrained mimetics of turn structures is of great importance to medicinal chemistry [5-7].

As part of our continuing investigations into the design of bicyclic peptidomimetics based on proline [8-12], we performed extensive molecular mechanics calculations employing MacroModel version 4.5 [13] and its implementation of the Monte Carlo conformational search [14], the Amber all atom force field [15] and the implicit water GB/SA solvation model [16]. The results of the computational studies indicate that 6,5-fused lactams of type **1** (Figure 1) show some families of minimum energy conformations with torsion angles close to those of classical β-turns [17]. These lactams can be viewed as conformationally constrained Ar-Pro dipeptide mimics and could be used as synthetic replacements for the *i+1* and *i+2* elements of the four consecutive residues of β-turn motifs, where Ar stands for an amino acid with an aryl side chain.

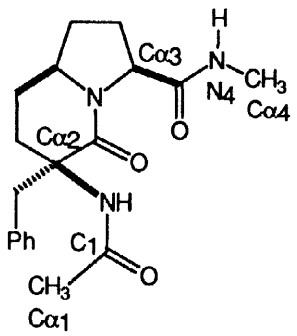


1

1a R = $COCH_3$ Ar = Ph R' = *t*-Bu

Figure 1. 6,5-bicyclic dipeptide analogs of type **1**.

However, quantitative characterization of their turn propensity suggests that these systems are more effective as reverse-turn than as β-turn mimetics, in agreement with the results obtained by Marshall on similar isosteric compounds [18,19]. As an example, the conformational parameters calculated for the model dipeptide derived from **1a** are shown (Figure 2). The virtual torsion angle β is defined by C_1, $C\alpha_2$, $C\alpha_3$ and N_4 [6] (the range 0±60° is retained to indicate tight reverse-turns), d is the distance between Cα1 and Cα4 (values of less than 7 Å are often used to define the presence of a reverse-turn), and $d_{O\text{-}H}$ is the distance between the carbonyl oxygen of residue *i* and the amide hydrogen of residue *i+3* (values of less than 4 Å are assumed to indicate the hydrogen bond characteristic of a β-turn).



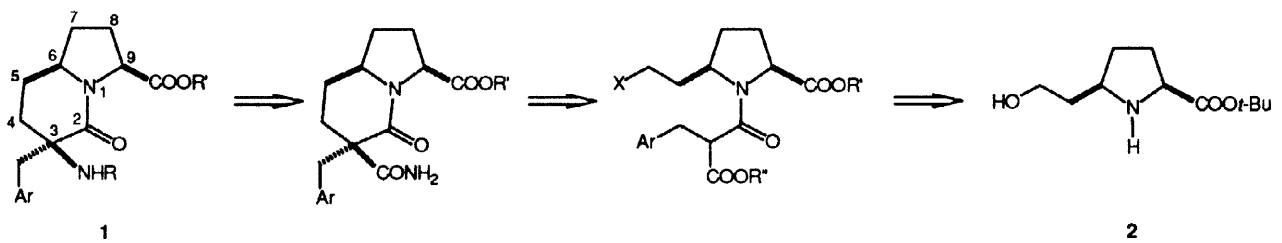
	No. of conformers < 12 kcal/mol	% $\|\beta\| < 60°$	% d < 7Å	% $d_{O\text{-}H}$ < 4Å
in vacuo	65	97	78	41
H_2O, GB/SA	70	90	76	34

Figure 2. Schematic of the model dipeptide derived from **1a** showing the parameters used to characterize reverse-turns.

Results and discussion

Earlier we reported a synthesis of **1a** [8] by a route involving as the key step a stereoselective radical cyclization, but a more flexible and versatile synthetic scheme was needed to allow the easy introduction of diversity elements at the level of the functional groups that constitute the side chain of the "Ar" residue. Herein we describe our efforts towards this goal.

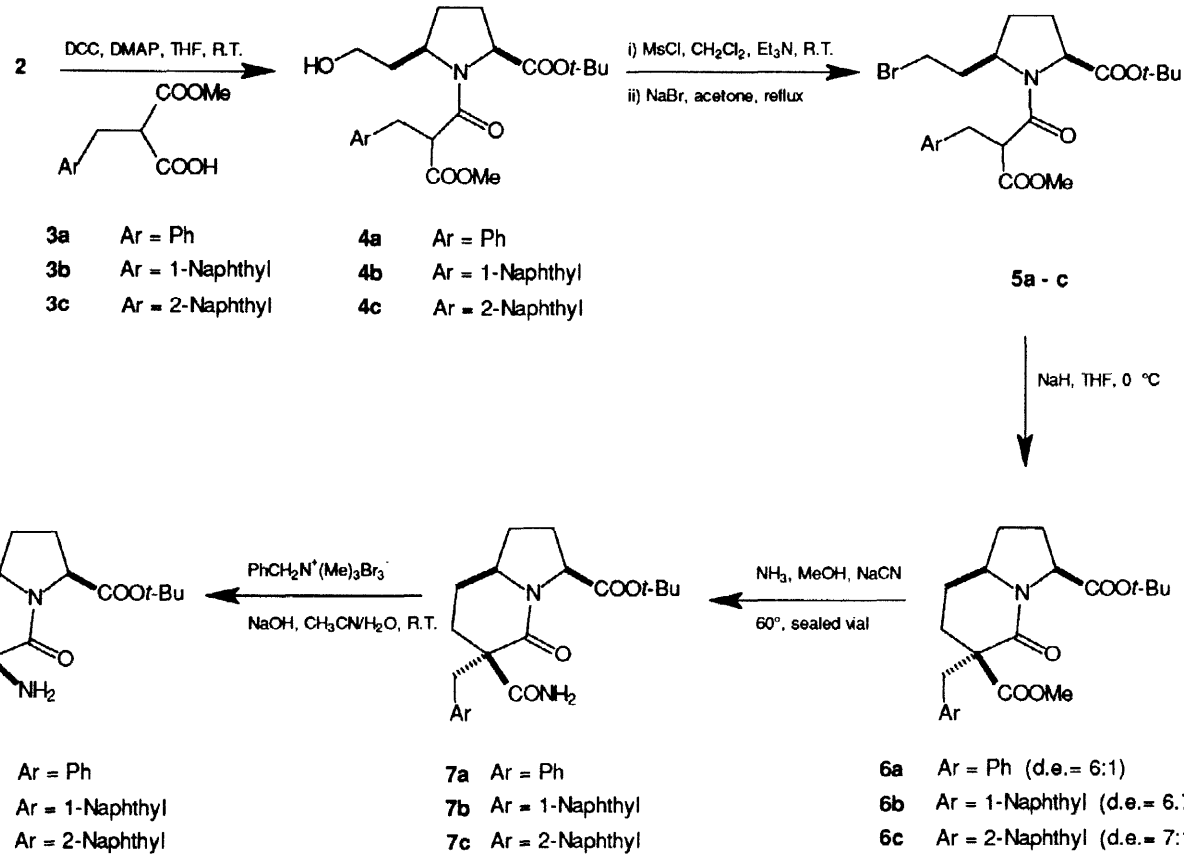
The convergency of the synthetic sequence (Scheme 1) was thought to be achievable by attachment of a properly substituted malonate unit to the (2S)-*cis*-5-(2-hydroxyethyl)proline derivative **2**. Intramolecular alkylation of the malonate should afford the 6-membered lactam fused to the 2-carbalkoxy pyrrolidine nucleus. The eventual conversion of the ester function on the quaternary carbon to amine should then be secured through either the Hoffman or Curtius rearrangement. A major concern was the stereochemical outcome of the intramolecular malonate alkylation, since only the 3-(*R*)-stereoisomer was shown by the above calculations to be a good β-turn mimetic.



Scheme 1.

In an effort to gain some insight into the level and direction of asymmetric induction in this reaction, we performed semiempirical AM1 calculations [20] on the transition states leading to the epimeric cyclized products. The results were encouraging as the transition state leading to the sought 3*R* isomer was predicted to be more stable by about 1 kcal/mol.

According to the retrosynthetic analysis outlined above, the common intermediate **2** [8,9,21] was then condensed with the 2-(arylmethyl)malonate monoacids **3a-c** (prepared by partial hydrolysis of the parent dimethylesters) in the presence of DCC and catalytic DMAP. The resulting amides **4a-c** display the complete carbon array of the final products and all the functional groups are placed so as to be serviceable for the following synthetic operations. Conversion of the alcohols **4a-c** into the bromides **5a-c** was performed through a standard protocol involving formation of the mesylate followed by displacement using NaBr in refluxing acetone.



Scheme 2.

The crucial intramolecular alkylation of the malonate unit was then attempted treating a THF solution of the crude bromides **5a-c** with NaH, under strictly anhydrous conditions, in order to prevent hydrolysis of the methyl ester from being a competitive process.[1] As predicted by AM1 calculations, the diastereoisomeric ratio of the cyclized products **6a-c** was relatively high in all the cases studied, as summarized in Scheme 2.

[1] In experiments performed with THF containing adventitious water, high proportions of carboxylic acid were formed. The corresponding ethyl esters, prepared in the same way with monoethyl malonate derivatives, were significantly less sensitive to basic hydrolysis but, at same time, less reactive in the subsequent step.

The configurational assignment of the newly created stereocenter by NMR experiments gave inconclusive results, so that the solution of this problem was postponed until obtaining a more advanced synthetic intermediate or derivative, whose crystallinity would allow an X-ray structural determination.

Attempts to convert the ester at position 3 into an amine function, *via* hydrolysis to carboxylic acid and subsequent acyl azide formation in view of the final Curtius rearrangement, met with limited success in terms of overall yields. Following this series of unsuccessful experiments we applied the Hoffman rearrangement and achieved good yields. The methyl ester function in **6a-c** could be selectively converted into a primary amide by reaction in a sealed vial at 60°C with a saturated solution of NH_3 in methanol in the presence of a stoichiometric amount of NaCN [22].

The final conversion of primary carboxamides **7a-c** into amines **8a-c** was then faced using a series of reagents known to promote high yielding Hoffman reactions involving rearrangement of quaternary centers [23]. Unexpectedly, the highest yields were obtained by the use of benzyltrimethylammonium tribromide [24], whose efficiency was stated to be limited to aromatic and low molecular weight aliphatic amides, in other cases the major product observed being ureas.

Our results are only seemingly at odds with the above statement and can be plausibly explained by a diminished reactivity of both the intermediate isocyanate and the final amine. As the Hoffman rearrangement is known to occur with retention of configuration, the two functional groups are placed on the same, rather crowded, face of the bicyclic system, and are, moreover, positioned on quaternary carbons, thus preventing the fast process that gives symmetric ureas. Indeed substantial amounts of urea sideproducts were obtained in the same reaction perfomed on the minor diastereoisomer.

Acetylation of the final amine **8a** gave the corresponding acetamide **1a** as a white powder that could be recrystallized, affording well-shaped crystals suitable for X-ray diffraction analysis. The diffractometric structure determination allowed the unequivocal assignment of the configuration at C-3 as *R*.[2] Given the retentive stereochemical behaviour of the Hoffman rearrangement, the predictive value of semiempirical calculations for the cyclization reaction leading to **6** was experimentally confirmed.

The X-ray crystal structure of **1a** is reproduced in Figure 3. The dihedral angles were -179.8° for ϕ_{i+1}, -163.6° for ψ_{i+1}, -63.2 for ϕ_{i+2}, +163.0° for ψ_{i+2} and -6.3° for the virtual torsion angle β [6] in the crystalline state, in agreement with the values observed in molecular mechanics global minimum.

[2]Crystallographic data for the structure **1a** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100388. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: Int. code +(1223) 336-033; e-mail: deposit@chemcrys.cam.ac.uk).

In conclusion, a convergent, versatile, and stereoselective synthetic scheme for the preparation of 6,5-fused bicyclic lactams has been presented. The study on the effectiveness of these compounds as initiators of β-turn motifs is under active investigation by our groups.

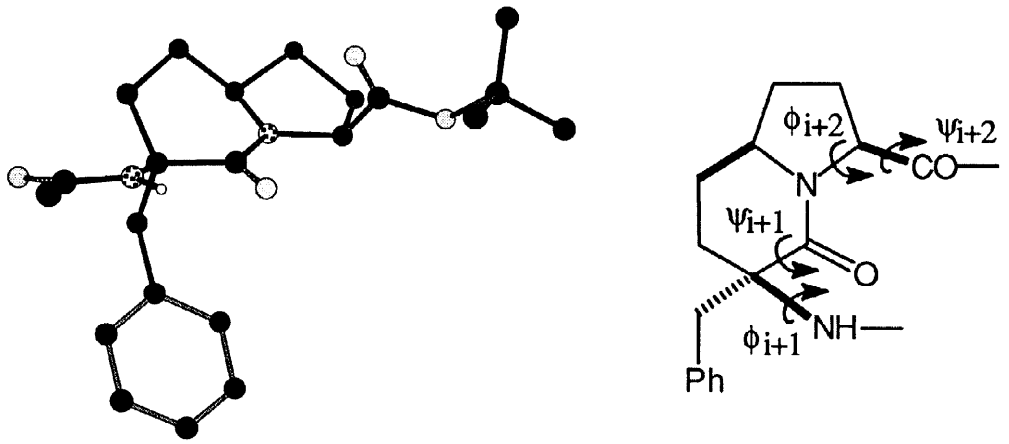


Figure 3. Conformation of compound **1a** by X-ray analysis.

Experimental

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ as indicated, at 200 (or 300) and 50.3 MHz, respectively. The chemical shift values are given in ppm and the coupling constants in Hz. Optical rotation data were obtained on Perkin-Elmer model 241 polarimeter. Thin-layer chromatography (TLC) was carried out using Merck precoated silica gel F-254 plates. Flash chromatography was carried out with Merck Silica Gel 60, 200-400 mesh. Solvents were dried with standard procedure, and reactions requiring anhydrous conditions were performed under a nitrogen atmosphere. Final product solutions were dried over Na_2SO_4, filtered and evaporated under reduced pressure on a Büchi rotary evaporator. Elemental analyses were performed by the microanalytical laboratory of our department.

(2*S*,5*S*)-1-[(2*S*,*R*)-methoxycarbonyl-3-phenyl-propionyl]-5-(2-hydroxyethyl) pyrrolidine-2-carboxylic acid *tert*-butyl ester (4a).

To a solution of **2** (35.1 mmol, 7.547 g) in dry THF (290 ml) were added DCC (52.6 mmol, 10.850 g), racemic **3a** (32.6 mmol, 6.790 g) and 4-DMAP (3.5 mmol, 0.429 g). The mixture was stirred at room temperature for 12 h. The solution was diluted with Et_2O (1000 ml) and filtered through a Celite® pad; the solvent was removed under reduced pressure and the residue was purified by chromatography (hexane/AcOEt = 1/1) affording **4a** (6.871 g, 52 %): ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.15 (m, 10H, Ar-H), 4.60 (dd, J = 7.5, 10.1 Hz, m, 2H, C<u>H</u>COOtBu), 3.72 (s, 3H, COOC<u>H</u>$_3$), 3.69 (s, 3H, COOC<u>H</u>$_3$), 3.65-3.10 (m, 14H, C<u>H</u>$_2$O<u>H</u>,

ArC$\underline{H}_2$, C$\underline{H}$COOMe, HOCH$_2$CH$_2$C$\underline{H}$N), 2.38-1.35(m, 12H, C$\underline{H}_2$CH$_2$OH, C$\underline{H}_2$C$\underline{H}_2$), 1.48 (s, 9H, CHCOO$\underline{t}$Bu), 1.45 (s, 9H, CHCOO$\underline{t}$Bu). Anal. Calcd for $C_{22}H_{31}NO_6$: C, 65.17; H, 7.71; N, 3.45. Found: C, 65.02; H, 7.70; N, 3.24.

(2*S*,5*S*)-1-[(2*S*,*R*)-methoxycarbonyl-3-(1'-naphthyl)-propionyl]-5-(2-hydroxyethyl) pyrrolidine-2-carboxylic acid *tert*-butyl ester (4b).

The reaction was performed using the same procedure as that for the compound **4a** affording **4b** (69 %): ^{1}H NMR ($CDCl_3$) δ 8.10-7.32 (m, 14H, Ar-H), 4.62 (m, 1H, C$\underline{H}$COOtBu), 4.48 (dd, J = 7.0, 9.2 Hz, 1H, C$\underline{H}$COOtBu), 4.40-4.15 (m, 2H, HOCH$_2$CH$_2$C$\underline{H}$N), 3.80 (s, 3H, COOC$\underline{H}_3$), 3.75 (s, 3H, COOC$\underline{H}_3$), 3.90-3.35 (m, 12H, C$\underline{H}_2$O$\underline{H}$, ArC$\underline{H}_2$, C$\underline{H}$COOMe), 2.71-2.35 (m, 4H, C$\underline{H}_2$CH$_2$OH), 1.85-1.30 (m, 8H, C$\underline{H}_2$C$\underline{H}_2$), 1.50 (s, 9H, CHCOO$\underline{t}$Bu), 1.40 (s, 9H, CHCOO$\underline{t}$Bu). Anal. Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.07. Found: C, 68.67; H, 7.25; N, 2.94.

(2*S*,5*S*)-1-[(2*S*,*R*)-methoxycarbonyl-3-(2'-naphthyl)-propionyl]-5-(2-hydroxyethyl) pyrrolidine-2-carboxylic acid *tert*-butyl ester (4c).

The reaction was performed using the same procedure as that for the compound **4a** affording **4c** (65 %): ^{1}H NMR ($CDCl_3$) δ 7.85-7.30 (m, 14H, Ar-H), 4.60 (dd, J = 7.4, 9.1 Hz, m, 2H, C$\underline{H}$COOtBu), 4.15 (m, 2H, HOCH$_2$CH$_2$C$\underline{H}$N), 3.80-3.20 (m, 12H, C$\underline{H}_2$O$\underline{H}$, ArC$\underline{H}_2$, C$\underline{H}$COOMe), 3.75 (s, 3H, COOC$\underline{H}_3$), 3.70 (s, 3H, COOC$\underline{H}_3$), 2.40-2.30 (m, 4H, C$\underline{H}_2$CH$_2$OH), 1.87-1.20 (m, 8H, C$\underline{H}_2$C$\underline{H}_2$), 1.45 (s, 9H, CHCOO$\underline{t}$Bu), 1.30 (s, 9H, CHCOO$\underline{t}$Bu). Anal. Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.07. Found: C, 68.37; H, 7.22; N, 2.89.

(2*S*,5*S*)-1-[(2*S*,*R*)-methoxycarbonyl-3-phenyl-propionyl]-5-(2-bromoethyl) pyrrolidine-2-carboxylic acid *tert*-butyl ester (5a).

To a stirred solution of **4a** (13.3 mmol, 5.401 g) in CH_2Cl_2 (66 ml) at 0 °C under nitrogen was added Et_3N (18.6 mmol, 2.59 ml), a catalytic amount of 4-DMAP and MsCl (16.0 mmol, 1.23 ml). The solution was stirred for 1 h at room temperature, before quenching the reaction with H_2O (40 ml). The mixture was extracted with CH_2Cl_2, the organic layer was dried and evaporated to give the mesyl derivative as a colorless oil in quantitative yield.

To a solution of this compound (13.3 mmol) in acetone (133 ml) was added NaBr (66.5 mmol, 6.850 g), and the suspension was refluxed for 4 h. The mixture was cooled and the solvent was removed under reduced pressure. CH_2Cl_2 (60 ml) was added to the residue which was then washed with H_2O (3 × 20 ml), the organic layers were dried, and the residue was purified by chromatography (hexane/AcOEt 7/3) affording **5a** (4.669 g, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 10H, Ar-H), 4.60 (dd, J=7.6, 9.5 Hz, 1H, C$\underline{H}$COOtBu), 4.40 (m, 1H, C$\underline{H}$COOtBu), 4.30-3.90 (m, 2H, BrCH$_2$CH$_2$C$\underline{H}$N), 3.80 (s, 3H, COOC$\underline{H}_3$), 3.70 (s, 3H, COOC$\underline{H}_3$), 3.69-3.10 (m, 10H, BrC$\underline{H}_2$, ArC$\underline{H}_2$, C$\underline{H}$COOMe), 2.51-1.30 (m, 12H, C$\underline{H}_2$CH$_2$Br,

CH_2CH_2), 1.45 (s, 9H, CHCOOtBu), 1.40 (s, 9H, CHCOOtBu). Anal. Calcd for $C_{22}H_{30}NO_5Br$: C, 56.41; H, 6.46; N, 2.99. Found: C, 56.53; H, 6.40; N, 2.80.

(2*S*,5*S*)-1-[(2*S*,*R*)-methoxycarbonyl-3-(1'-naphthyl)-propionyl]-5-(2-bromoethyl) pyrrolidine-2-carboxylic acid *tert*-butyl ester (5b).

The reaction was performed using the same procedure as that for the compound **5a** affording **5b** (75 %): ^{1}H NMR ($CDCl_3$) δ 7.85-7.15 (m, 14H, Ar-H), 4.65 (dd, J = 8.0, 10.2 Hz, 1H, CHCOOtBu), 4.35 (m, 1H, CHCOOtBu), 4.20-4.00 (m, 2H, $BrCH_2CH_2CHN$), 3.80 (s, 3H, $COOCH_3$), 3.75 (s, 3H, $COOCH_3$), 3.70-3.00 (m, 10H, $BrCH_2$, $ArCH_2$, CHCOOMe), 2.60-1.35 (m, 12H, CH_2CH_2Br, CH_2CH_2), 1.40 (s, 9H, CHCOOtBu), 1.35 (s, 9H, CHCOOtBu). Anal. Calcd for $C_{26}H_{32}NO_5Br$: C, 60.23; H, 6.22; N, 2.70. Found: C, 60.15; H, 6.18; N, 2.61.

(2*S*,5*S*)-1-[(2S,R)-methoxycarbonyl-3-(2'-naphthyl)-propionyl]-5-(2-bromoethyl) pyrrolidine-2-carboxylic acid *tert*-butyl ester (5c).

The reaction was performed using the same procedure as that for the compound **5a** affording **5c** (72 %): ^{1}H NMR ($CDCl_3$) δ 7.88-7.32 (m, 14H, Ar-H), 4.63 (dd, J = 7.5, 9.8 Hz, 1H, CHCOOtBu), 4.45 (m, 1H, CHCOOtBu), 4.25-4.00 (m, 2H, $BrCH_2CH_2CHN$), 3.80 (s, 3H, $COOCH_3$), 3.70 (s, 3H, $COOCH_3$), 3.65-3.00 (m, 10H, $BrCH_2$, $ArCH_2$, CHCOOMe), 2.60-1.25 (m, 12H, CH_2CH_2Br, CH_2CH_2), 1.45 (s, 9H, CHCOOtBu), 1.40 (s, 9H, CHCOOtBu). Anal. Calcd for $C_{26}H_{32}NO_5Br$: C, 60.23; H, 6.22; N, 2.70. Found: C, 60.08; H, 6.14; N, 2.59.

(3*R*,6*S*,9*S*) and (3*S*,6*S*,9*S*)-1-Aza-2-oxo-3-methoxycarbonyl-3-benzyl-9-*tert*-butoxycarbonyl -bicyclo[4.3.0]nonane (6a, 6a').

To a suspension of NaH (8.0 mmol, 0.192 g) in dry THF (730 ml) at 0 °C under nitrogen was added a solution of **5a** (7.3 mmol, 3.403 g) in THF (121 ml). The mixture was stirred at this temperature for 16 h before quenching the reaction with a saturated solution of NH_4Cl (500 ml). The mixture was extracted with AcOEt, the extract was dried and the solvent was evaporated under reduced pressure and the residue purified by chromatography (hexane/AcOEt = 7/3) affording **6a**, **6a'** (2.081 g, 74 %) in a diastereisomeric ratio of 6.0 : 1 determined by ^{1}H NMR. Data for **6a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.10 (m, 5H, Ar-H), 4.20 (dd, J = 7.6, 8.9 Hz, 1H, CHCOOtBu), 3.80 (s, 3H, $COOCH_3$), 3.60 (d, J = 12.5 Hz, 1H, ArHCH), 3.00 (d, J = 12.5 Hz, 1H, ArHCH), 2.75 (m, 1H, CH_2CH_2CHN), 2.10-1.70(m, 8H, CH_2CH_2, CH_2CH_2), 1.49 (s, 9H, CHCOOtBu). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 68.33; H, 7.50; N, 3.49.

(3*R*,6*S*,9*S*) and (3*S*,6*S*,9*S*)-1-Aza-2-oxo-3-methoxycarbonyl-3-(1'-naphthylmethyl)-9-*tert*-butoxycarbonyl-bicyclo[4.3.0]nonane (6b, 6b').

The reaction was performed using the same procedure as that for the compound **6a** affording **6b, 6b'** (86 %) with a diastereoisomeric ratio of 6.7 : 1. Data for **6b**: ^{1}H NMR ($CDCl_3$) δ 8.15-7.25 (m, 7H, Ar-H), 4.20 (dd, J = 0.9, 10.2 Hz, 1H, C<u>H</u>COOtBu), 3.95 (d, J = 12.8 Hz, 1H, Ar<u>H</u>CH), 3.80 (s, 3H, COOC<u>H</u>$_3$), 3.78 (d, J = 12.8 Hz, 1H, ArHC<u>H</u>), 2.50 (m, 1H, $CH_2CH_2C\underline{H}N$), 2.15-1.55 (m, 8H, C<u>H</u>$_2$C<u>H</u>$_2$, C<u>H</u>$_2$C<u>H</u>$_2$), 1.50 (s, 9H, CHCOO<u>tBu</u>). Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.29; H, 7.09; N, 2.98.

(3*R*,6*S*,9*S*) and (3*S*,6*S*,9*S*)-1-Aza-2-oxo-3-methoxycarbonyl-3-(2'-naphthylmethyl)-9-*tert*-butoxycarbonyl-bicyclo[4.3.0]nonane (6c, 6c').

The reaction was performed using the same procedure as that for the compound **6a** affording **6c, 6c'** (89 %) with a diastereoisomeric ratio of 7.0 : 1. Data for **6c**: ^{1}H NMR ($CDCl_3$) δ 7.85-7.25 (m, 7H, Ar-H), 4.15 (dd, J = 0.7, 9.6 Hz, 1H, C<u>H</u>COOtBu), 3.80 (s, 3H, COOC<u>H</u>$_3$), 3.77 (d, J = 12.7 Hz, 1H, Ar<u>H</u>CH), 3.15 (d, J = 12.7 Hz, 1H, ArHC<u>H</u>), 2.65 (m, 1H, $CH_2CH_2C\underline{H}N$), 2.15-1.65(m, 8H, C<u>H</u>$_2$C<u>H</u>$_2$, C<u>H</u>$_2$C<u>H</u>$_2$), 1.50 (s, 9H, CHCOO<u>tBu</u>). Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.25; H, 7.10; N, 3.04.

(3*S*,6*S*,9*S*)-1-Aza-2-oxo-3-aminocarbonyl-3-benzyl-9-*tert*-butoxycarbonyl-bicyclo[4.3.0] nonane (7a).

A mixture of **6a** (3.1 mmol, 1.200 g) and NaCN (3.1 mmol, 0.152 g) in MeOH (31 ml) was saturated at 0 °C with ammonia and heated at 60 °C in a sealed glass tube for 4 days. The solvent was evaporated, and the residue was dissolved in AcOEt (70 ml) and washed with H_2O (3 × 50 ml). The organic phase was dried and the solvent evaporated under reduced pressure and the residue purified by chromatography (hexane/AcOEt = 7/3) affording **7a** (0.808 g, 70 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (bs, 1H, CO<u>H</u>NH), 7.30-7.15 (m, 5H, Ar-H), 5.45 (bs, 1H, COHN<u>H</u>), 4.35 (dd, J = 0.8, 10.2 Hz, 1H, C<u>H</u>COOtBu), 3.65 (d, J = 14.2 Hz, 1H, Ar<u>H</u>CH), 3.15 (m, 1H, $CH_2CH_2C\underline{H}N$), 3.00 (d, J = 14.2 Hz, 1H, ArHC<u>H</u>), 2.50-1.55 (m, 8H, C<u>H</u>$_2$C<u>H</u>$_2$, C<u>H</u>$_2$C<u>H</u>$_2$), 1.50 (s, 9H, CHCOO<u>tBu</u>); ^{13}C NMR δ 174.42, 171.34, 169.93, 136.87, 130.35, 127.93, 127.83, 126.41, 81.64, 60.66, 59.30, 55.56, 41.63, 31.05, 28.42, 27.81, 27.67, 25.94. Anal. Calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.52. Found: C, 67.88; H, 7.51; N, 7.39.

(3*S*,6*S*,9*S*)-1-Aza-2-oxo-3-aminocarbonyl-3-(1'-naphthylmethyl)-9-*tert*-butoxycarbonyl-bicyclo[4.3.0]nonane (7b).

The reaction was performed using the same procedure as that for the compound **7a** affording **7b** (97 %): ^{1}H NMR ($CDCl_3$) δ 8.25-7.35 (m, 8H, Ar-H, CO<u>H</u>NH), 5.60 (bs, 1H, COHN<u>H</u>), 4.35 (dd, J = 1.5, 8.8 Hz, 1H, C<u>H</u>COOtBu), 3.95 (d, J = 13.0 Hz, 1H, Ar<u>H</u>CH), 3.85 (d, J = 13.0 Hz, 1H, ArHC<u>H</u>), 3.00 (m, 1H, $CH_2CH_2C\underline{H}N$), 2.00-1.55 (m, 8H, C<u>H</u>$_2$C<u>H</u>$_2$, C<u>H</u>$_2$C<u>H</u>$_2$), 1.50 (s, 9H, CHCOO<u>tBu</u>); ^{13}C NMR δ 174.66, 171.53, 170.26, 133.78, 133.58, 133.43, 128.52, 128.22, 127.16, 125.80, 125.40, 125.24, 124.45, 81.83, 60.56, 59.49, 56.97, 36.15, 31.10, 28.97, 27.82,

27.81, 26.04. Anal. Calcd for $C_{25}H_{30}N_2O_4$: C, 71.07; H, 7.16; N, 6.63. Found: C, 70.94; H, 7.09; N, 6.74.

(3*S*,6*S*,9*S*)-1-Aza-2-oxo-3-aminocarbonyl-3-(2'-naphthylmethyl)-9-*tert*-butoxycarbonyl-bicyclo[4.3.0]nonane (7c).

The reaction was performed using the same procedure as that for the compound **7a** affording **7c** (84 %): ^{1}H NMR ($CDCl_3$) δ 7.85-7.65 (m, 3H, Ar-H), 7.55 (bs, 1H, CO<u>H</u>NH), 7.48-7.30 (m, 4H, Ar-H), 5.65 (bs, 1H, COHN<u>H</u>), 4.35 (dd, J = 0.7, 10.2 Hz, 1H, C<u>H</u>COOtBu), 3.80 (d, J = 13.3 Hz, 1H, Ar<u>H</u>CH), 3.20 (d, J = 13.3 Hz, 1H, ArHC<u>H</u>), 3.15 (m, 1H, $CH_2CH_2C\underline{H}N$), 2.55-1.60 (m, 8H, $C\underline{H}_2C\underline{H}_2$, $C\underline{H}_2C\underline{H}_2$), 1.50 (s, 9H, CHCOO<u>tBu</u>); ^{13}C NMR δ 174.59, 171.49, 170.02, 134.70, 133.23, 132.17, 129.26, 128.78, 127.62, 127.52, 127.37, 125.75, 125.40, 81.83, 60.74, 59.39, 55.86, 41.76, 31.09, 28.62, 27.90, 27.77, 26.00. Anal. Calcd for $C_{25}H_{30}N_2O_4$: C, 71.07; H, 7.16; N, 6.63. Found: C, 71.18; H, 7.11; N, 6.52.

(3*R*,6*S*,9*S*)-1-Aza-2-oxo-3-amino-3-benzyl-9-*tert*-butoxycarbonyl-bicyclo[4.3.0]nonane (8a).

To a solution of NaOH (12.0 mmol, 0.480 g) in CH_3CN/H_2O 1.5/1 (17 ml) were added **7a** (2.0 mmol, 0.745 g) and BTMA Br_3 (2.0 mmol, 0.780 g), and the mixture was stirred for 12 h. During the period of stirring, BTMA Br_3 (orange red) soon dissolved in the alkaline solution and the mixture turned to light yellow. The resulting two phase solution was saturated with NaCl and extracted with AcOEt (4 × 10 ml). The collected organic layers were dried and the solvent evaporated under reduced pressure and the residue purified by chromatography (AcOEt/MeOH = 9/1) affording **8a** (0.558 g, 81 %) as a colorless oil: $[\alpha]^{20}_D$ -83.4° (c 1.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.10 (m, 5H, Ar-H), 4.21 (dd, J = 0.6, 10.1 Hz, 1H, C<u>H</u>COOtBu), 3.21 (d, J = 15.2 Hz, 1H, Ar<u>H</u>CH), 3.11 (m, 1H, $CH_2CH_2C\underline{H}N$), 2.72 (d, J = 15.2 Hz, 1H, ArHC<u>H</u>), 2.10-1.30 (m, 10H, $N\underline{H}_2$, $C\underline{H}_2C\underline{H}_2$, $C\underline{H}_2C\underline{H}_2$), 1.50 (s, 9H, CHCOO<u>tBu</u>); ^{13}C NMR δ 173.22, 170.84, 136.82, 130.35, 127.81, 126.23, 80.91, 60.12, 59.24, 56.61, 46.09, 32.61, 31.18, 27.94, 27.75, 25.77. Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13. Found: C, 69.68; H, 8.22; N, 8.21.

(3*R*,6*S*,9*S*)-1-Aza-2-oxo-3-amino-3-(1'-naphthylmethyl)-9-*tert*-butoxycarbonyl-bicyclo [4.3.0]nonane (8b).

The reaction was performed using the same procedure as that for the compound **8a** affording **8b** (40 %): mp 89-90 °C; $[\alpha]^{20}_D$ -92.8° (c 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.20 (m, 1H, Ar-H), 7.89-7.68 (m, 2H, Ar-H), 7.60-7.32 (m, 4H, Ar-H), 4.27 (dd, J = 0.7, 9.6 Hz, 1H, C<u>H</u>COOtBu), 3.61 (d, J = 15.0 Hz, 1H, Ar<u>H</u>CH), 3.48 (d, J = 15.0 Hz, 1H, ArHC<u>H</u>), 3.05 (m, 1H, $CH_2CH_2C\underline{H}N$), 2.00-1.52 (m, 10H, $N\underline{H}_2$, $C\underline{H}_2C\underline{H}_2$, $C\underline{H}_2C\underline{H}_2$), 1.50 (s, 9H, CHCOO<u>tBu</u>); ^{13}C NMR δ 173.41, 170.93, 133.69, 133.44, 133.14, 128.58, 128.43, 127.07, 125.65, 125.19,

124.39, 80.98, 59.97, 59.45, 57.79, 40.71, 33.06, 31.16, 29.53, 27.86, 25.84. Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 73.25; H, 7.58; N, 7.20.

(3*R*,6*S*,9*S*)-1-Aza-2-oxo-3-amino-3-(2'-naphthylmethyl)-9-*tert*-butoxycarbonyl-bicyclo [4.3.0]nonane (8c).

The reaction was performed using the same procedure as that for the compound **8a** affording **8c** (73 %): mp 107-109 °C; $[\alpha]^{20}_D$ -102.0° (c 0.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.90-7.60 (m, 4H, Ar-H), 7.50-7.30 (m, 3H, Ar-H), 4.25 (dd, J = 0.8, 10.5 Hz, 1H, C<u>H</u>COOtBu), 3.45 (d, J = 15.2 Hz, 1H, Ar<u>H</u>CH), 3.02 (m, 1H, $CH_2CH_2C\underline{H}N$), 2.92 (d, J = 15.2 Hz, 1H, ArHC<u>H</u>), 2.70 (bs, 2H, $N\underline{H}_2$), 2.00-1.50 (m, 8H, $C\underline{H}_2C\underline{H}_2$, $C\underline{H}_2C\underline{H}_2$), 1.50 (s, 9H, CHCOO<u>tBu</u>); ^{13}C NMR δ 138.50, 136.53, 135.28, 129.09, 128.93, 127.57, 127.39, 125.70, 60.21, 59.34, 46.16, 32.66, 31.25, 28.02, 27.86, 25.84. Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 72.91; H, 7.72; N, 7.18.

Acknowledgments

This work was supported by the C.N.R. (National Research Council), Progetto Strategico "Tecnologie Chimiche Innovative" and the MURST (Ministero dell'Università e della Ricerca Scientifica e Tecnologica). We are also grateful to Professor W.C. Still for the use of the program MacroModel and to Molecular Design, Ltd. for the use of the program REACCS.

References

[1] Gallop MA, Barrett RW, Dower WJ, Fodor SPA, Gordon EM. J. Med. Chem. 1994;37:1233-1251.
[2] Gordon EM, Barrett RW, Dower WJ, Fodor SPA, Gallop MA. J. Med. Chem. 1994;37:1385-1401.
[3] Giannis A, Kolter T. Angew. Chem. Int. Ed. Eng. 1993;32:1244-1267.
[4] Gante J. Angew. Chem. Int. Ed. Eng. 1994;33:1699-1720.
[5] Kahn M, editor. Peptide Secondary Structure Mimetics. Tetrahedron Symposia-in-Print No. 50, 1993;49:3433-3689.
[6] Ball JB, Hughes RA, Alewood PF, Andrews PR. Tetrahedron 1993;49:3467-3478.
[7] Kitagawa O, Velde DV, Dutta D, Morton M, Takusagawa F, Aubé J. J. Am. Chem. Soc. 1995;117:5169-5178.
[8] Colombo L, Di Giacomo M, Belvisi L, Manzoni L, Scolastico C, Salimbeni A. Gazz. Chim. It. 1996;126:543-554.
[9] Colombo L, Di Giacomo M, Scolastico C, Manzoni L, Belvisi L, Molteni V. Tetrahedron Lett. 1995;36:625-628.
[10] Hanessian S, McNaughton-Smith G, Lombart HG, Lubell WD. Tetrahedron Report No. 426. Tetrahedron 1997;53:12789-12854 and references therein.
[11] Kim K, Dumas JP, Germanas JP. J. Org. Chem. 1996;61:3138-3144.
[12] Li W, Hanau CE, d'Avignon A, Moeller KD. J. Org. Chem. 1995;60:8155-8170.
[13] Mohamadi F, Richards NGJ, Guida WC, Liskamp R, Lipton M, Caufield C, Chang G, Hendrickson T, Still WC. J. Comput. Chem. 1990;11:440-467.
[14] Chang G, Guida WC, Still WC. J. Am. Chem. Soc. 1989;111:4379-4386.
[15] Weiner SJ, Kollman PA, Nguyen DT, Case DA. J. Comput. Chem. 1986;7:230-252.

[16] Still WC, Tempczyk A, Hawley RC, Hendrickson T. J. Am. Chem. Soc. 1990;112:6127-6129.
[17] Richardson JS. Adv. Protein Chem. 1981;34:167-339.
[18] Slomczynska U, Chalmers DK, Cornille F, Smythe ML, Beusen DD, Moeller KD Marshall GR. J. Org. Chem. 1996;61:1198-1204.
[19] Chalmers DK, Marshall GR. J. Am. Chem. Soc. 1995;117:5927-5937.
[20] Stewart JJP. MOPAC Version 6.0, F.J. Seiler Research Laboratory, U.S. Air Force Academy, CO 80840, QCPE 455.
[21] Chiesa MV, Manzoni L, Scolastico C. Synlett 1996;5:441-443.
[22] Högberg T, Ström P, Ebner M, Rämsby S. J. Org. Chem. 1987;52:2033-2036.
[23] Huang X, Keillor JW. Tetrahedron Lett. 1997;38:313-316 and references therein.
[24] Kajigaeshi S, Asano K, Fujisaki S, Kakinami T, Okamoto T. Chem. Lett. 1989; 463-464.