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Solution-phase synthesis of novel seven-membered cyclic dipeptides containing α- and β-amino acids

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ABSTRACT

A convenient synthetic procedure for the preparation of seven-membered cyclic α,β-dipeptides is described. Following coupling of *N*-protected α-amino acids with *N*-substituted β-amino acid *tert*-butyl esters, that affords linear α,β-dipeptides, the protecting groups at the terminal functionalities were removed and the open-chain dipeptides were cyclized with phenylphosphonic dichloride, $PhP(O)Cl_2$, to give the desired cyclic α,β-dipeptides in good yields. NMR studies, X-ray diffraction analysis, and DFT calculations provided evidence for the conformation adopted by these cyclic dipeptides in solution, in the solid-state, and in the gas phase.

1. Introduction

Cyclic peptides are of great relevance because of their unique biological properties.[1] For instance, since hydrolytic breakdown of peptides usually begins at C- or N-termini, cyclic peptides tend to be resistant to enzymatic degradation. Thus, they possess greater in vivo stability relative to their linear analogues, and this imparts them high potential in drug,[2] materials,[3] and organocatalysis[4] development. Furthermore, there is the possibility that their restricted flexibility will facilitate attainment of the bioactive conformation that gives rise to receptor site selectivity and pharmacological specificity.[5]

In this context, although numerous cyclopeptides of natural origin containing non-proteinogenic β-amino acids display important biological activities,[6] the preparation of medium size (7–10-membered) lactams is still a significant synthetic problem. Indeed, linear dipeptides made up of an α- and β-amino acid, which represent potential precursors to the monocyclic seven-membered [1,4]diazepine-2,5-dione (or 'homodiketopiperazine') skeleton are especially resistant to ring closure.[7] The main reason for the failure of open-chain α,β-dipeptides to undergo cyclization is the predominant *transoid* arrangement of the reacting functions emanating from the central amide bond, which prevents the required spatial positioning of the terminal amine and activated carboxy groups for cyclization to occur.[8] Consequently, only a limited number of cyclo-α,β-dipeptides have been described. Nevertheless, this family of derivatives offers very useful frameworks for the discovery of new biologically active compounds.[9]

There exist several literature reports concerning the synthesis of the [1,4]benzodiazepine-2,5-dione ring system[10] but only a few describing the preparation, mostly by solid-phase synthesis, of the non-aromatic [1,4]diazepine-2,5-dione system.[9a,11] In this context, Martinez and co-workers[12] reported a procedure for the preparation of seven-membered ring cyclic dipeptides from functionalized β-amino acids.

An ingenious strategy for the synthesis of several seven-membered ring [1,4]diazepine-2,5-diones was developed by van Maarseveen and co-workers,[11a,13] based on the use of a 'pincer' auxiliary that facilitates ring closure in the linear dipeptide precursor. In particular, an *ortho*-hydroxybenzaldehyde derivative 'pincer' is incorporated within the backbone of the linear dipeptide to induce an 'U'-type conformation where the reacting functions (the terminal amine and activated carboxy groups) are brought into proximity; i.e., the auxiliary serves as a tethering hinge that facilitates the reactive terminal functional groups to approach one another (Scheme 1).

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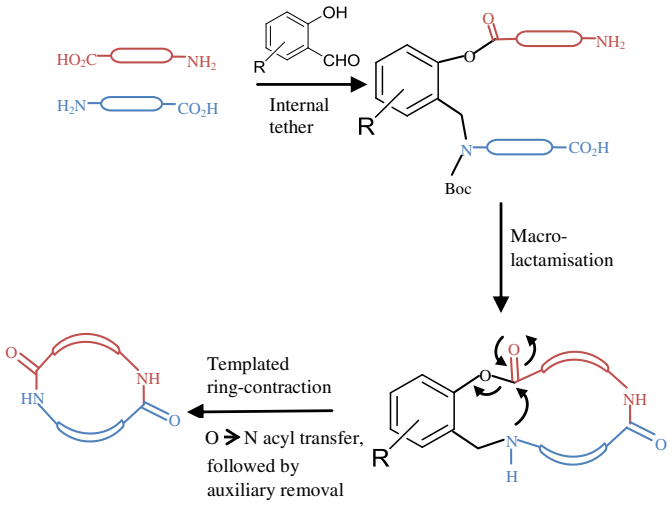


Scheme 1. Maarseven's procedure for the preparation in solution of seven-membered ring cyclic dipeptides, by means of a 'pincer' auxiliary that facilitates the proper orientation of the amino and carboxylic termini in the linear precursor for amide bond formation.[11a,13]

In order to extend the structural diversity of available [1,4]diazepine-2,5-diones, we report here a convenient and practical solution-phase method for the preparation of seven-membered cyclic α,β-dipeptides. This method makes use of phenylphosphonic dichloride, $PhP(O)Cl_2$,[14] as activating agent for the cyclization of linear α,β-dipeptides.

2. Results and discussion

2.1. Synthesis of the cyclo-α,β-dipeptides

2.1.1. Amino acid coupling reaction. There are many reagents that are used to activate the carboxylic function in an amino acid for the coupling reaction with an amino group in a second amino acid, giving rise to the desired amide bond.[15] Among the most commonly used activating agents are HATU, HBTU, DIEA, EDC, and HOBt. In the present work, we chose to follow literature reports[16] recommending the use of isobutyl chloroformate to form the corresponding mixed anhydride of *N*-α-protected amino acids, which are subsequently added to *N*-benzyl-*tert*-butyl-β-aminoesters, leading to the formation of the expected linear α,β-dipeptide. As it can be seen in Table 1, the observed yields varied from moderate to good, apparently depending at least in part on the steric hindrance imposed by the amino substituents.

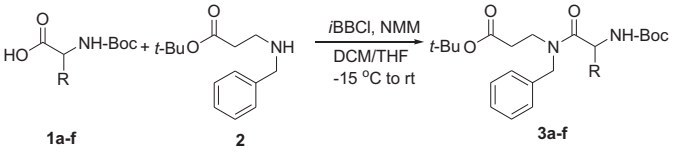
Suitable crystals of product (±)-**3c** were obtained by crystallization from dichloromethane/hexane (1:9) and were subjected to X-ray diffraction analysis. The recorded structure (Fig. 1) confirms the presence of the two amino acid residues joined by the amide bond, and the two *tert*-butyl groups oriented to opposite extremes of the main chain (Fig. 1).[17] As anticipated from literature reports,[18] the *N*-benzyl substituent apparently induces a conformation where the carboxyl and amino termini approach each other facilitating ring closure.

When the side chain consists of a highly sterically demanding group, the coupling reaction does not proceed. The use of alternative coupling reagents such as HBTU/HOBt afforded the desired product in moderate yield (Scheme 2).

2.1.2. Removal of the N-protecting group and hydrolysis of the tert-butyl ester function. The unprotected linear α,β-dipeptides **4a**–**f** were formed by removal of both the *N*-Boc protecting group and the carboxylic *O*-*tert*-butyl ester function with TFA in dichloromethane (1:1 ratio) at ambient temperature. Trifluoroacetate salts **4a**–**f**·TFA were obtained in quantitative yields (Scheme 3). For most compounds yields were determined after purification from Dowex ion-exchange resin column. Since TFA apparently does not affect the cyclization reaction, linear peptides were used as the corresponding TFA salts.

2.1.3. Cyclization reaction. The crucial step, the cyclization of the linear precursors required the activation of the carboxyl group, which is frequently carried out by means of an organophosphorus reagent.[19] In this regard, Escalante and co-workers[14] have reported

Table 1
Coupling reaction between *N*-Boc-protected α-amino acids **1a**–**f** and *N*-benzyl-*tert*-butyl-β-alanine ester **2** to give linear α,β-dipeptides **3a**–**f**



1a-f 2 3a-f

Entry	Product	R	Yield (%)
1	(±)-**3a**	CH_3	81
2	(*S*)-**3a**	CH_3	79
3	(*R*)-**3a**	CH_3	68
4	(±)-**3b**	$CH(CH_3)_2$	46
5	(*S*)-**3b**	$CH(CH_3)_2$	40
6	(*R*)-**3b**	$CH(CH_3)_2$	44
7	(±)-**3c**	$CH_2CH(CH_3)_2$	44
8	(*S*)-**3c**	$CH_2CH(CH_3)_2$	50
9	(*R*)-**3c**	$CH_2CH(CH_3)_2$	51
10	(*S*,*S*)-**3d**	$CH(CH_3)CH_2CH_3$	30
11	(*R*,*R*)-**3d**	$CH(CH_3)CH_2CH_3$	31
12	(±)-**3e**	CH_2Ph	68
13	(*S*)-**3e**	CH_2Ph	68
14	(*R*)-**3e**	CH_2Ph	65
15	(±)-**3f**	Ph	63
16	(*S*)-**3f**	Ph	60
17	(*R*)-**3f**	Ph	61

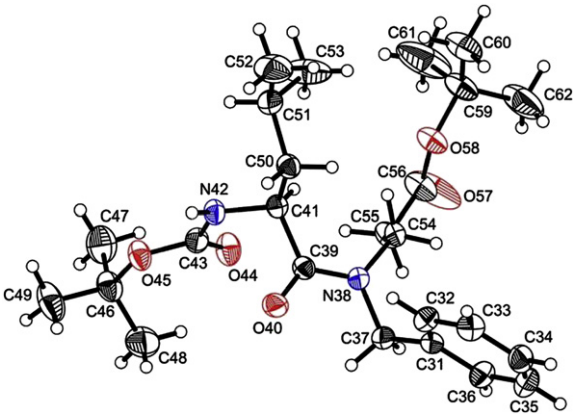
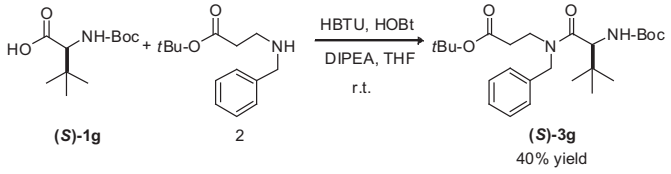
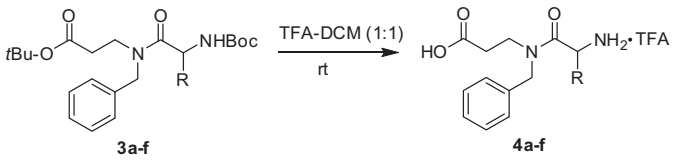


Fig. 1. X-ray crystallographic structure and conformation of linear dipeptide (±)-**3c** (for the crystal cell showing the packing arrangement of both enantiomers of the racemic mixture, see page S-30 in Supplementary data).[17]



(*S*)-1g 2 (*S*)-3g
40% yield

Scheme 2. Coupling reaction of *N*-Boc-L-*tert*-leucine (a highly hindered amino acid) and *N*-benzyl-β-alanine-*tert*-butyl ester.

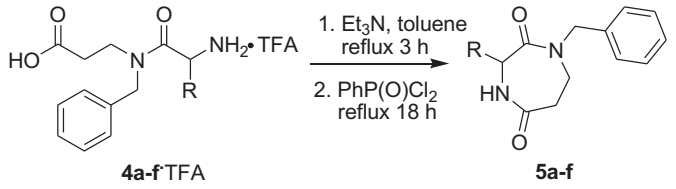


Scheme 3. Removal of the *N*-protecting group and hydrolysis of the *tert*-butyl ester function.

the use of phenylphosphonic dichloride [$PhP(O)Cl_2$] in Et_3N as a particularly effective activating agent for the formation of cyclo-β-dipeptides.

Removal of trifluoroacetic acid from **4a**–**f**·TFA was achieved with 3 equiv of triethylamine in toluene under reflux for 3 h, and then the free dipeptides were treated under high dilution (0.01 M) with 1.5 equiv of phenylphosphonic dichloride under reflux for 18 h to give the desired α,β-cyclodipeptides **5a**–**f** in moderate to good yields (Table 2).

Table 2
Cyclization of α,β-dipeptides **4a**–**f** with phenylphosphonic dichloride to afford the desired cyclic dipeptides **5a**–**f**



Entry	Product	R	Yield (%)
1	(±)-**5a**	CH_3	82
2	(*S*)-**5a**	CH_3	72
3	(*R*)-**5a**	CH_3	70
4	(±)-**5b**	$CH(CH_3)_2$	70
5	(*S*)-**5b**	$CH(CH_3)_2$	77
6	(*R*)-**5b**	$CH(CH_3)_2$	77
7	(±)-**5c**	$CH_2CH(CH_3)_2$	50
8	(*S*)-**5c**	$CH_2CH(CH_3)_2$	90
9	(*R*)-**5c**	$CH_2CH(CH_3)_2$	90
10	(*S*,*S*)-**5d**	$CH(CH_3)CH_2CH_3$	70
11	(*R*,*R*)-**5d**	$CH(CH_3)CH_2CH_3$	68
12	(±)-**5e**	CH_2Ph	40
13	(*S*)-**5e**	CH_2Ph	40
14	(*R*)-**5e**	CH_2Ph	39
15	(±)-**5f**	Ph	40
16	(*S*)-**5f**	Ph	35
17	(*R*)-**5f**	Ph	38

In order to discard the possibility of (partial) inversion of configuration of the stereogenic center during the cyclization process, products **5b** and **5f** were analyzed by chiral phase HPLC. It could be established that in the case of **5b** [with an alkyl substituent at C(3)], the cyclization reaction proceeded without racemization. Nevertheless, when R is a phenyl group, product **5f** was obtained as a 70:30 mixture of enantiomers, apparently as the result of partial removal of the acidic benzylic hydrogen H(3) in basic media (triethylamine). Thus, formation of an achiral enolate, leads to partial racemization. In order to minimize the detrimental epimerization with phenylglycine, the cyclization reaction was performed with the free dipeptide and only 1.5 equiv of Et_3N; nevertheless, partial racemization was still observed, in accord with literature precedent in related systems.[9a]

2.2. Conformational analysis of the cyclo-α,β-dipeptides 5a–f

Cyclo-α,β-dipeptides **5a**–**f** were purified by column chromatography using DCM/methanol (98:2) or ethyl acetate as mobile phase, followed by recrystallization. In the case of (*R*)-**5c** and (*R*)-**5f** it was possible to obtain suitable crystals for X-ray diffraction analysis (Figs. 2 and 3, respectively).[20,21] The structure determined for compound (*R*)-**5c** confirms the formation of the seven-membered heterocycle. It can be appreciated that the compound

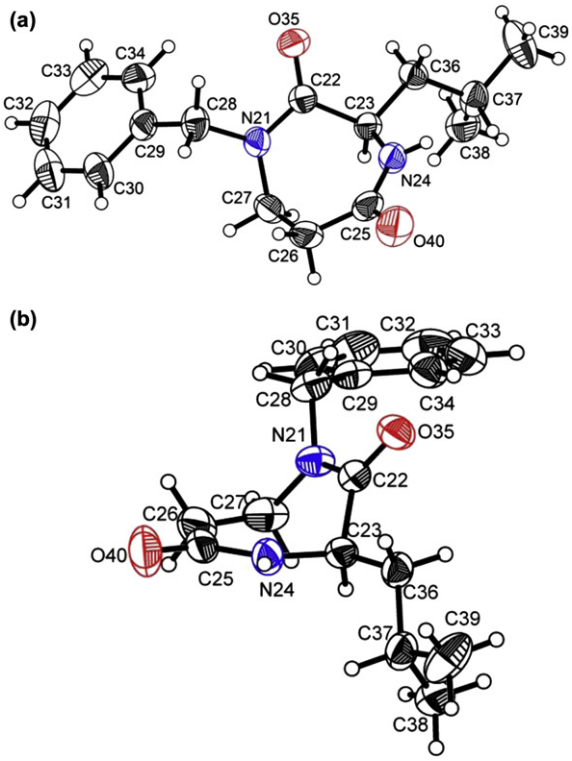


Fig. 2. X-ray crystallographic structure of (*R*)-**5c** showing its solid-state conformation: (a) 'top' view, (b) 'side' view.[20]

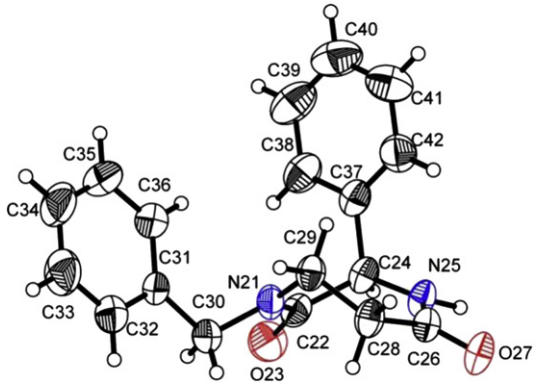


Fig. 3. X-ray crystallographic structure of (*R*)-**5f** showing the axial orientation of the phenyl substituent.[21]

adopts an envelope conformation made up of two planes, containing the peptidic segments (Fig. 2b). Worthy of mention is the observation that the isobutyl group occupies an equatorial orientation as anticipated from steric effects (see, however, below).

By contrast with the solid-state structure of compound (*R*)-**5c** showing the pseudo-equatorial orientation of the C(3) substituent (Fig. 2), the solid-state conformation adopted by (*R*)-**5f** shows that the phenyl substituent at C(3) adopts a pseudo-axial orientation, which might be explained in terms of T-shape π staking between the aromatic groups (Fig. 3). The distance between the aromatic rings is 4.327 Å, which is reasonable for the proposed π-stacking

interaction.[22c] This type of interaction may stabilize the axial conformation by as much as 2 or 3 kcal mol^{-1}.[22]

In solution, NMR ROESY experiments performed for the cyclic dipeptides prepared in this work showed a clear correlation between the axial H(3) and H(7) hydrogen atoms in the case of **5a**–**e**, as shown in Figs. 4 and 5. This observation suggests that those isomers with equatorial substituent at C(3) correspond to the preferred conformers in **5a**–**e**. The values determined for the nuclear Overhauser effect in **5a**–**f** are shown in Table 3.

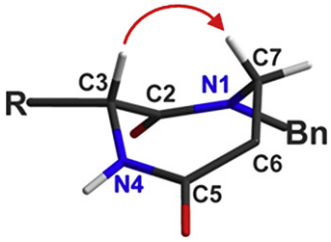


Fig. 4. Nuclear Overhauser effect between pseudo-axial H(3) and H(7) hydrogens in **5a**–**e**.

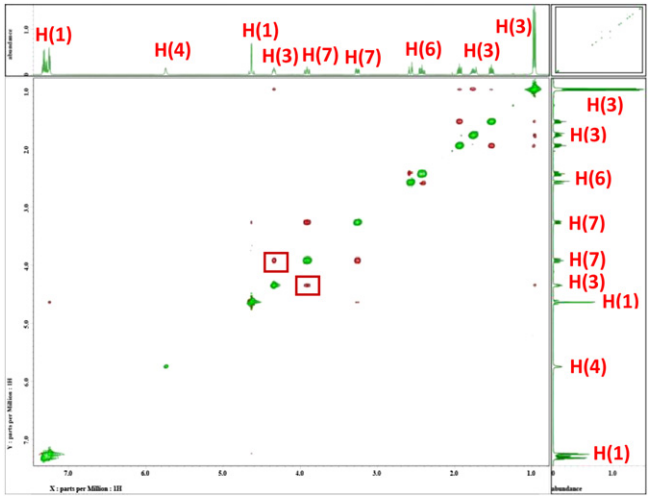
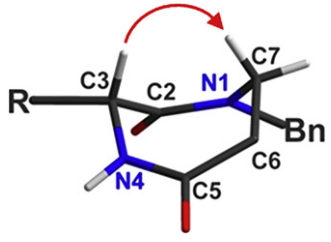


Fig. 5. Nuclear Overhauser effect between pseudo-axial H(3) and H(7) hydrogen in (*R*)-**5c** observed by NMR ROESY experiments.

Table 3
Magnitude of the nuclear Overhauser effect (NOE) between pseudo-axial H(3) and H(7) hydrogens in cyclic dipeptides **5a**–**f**



Entry	Cyclic dipeptide	R	NOE[a] (%)
1	(*S*)-**5a**	CH_3	4.6
2	(*S*)-**5b**	$CH(CH_3)_2$	4.8
3	(*R*)-**5c**	$CH_2CH(CH_3)_2$	6.3
4	(*S*,*S*)-**5d**	$CH(CH_3)CH_2CH_3$	5.2
5	(*S*)-**5e**	CH_2Ph	6.6
6	(*R*)-**5f**	Ph	—

[a] Determined by integration of the relevant ^{1}H NMR signals.

NMR ROESY and NOE experiments were performed in order to confirm that cyclic dipeptide (*R*)-**5f** adopts predominantly a conformation with a pseudo-axial phenyl group. Indeed, ROESY spectra showed a clear correlation between the signal for the aromatic group at δ=7.4 ppm and the corresponding pseudo-axial H(7) proton at δ=3.3 ppm. This interaction was confirmed by NOE measurements that revealed a nuclear Overhauser effect of 3.66% (Fig. 6).

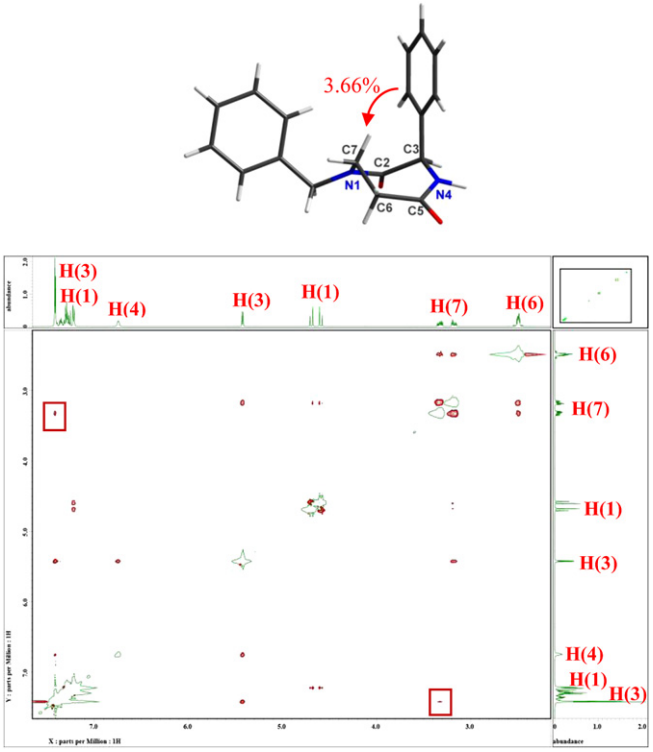


Fig. 6. Nuclear Overhauser effect between the pseudo-axial aromatic group at C(3) and the pseudo-axial H(7) hydrogen in (*R*)-**5f**, as evidenced by NMR ROESY experiments.

In addition, H NMR spectra afforded the vicinal coupling constants ^3J(HN–CαH), from which the corresponding τ dihedral angles were calculated using the Karplus equation.[23] Comparison with the dihedral angles measured from the X-ray crystallographic structures for crystalline compounds (*R*)-**5c** and (*R*)-**5f**, indicates that the observed solid-state conformation is also the predominant one in solution (Table 4).

Table 4
τ Dihedral angles in the solid-state and in solution

Entry	cyclic dipeptide	τ Dihedral angles in the solid-state	τ Dihedral angles in solution
1	(*R*)-**5c**	109.0°	109.8°
2	(*R*)-**5f**	21.4°	20.9°

Regarding the preferred conformations in the gas phase, DFT molecular modeling studies were performed at the B3LYP 6-31G* level of theory (Gaussian 03 program[24]) for dipeptides (*R*)-**5c** and (*R*)-**5f**. This study confirms that for those derivatives with alkyl substituents at C(3) in the cyclic dipeptide, the preferred conformer is the one with this group in pseudo-equatorial orientation. By contrast, when R is an aromatic substituent, the more stable conformation corresponds to the pseudo-axial one (Figs. 7 and 8). For

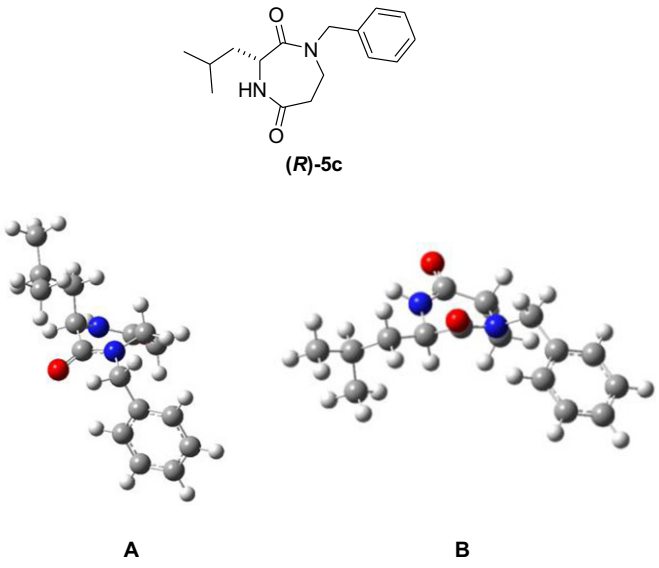


Fig. 7. Optimized structures (DFT B3LYP 6-31G* level of theory, Gaussian 03 program[24]) for pseudo-axial and pseudo-equatorial conformers of cyclic peptides (*R*)-**5c**.

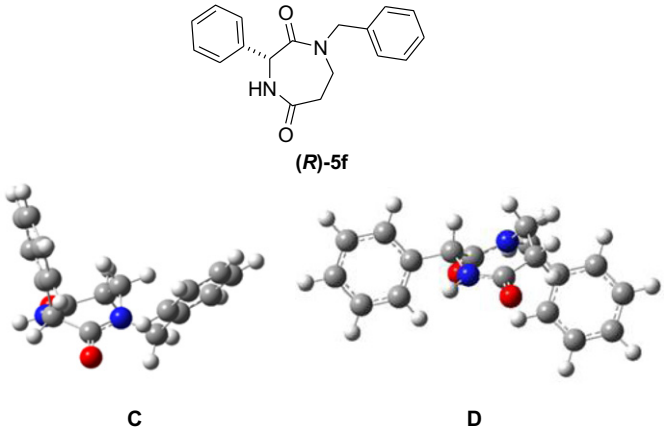
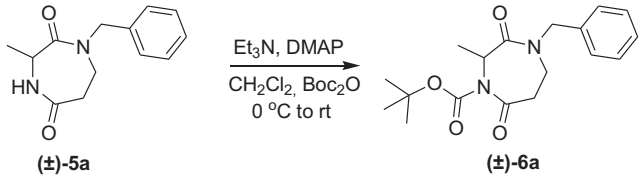


Fig. 8. Optimized structures (DFT B3LYP 6-31G* level of theory, Gaussian 03 program[24]) for pseudo-axial and pseudo-equatorial conformers of cyclic peptide (*R*)-**5f**.

(*R*)-**5c**, the energy difference between conformers **A** (pseudo-axial, higher energy) and **B** (pseudo-equatorial, lower energy) is 3.16 kcal mol^{-1}. In contrast, for (*R*)-**5f** the axial conformer **C** is more stable than the equatorial **D** by 0.76 kcal mol^{-1}. This is consistent with the observations made in solid-state and in solution.

Following the successful preparation of α,β-cyclodipeptides **5a**–**f**, protection of the NH group in **5a** with the Boc protecting group was carried out with Boc_2O in the presence of Et_3N and DMAP (Scheme 4).

Recrystallization of *N*-Boc derivative (±)-**6a** afforded crystals suitable for X-ray diffraction analysis.[25] The resulting structure showed that incorporation of the *N*-Boc group induces the axial orientation of the CH_3 substituent (Fig. 9), probably as the result of



Scheme 4. Derivatization of (±)-**5a** by formation of the *N*-Boc derivative.

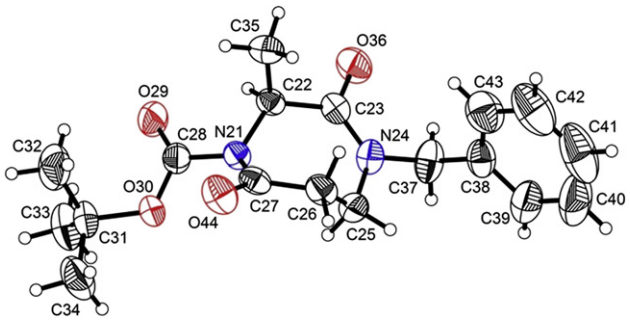


Fig. 9. X-ray crystallographic structure of (±)-**6a** showing the solid-state pseudo-axial orientation of the methyl group (for the crystal cell showing the packing arrangement of both enantiomers of the racemic mixture, see page S-31 in Supplementary data).[25].

allylic $A^{1,3}$ strain.[26] According to this concept, sterically demanding substituents adjacent to the partial double bond present in a cyclic amide moiety prefer to occupy an axial conformation to avoid the dominant steric repulsion present in the equatorial conformer. Similar conformational observations have been reported by De Borggraeve and co-workers,[10g] although no explanation was advanced.

3. Conclusions

An effective synthetic procedure for the preparation of seven-membered cyclic α,β-dipeptides is reported. It is shown that phenylphosphonic dichloride is an efficient activating agent for the formation of the cyclic dipeptides from linear dipeptide precursors. X-ray diffraction analysis of α,β-cyclodipeptides (*R*)-**5c** and (*R*)-**5f**, as well as NOE and ROESY NMR experiments confirm the formation of the cyclized derivatives and provide evidence for the conformation adopted by these heterocycles in solid-state and solution. DFT calculations suggest that the preferred conformation in the gas phase is the same.

4. Experimental section

4.1. General information

Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organometallic compounds were dried for ca. 12 h at 120 °C and allowed to cool in a desiccator over anhydrous $CaSO_4$. Anhydrous solvents were obtained by distillation from benzophenone/ketyl radical. TLC: Merck DC-F_{254} plates, detection UV light, iodine vapor. Flash chromatography: Merck silica gel (0.040–0.063 mm). Melting points: Melt Temp apparatus, not corrected. ^1H NMR spectra: Jeol ECA-500 (500 MHz), Jeol Eclipse-400 (400 MHz), and Bruker Ultra Shield (300 MHz) spectrometers; ^{13}C NMR spectra: Jeol ECA-500 (125.7 MHz), Jeol Eclipse-400 (100 MHz), and Bruker Ultra Shield (75 MHz). Chemical shifts δ are given in parts per million relative to Me_4Si as an internal reference; coupling constants are given in *J* (hertz). Mass spectra were obtained in a Hewlett-Packard HP-5986 instrument. High-resolution mass spectra (HRMS) were obtained on an HPLC 1100 coupled to MSD-TOF Agilent Technologies mod. 1969A.

4.2. Amino acid coupling reaction—general procedure

A stirred solution of *N*-α-protected amino acids **1a**–**f** (10.58 mmol) and *N*-methylmorpholine (11.66 mmol) in anhydrous THF (16 mL) was cooled to −15 °C under nitrogen atmosphere, before the very slow addition of isobutyl chloroformate (11.86 mmol) in anhydrous DCM (5.3 mL). After 1 h of stirring,

a solution of *N*-benzyl-*tert*-butyl-β-aminoesters **2** (10.58 mmol) and *N*-methylmorpholine (12.65 mmol) in anhydrous DCM was added slowly. The mixture was stirred for two additional hours at −15 °C and then was allowed to warm to room temperature, and stirring was continued for 18 h. The solvent was removed under vacuum and ethyl acetate (30 mL) was added to the residue. The resulting solution was washed sequentially with water, 1 N HCl, water, saturated solution of $NaHCO_3$, and water. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. In order to have a complete analysis of the physical and spectroscopic properties of the chiral dipeptides it was decided to prepare both enantiomers and also the racemic mixture to serve as chiral HPLC standards.

*4.2.1. Boc-(±)-Ala-N-Bn-β-Ala-O-t-Bu, (±)-**3a**.* The general procedure was followed with 5 g (26.5 mmol) of (±)-**1a** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) to afford 8.7 g (81% yield) of (±)-**3a** as a white solid, mp 92–94 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, 120 °C) δ (ppm): 1.20 (d, 3H, *J*=6.6, *CHC*H*$_3$), 1.38 (s, 9H, C(C*H*$_3$)$_3$), 1.39 (s, 9H, C(C*H*$_3$)$_3$), 2.45 (m, 2H, C*H*$_2$CH$_2$N), 3.51 (m, 2H, CH$_2$C*H*$_2$N), 4.49 (m, 1H, *CH), 4.58 (s, 2H, C*H*$_2$Ph), 6.21 (br, 1H, N*H*), 7.27 (m, 5H, Ar*H*); ^{13}C NMR (DMSO-d_6, 75.5 MHz, 120 °C) δ (ppm): 18.59(*CHC*H*$_3$), 28.31 (C(*C*H$_3$)$_3$), 28.68(C(*C*H$_3$)$_3$), 34.65 (*C*H$_2$CH$_2$N), 42.97 (CH$_2$*C*H$_2$N), 46.94 (*C*H$_2$Ph), 49.99 (*CH), 78.89 (*C*(CH$_3$)$_3$), 80.69 (*C*(CH$_3$)$_3$), 127.51 (Ar*C*), 127.64 (Ar*C*), 128.83 (Ar*C*), 138.11 (C*ipso*), 155.25 (*C*ONH), 170.67 (*C*O*CH), 173.39 (*C*OCH$_2$); EM (20 eV): *m*/*z* 407 (M$^+$), 350, 294, 277, 206, 178, 144, 91, 88, 57, 44. IR (KBr, cm^{-1}): ν_{max} 3359, 1713, 1641, 1447, 1366, 1150, 1049, 721. Elemental Anal. Calcd for $C_{22}H_{34}O_5N_2$: C, 65.00; H, 8.43; N, 6.89. Found: C, 65.32; H, 8.80; N, 7.10.

*4.2.2. Boc-(S)-Ala-N-Bn-β-Ala-O-t-Bu, (S)-**3a**.* The general procedure was followed with 5.0 g (26.5 mmol) of (*S*)-**1a** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) as eluent to give 8.5 g (79% yield) of (*S*)-**3a** a white solid, mp 82 °C. $[\alpha]_D^{25}$ −13 (*c* 1.0, $CHCl_3$). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**3a**.

*4.2.3. Boc-(R)-Ala-N-Bn-β-Ala-O-t-Bu, (R)-**3a**.* The general procedure was followed with 5.0 g (26.5 mmol) of (*R*)-**1a** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) to give 13.2 g (68% yield) of (*R*)-**3a** as a white solid, mp 82 °C. $[\alpha]_D^{25}$ +13.2 (*c* 1.0, $CHCl_3$). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**3a**.

*4.2.4. Boc-(±)-Val-N-Bn-β-Ala-O-t-Bu, (±)-**3b**.* The general procedure was followed with 1.5 g (6.9 mmol) of (±)-**1b** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) as eluent to give 1.4 (46% yield) of (±)-**3b** as a colorless oil. ^{1}H NMR (DMSO-d_6, 300 MHz, 120 °C) δ (ppm): 0.89 (m, 6H, *CHCH(C*H$_3$)$_2$), 1.39 (s, 9H, C(C*H*$_3$)3), 1.4 (s, 9H, C(C*H*$_3$)$_3$), 2.0 (m, 1H, CHC*H*(CH$_3$)$_2$), 2.47 (m, 2H, C*H*$_2$CH$_2$N), 3.55 (m, 2H, CH$_2$C*H*$_2$N), 4.29 (m, 1H, *CH), 4.54 (d, 1H, *J*=15.9, C*H*$_2$Ph), 4.67 (d, 1H, *J*=15.9, C*H*$_2$Ph), 6.0 (d, 1H, *J*=6.9, N*H*), 7.27 (m, 5H, Ar*H*); ^{13}C NMR (DMSO-d_6, 75.5 MHz, 120 °C) δ (ppm): 18.04(*CHCH(*C*H$_3$)$_2$), 19.74 (*CHCH(*C*H$_3$)$_2$), 28.32 (C(*C*H$_3$)$_3$), 28.63(C(*C*H$_3$)$_3$), 31.06 ((*CHCH(CH$_3$)$_2$), 34.62 (*C*H$_2$CH$_2$N), 42.98 (CH$_2$*C*H$_2$N), 50.26 (*C*H$_2$Ph), 56.23 (*CH), 78.95 (*C*(CH$_3$)), 80.66 (*C*(CH$_3$)), 127.57 (Ar*C*), 127.76 (Ar*C*), 128.81 (Ar*C*), 138.11 (C*ipso*), 155.73 (*C*ONH), 170.70 (*C*O*CH), 172.40 (*C*OCH$_2$). MS (20 eV): *m*/*z* 434 (M$^+$), 322, 234, 207, 178, 172, 116, 91, 72, 56. TOF-MS calculated for $C_{24}H_{39}O_5N_2$: 435.2853; found: 435.2853. IR (KBr, cm^{-1}): ν_{max} 2973, 1714, 1638, 1365, 1243, 1148, 699.

*4.2.5. Boc-(S)-Val-N-Bn-β-Ala-O-t-Bu, (S)-**3b**.* The general procedure was followed with 5.0 g (23.0 mmol) of (*S*)-**1b** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) to afford 4.0 g (40% yield) of (*S*)-**3b** as a colorless oil. $[\alpha]_D^{25}$ −23.0 (*c* 1.0, $CHCl_3$). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**3b**. TOF-MS calculated for $C_{24}H_{39}O_5N_2$: 435.2853; found: 435.2853.

*4.2.6. Boc-(R)-Val-N-Bn-β-Ala-O-t-Bu, (R)-**3b**.* The general procedure was followed with 3.0 g (13.8 mmol) of (*R*)-**1b** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) to give 2.6 g (44% yield) of (*R*)-**3b** as a colorless oil. $[\alpha]_D^{25}$ +23.0 (*c* 1.0, $CHCl_3$). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**3b**.

*4.2.7. Boc-(±)-Leu-N-Bn-β-Ala-O-t-Bu, (±)-**3c**.* The general procedure was followed with 5.0 g (21.7 mmol) of (±)-**1c** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) to give 4.3 g (44% yield) of (±)-**3c** as a white solid, mp 92–94 °C. ^{1}H NMR (DMSO-d_6, 500 MHz, 120 °C) δ (ppm): 0.85 (d, 6H, *J*=5.5, *CHCH$_2$CH(C*H$_3$)$_2$), 1.36 (s, 9H, C(C*H*$_3$)$_3$), 1.38 (s, 9H, C(C*H*$_3$)$_3$), 1.39 (m, 1H, CHCH$_2$C*H*(CH$_3$)$_2$), 1.52 (m, 1H, CHC*H*$_2$CH(CH$_3$)$_2$), 1.64 (m, 1H, CHC*H*$_2$CH(CH$_3$)$_2$), 2.46 (m, 2H, C*H*$_2$CH$_2$N), 3.49 (m, 2H, CH$_2$C*H*$_2$N), 4.45 (m, 1H, *CH), 4.57 (s, 2H, C*H*$_2$Ph), 6.27 (br, 1H, N*H*), 7.25 (m, 5H, Ar*H*); ^{13}C NMR (DMSO-d_6, 125.8 MHz, 120 °C) δ (ppm): 22.02 (*CHCH$_2$CH(*C*H$_3$)$_2$), 23.41 (*CHCH$_2$CH(*C*H$_3$)$_2$), 24.84 (*CHCH$_2$*C*H(CH$_3$)$_2$), 28.32 (C(*C*H$_3$)$_3$), 28.73 (C(*C*H$_3$)$_3$), 34.63 (*C*H$_2$CH$_2$N), 41.85 (*CHC*H$_2$CH(CH$_3$)$_2$), 43.14 (CH$_2$*C*H$_2$N), 48.60 (br, *C*H$_2$Ph), 49.85 (*CH), 78.91 (*C*(CH$_3$)), 80.74 (*C*(CH$_3$)), 127.60 (2×Ar*C*), 128.91 (Ar*C*), 138.22 (C*ipso*), 155.67 (*C*ONH), 170.67 (*C*O*CH), 173.24 (*C*OCH$_2$). MS (20 eV): *m*/*z* 448, 262, 234, 207, 186, 130, 105, 86, 56. IR (KBr, cm^{-1}): ν_{max} 2954, 1731, 1695, 1646, 1365, 1254, 1154, 1043, 699. Elemental Anal. Calcd for $C_{25}H_{40}O_5N_2$: C, 66.94; H, 8.99; N, 6.24. Found: C, 67.14; H, 9.27; N, 6.22.

*4.2.8. Boc-(S)-Leu-N-Bn-β-Ala-O-t-Bu, (S)-**3c**.* The general procedure was followed with 1.5 g (6.5 mmol) of (*S*)-**1c** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) to afford 1.5 g (50% yield) of (*S*)-**3c** as a colorless oil. $[\alpha]_D^{25}$ −29.0 (*c* 1.0, $CHCl_3$). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**3c**. TOF-MS calculated for $C_{25}H_{41}O_5N_2$: 449.3009; found: 449.3017.

*4.2.9. Boc-(R)-Leu-N-Bn-β-Ala-O-t-Bu, (R)-**3c**.* The general procedure was followed with 1.5 g (6.5 mmol) of (*R*)-**1c** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) to afford 1.5 (51% yield) of (*R*)-**3c** as a colorless oil. $[\alpha]_D^{25}$ +30.0 (*c* 1.0, $CHCl_3$). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**3c**. TOF-MS calculated for $C_{25}H_{41}O_5N_2$: 449.3009; found: 449.3008.

*4.2.10. Boc-(S,S)-Ile-N-Bn-β-Ala-O-t-Bu, (S,S)-**3d**.* The general procedure was followed with 2.5 g of (*S*,*S*)-**1d** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) to give 1.3 g (30% yield) of (*S*,*S*)-**3d** as a colorless oil. $[\alpha]_D^{25}$ −33.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 °C) δ (ppm): 0.85 (m, 6H, *CHC*H$_3$, CH$_2$C*H*$_3$), 1.10 (m, 1H, C*H*$_2$CH$_3$), 1.38 (s, 9H, C(C*H*$_3$)$_3$), 1.40 (s, 9H, C(C*H*$_3$)$_3$), 1.53 (m, 1H, C*H*$_2$CH$_3$), 1.79 (m, 1H, *C*H*CH$_3$), 2.46 (m, 2H, C*H*$_2$CH$_2$N), 3.46 (m, 2H, CH$_2$C*H*$_2$N), 4.34 (m, 1H, *CH), 4.56 (d, 1H, *J*=15.9, C*H*$_2$Ph), 4.67 (d, 1H, *J*=15.9, C*H*$_2$Ph), 6.04 (d, 1H, *J*=7.5, N*H*), 7.27 (m, 5H, Ar*H*); ^{13}C NMR (DMSO-d_6, 75.5 MHz, 120 °C) δ (ppm): 11.10 (CH$_2$*C*H$_3$), 15.98 (*CHCH$_3$), 24.46 (*C*H$_2$CH$_3$), 28.31 (C(*C*H$_3$)$_3$), 28.63 (C(*C*H$_3$)$_3$), 34.66 (*C*H$_2$CH$_2$N), 37.47 (*CHCH$_3$), 43.02 (CH$_2$*C*H$_2$N), 50.17 (*C*H$_2$Ph), 55.20 (*CH), 78.95 (*C*(CH$_3$)), 80.67 (*C*(CH$_3$)), 127.56 (Ar*C*), 127.78 (Ar*C*), 128.79 (Ar*C*), 138.13 (C*ipso*), 155.66 (*C*ONH), 170.67 (*C*O*CH),

172.54 ($COCH_2$). TOF-MS calculated for $C_{25}H_{41}O_5N_2$: 449.3009; found: 449.3009.

*4.2.11. Boc-(R,R)-Ile-N-Bn-β-Ala-O-t-Bu, (R,R)-**3d**.* The general procedure was followed with 1.0 g (4.3 mmol) of (*R*,*R*)-**1d** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) to give 0.59 g (31% yield) of (*R*,*R*)-**3d** as a colorless oil. $[\alpha]_D^{25}$ +33.0 (*c* 1.0, $CHCl_3$). ^1H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for(*S*,*S*)-**3d**. TOF-MS calculated for $C_{25}H_{41}O_5N_2$: 449.3009; found: 449.3012.

*4.2.12. Boc-(±)-Phe-N-Bn-β-Ala-O-t-Bu, (±)-**3e**.* The general procedure was followed with 3.0 g (11.3 mmol) of (±)-**1e** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) to afford 3.7 g (68% yield) of (±)-**3e** as a white solid, mp 114–116 °C. ^1H NMR (DMSO-d_6, 300 MHz, 120 °C) δ (ppm): 1.31 (s, 9H, C(CH_3)$_3$), 1.38 (s, 9H, C(CH_3)$_3$), 2.33 (m, 2H, CH_2CH_2N), 2.91 (overlapped with water, 2H, *CHCH_2Ph), 3.45 (m, 2H, CH_2CH_2N), 4.53 (s, 2H, CH_2Ph), 4.68 (m, 1H, *CH), 6.30 (d, 1H, *J*=6, N*H*), 7.22 (m, 10H, Ar*H*); ^{13}C NMR (DMSO-d_6, 75.5 MHz, 120 °C) δ (ppm): 28.28 (C(CH_3)$_3$), 28.55 (C(CH_3)$_3$), 34.54 (CH_2CH_2N), 38.93 (*CHCH_2Ph), 43.04 (CH_2CH_2N), 50.03 (CH_2Ph), 52.60 (*CH), 79.08 (*C*(CH$_3$)), 80.71 (*C*(CH$_3$)), 126.73 (Ar*C*), 127.51 (Ar*C*), 127.64 (Ar*C*), 128.48 (Ar*C*), 128.79 (Ar*C*), 129.67 (Ar*C*), 137.87 (C*ipso*), 137.98 (C*ipso*), 155.24 (*C*ONH), 170.61 (*C*O*CH), 172.63 ($COCH_2$). IR (KBr, cm^{-1}): ν_{max} 2977, 1731, 1648, 1523, 1365, 1250, 1148, 1020, 699. MS (20 eV): *m*/*z* 308 (M^+ [482]−174, 100), 281, 217, 207, 190, 120, 106, 91. Elemental Anal. Calcd for $C_{28}H_{38}O_5N_2$: C, 69.68; H, 7.94; N, 5.80. Found: C, 69.68; H, 7.89; N, 5.80.

*4.2.13. Boc-(S)-Phe-N-Bn-β-Ala-O-t-Bu, (S)-**3e**.* The general procedure was followed with 3.0 g (11.3 mmol) of (*S*)-**1e** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) to give 3.7 g (68% yield) of (±)-**3e** as a colorless oil. $[\alpha]_D^{25}$ −7.4 (*c* 1.0, $CHCl_3$). ^1H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**3e**. TOF-MS calculated for $C_{28}H_{39}O_5N_2$: 483.2853; found: 483.2856.

*4.2.14. Boc-(R)-Phe-N-Bn-β-Ala-O-t-Bu, (R)-**3e**).* The general procedure was followed with 3.0 g (11.3 mmol) of (*R*)-**1e** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) to give 3.4 g (65% yield) of (±)-**3e** as a colorless oil. $[\alpha]_D^{25}$ +7.0 (*c* 1.0, $CHCl_3$). ^1H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**3e**. TOF-MS calculated for $C_{28}H_{39}O_5N_2$: 483.2853; found: 483.2855.

*4.2.15. Boc-(±)-Phg-N-Bn-β-Ala-O-t-Bu, (±)-**3f**.* The general procedure was followed with 3.0 g (11.9 mmol) of (±)-**1f** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) to afford 3.5 g (63% yield) of (±)-**3f** as a colorless oil. ^1H NMR (DMSO-d_6, 300 MHz, 120 °C) δ (ppm): 1.37 (s, 18H, C(CH_3)$_3$), 2.46 (m, 2H, CH_2CH_2N), 3.37 (m, 1H, CH_2CH_2N), 3.55 (m, 1H, CH_2CH_2N), 4.47 (d, 1H, *J*=15.8, CH_2Ph), 4.63 (d, 1H, *J*=15.8, CH_2Ph), 5.5 (d, 1H, *J*=8.1, *CH), 6.4 (d, 1H, *J*=6, N*H*), 7.29 (m, 10H, Ar*H*); ^{13}C NMR (DMSO-d_6, 75.5 MHz, 120 °C) δ (ppm): 28.27 (C(CH_3)$_3$), 28.61 (C(CH_3)$_3$), 34.33 (CH_2CH_2N), 43.04 (CH_2CH_2N), 50.10 (CH_2Ph), 55.90 (*CH), 79.32 (*C*(CH$_3$)), 80.78 (*C*(CH$_3$)), 127.65 (2×Ar*C*), 128.15 (Ar*C*), 128.28 (Ar*C*), 128.79 (Ar*C*), 128.93 (Ar*C*), 137.56 (C*ipso*), 138.43 (C*ipso*), 154.98 (*C*ONH), 170.49 (*C*O*CH), 170.76 ($COCH_2$). IR (KBr, cm^{-1}): ν_{max} 2976, 1712, 1645, 1365, 1246, 1149, 1045, 698. MS (20 eV): *m*/*z* 468, 429, 295, 281, 266, 207, 178, 106, 91. TOF-MS calculated for $C_{27}H_{37}O_5N_2$: 469.2696; found: 469.2700.

*4.2.16. Boc-(S)-Phg-N-Bn-β-Ala-O-t-Bu, (S)-**3f**.* The general procedure was followed with 3.0 g (11.9 mmol) of (*S*)-**1f** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) to give 3.3 g (60% yield) of (*S*)-**3f** as a colorless oil. $[\alpha]_D^{25}$ +35.6 (*c* 1.0, $CHCl_3$). ^1H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**3f**. TOF-MS calculated for $C_{27}H_{37}O_5N_2$: 469.2696; found: 469.2698.

*4.2.17. Boc-(R)-Phg-N-Bn-β-Ala-O-t-Bu, (R)-**3f**.* The general procedure was followed with 3.0 g (11.9 mmol) of (*R*)-**1f** and the crude product was purified by flash chromatography using hexane/EtOAc (80:20) to afford 3.3 g (60% yield) of (*R*)-**3f** as a colorless oil. $[\alpha]_D^{25}$ −37.5 (*c* 1.0, $CHCl_3$). ^1H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**3f**. TOF-MS calculated for $C_{27}H_{37}O_5N_2$: 469.2701; found: 469.2698.

*4.2.18. Boc-(S)-Tle-N-Bn-β-Ala-O-t-Bu, (S)-**3g**.* A solution of *N*-α-protected amino acid **1g** (0.1 g, 0.43 mmol), DIPEA (0.09 mL, 0.52 mmol), HOBt (0.06 g, 0.39 mmol), HBTU (0.15 g, 0.39 mmol) in anhydrous THF (5 mL) was stirred at room temperature under nitrogen atmosphere. After 1 h of stirring, a solution of *N*-benzyl-*tert*-butyl-β-aminoesters **2** (0.20 g, 0.86 mmol) and DIPEA (0.30 mL, 1.7 mmol) in anhydrous THF (5 mL) was added. The mixture was stirred for 18 h at room temperature. The solvent was removed under vacuum and ethyl acetate (15 mL) was added to the residue. The resulting solution was washed sequentially with water, 1 N HCl, water, saturated solution of $NaHCO_3$, and water. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography using hexane/EtOAc (9:1) to give 0.078 g (40% yield) of a colorless oil. $[\alpha]_D^{25}$ −54 (c 1.0, $CHCl_3$). ^1H NMR (DMSO-d_6, 500 MHz, 90 °C) δ (ppm): 0.92 (m, 9H, *CHC(CH_3)$_3$), 1.37 (s, 18H, C(CH_3)$_3$), 2.47 (m, 2H, CH_2CH_2N), 3.63 (m, 2H, CH_2CH_2N), 4.70 (m, 3H, *C*H*, CH_2Ph), 6.02 (br, 1H, N*H*), 7.22 (m, 5H, Ar*H*); ^{13}C NMR (DMSO-d_6, 125.8 MHz, 90 °C) δ (ppm): 26.87 (*CHC(CH_3)$_3$), 28.32 (C(CH_3)$_3$), 28.61 (C(CH_3)$_3$), 33.82 (CH_2CH_2N), 35.51 ((*CHC(CH_3)$_3$), 43.12 (CH_2CH_2N), 50.52 (CH_2Ph), 56.70 (*CH), 79.04 (*C*(CH$_3$)), 80.66 (*C*(CH$_3$)), 127.70 (Ar*C*), 127.86 (Ar*C*), 128.92 (Ar*C*), 138.63 (*Cipso*), 155.73 (*C*ONH), 170.82 (*C*O*CH), 171.93 ($COCH_2$). TOF-MS calculated for $C_{25}H_{40}O_5N_2H$: 449.3009; found: 449.3015. IR (neat, cm^{-1}): ν_{max} 2976, 1714, 1638, 1495, 1365, 1148, 845, 700, 660.

4.3. General procedure for the removal of the *N*-protecting group and hydrolysis of the *tert*-butyl ester function

The protected linear dipeptides **3a**–**f** (3.8 mmol) were treated with trifluoroacetic acid (0.4 mL/mmol) in DCM (0.4 mL/mmol) at ambient temperature for 2 h. The resulting mixture was concentrated under vacuum and the corresponding trifluoroacetate salts **4a**–**f** were dried under high vacuum.

*4.3.1. (±)-Ala-N-Bn-β-Ala·TFA, (±)-**4a**.* The general procedure was followed with 8.0 g (19.7 mmol) of (±)-**3a** to afford the desired product (±)-**4a** as a brownish oil in quantitative yield (7.2 g). ^1H NMR (DMSO-d_6, 500 MHz, 120 °C) δ (ppm): 1.38 (d, 3H, *J*=4.8, *CHCH_3), 2.50 (m, 2H, CH_2CH_2N), 3.44 (br, 1H, CH_2CH_2N), 3.61 (m, 1H, CH_2CH_2N), 4.39 (br, 1H, *CH), 4.51 (d, 1H, *J*=15.55, CH_2Ph), 4.69 (d, 1H, *J*=15.85, CH_2Ph), 7.27 (m, 5H, Ar*H*); ^{13}C NMR (DMSO-d_6, 125.8 MHz, 120 °C) δ (ppm): 17.19 (*CHCH_3), 32.68 (CH_2CH_2N), 42.97 (CH_2CH_2N), 46.99 (CH_2Ph), 50.70 (*CH), 127.86 (Ar*C*), 128.26 (Ar*C*), 129.02 (Ar*C*), 137.50 (C*ipso*), 170.51 (*C*O*CH), 172.52 ($COCH_2$). IR (KBr, cm^{-1}): ν_{max} 2990, 1718, 1667, 1530, 1498, 1184, 1139, 799, 731, 698. MS (20 eV): *m*/*z* 232 (M^+ [250]−18, 100), 204, 190, 154, 141, 133, 91, 56. TOF-MS calculated for $C_{13}H_{19}O_3N_2$: 251.1390; found: 251.1390.

*4.3.2. (S)-Ala-N-Bn-β-Ala·TFA, (S)-**4a**.* The general procedure was followed with 8.0 g (19.7 mmol) of (*S*)-**3a** to afford the desired product (*S*)-**4a** as a brownish oil in quantitative yield (7.2 g). $[\alpha]_D^{25}$

−15.0 (*c* 1.0, MeOH). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**4a**. TOF-MS calculated for $C_{13}H_{19}O_3N_2$: 251.1390; found: 251.1392.

*4.3.3. (R)-Ala-N-Bn-β-Ala·TFA, (R)-**4a**.* The general procedure was followed with 7.0 g (17.2 mmol) of (*R*)-**3a** to afford the desired product (*R*)-**4a** as a brownish oil in quantitative yield (6.3 g). $[\alpha]_D^{25}$ +15.2 (*c* 1.0, MeOH). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**4a**. TOF-MS calculated for $C_{13}H_{19}O_3N_2$: 251.1390; found: 251.1394.

*4.3.4. (±)-Val-N-Bn-β-Ala·TFA, (±)-**4b**.* The general procedure was followed with 1.2 g (2.8 mmol) of (±)-**3b** to afford the desired product (±)-**4a** as a brownish oil in quantitative yield (1.1 g). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 °C) δ (ppm): 0.98 (m, 6H, *CHCH(CH_3)$_2$), 2.13 (m, 1H, CHCH(CH$_3$)$_2$), 2.50 (m, 2H, CH_2CH$_2$N), 3.69 (m, 2H, CH$_2$CH_2N), 4.19 (s, 1H, *CH), 4.47 (d, 1H, *J*=15, CH_2Ph), 4.79 (d, 1H, *J*=15, CH_2Ph), 7.31 (m, 5H, ArH); ^{13}C NMR (DMSO-d_6, 75.5 MHz, 120 °C) δ (ppm): 17.20 (*CHCH(CH_3)$_2$), 19.06 (*CHCH(CH_3)$_2$), 32.80 ((*CHCH(CH$_3$)$_2$), 35.37 (CH_2CH$_2$N), 42.90 (CH$_2$CH_2N), 50.42 (CH_2Ph), 55.35 (*CH), 127.55 (Ar*C*), 128.17 (Ar*C*), 128.90 (Ar*C*), 138.44 (C*ipso*), 171.49 (*C*O*CH), 172.46 (*C*OCH$_2$). IR (KBr, cm^{-1}): ν_{max} 3098, 1651, 1453, 1194, 1134, 797, 719. MS (20 eV): *m*/*z* 279, 223, 195, 176, 159, 120, 91, 72, 54. TOF-MS calculated for $C_{15}H_{23}O_3N_2$: 279.1703; found: 279.1704.

*4.3.5. (S)-Val-N-Bn-β-Ala·TFA, (S)-**4b**.* The general procedure was followed with 2.8 g (6.4 mmol) of (*S*)-**3b** to afford the desired product (*S*)-**4a** as a brownish oil in quantitative yield (2.5 g). $[\alpha]_D^{25}$ −4.3 (*c* 1.0, MeOH). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**4b**. TOF-MS calculated for $C_{15}H_{23}O_3N_2$: 279.1703; found: 279.1709.

*4.3.6. (R)-Val-N-Bn-β-Ala·TFA, (R)-**4b**.* The general procedure was followed with 2.0 g (4.6 mmol) of (*R*)-**3b** to afford the desired product (*R*)-**4a** as a brownish oil in quantitative yield (1.8 g). $[\alpha]_D^{25}$ +4.0 (*c* 1.0, MeOH). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**4b**). TOF-MS calculated for $C_{15}H_{23}O_3N_2$: 279.1703; found: 279.1709.

*4.3.7. (±)-Leu-N-Bn-β-Ala·TFA, (±)-**4c**).* The general procedure was followed with 3.0 g (6.7 mmol) of (±)-**3c** to afford the desired product (±)-**4c** as a brownish oil in quantitative yield (2.7 g). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 °C) δ (ppm): 0.89 (d, 6H, *J*=6, *CHCH$_2$CH(CH_3)$_2$), 1.55 (m, 1H, CHCH$_2$CH(CH$_3$)$_2$), 1.72 (m, 2H, CHCH_2CH(CH$_3$)$_2$), 2.51 (m, 2H, CH_2CH$_2$N), 3.59 (m, 2H, CH$_2$CH_2N), 4.34 (m, 1H, *CH), 4.52 (d, 1H, *J*=15.9, CH_2Ph), 4.68 (d, 1H, *J*=15.9, CH_2Ph), 7.31 (m, 5H, ArH); ^{13}C NMR (DMSO-d_6, 75.5 MHz, 120 °C) δ (ppm): 21.84 (*CHCH$_2$CH(CH_3)$_2$), 23.27 (*CHCH$_2$CH(CH_3)$_2$), 24.02 (*CHCH$_2$CH(CH$_3$)$_2$), 33.11 (CH_2CH$_2$N), 35.38 (*CHCH_2CH(CH$_3$)$_2$), 40.85 (CH$_2$CH_2N), 43.11 (CH_2Ph), 49.50 (*CH), 127.87 (Ar*C*), 128.83 (Ar*C*), 128.98 (Ar*C*), 137.23 (C*ipso*), 170.11 (*C*O*CH), 172.40 (*C*OCH$_2$). MS (20 eV): *m*/*z* 274 (M$^+$ [292]−18, 100), 246, 230, 218, 190, 183, 133, 106, 86. IR (KBr, cm^{-1}): ν_{max} 2960, 1657, 1453, 1182, 1132, 798, 721, 698. TOF-MS calculated for $C_{16}H_{25}O_3N_2$: 293.1859; found: 293.1863.

*4.3.8. (S)-Leu-N-Bn-β-Ala·TFA, (S)-**4c**).* The general procedure was followed with 2.0 g (4.5 mmol) of (*S*)-**3c** to afford the desired product (*S*)-**4c** as a brownish oil in quantitative yield (1.8 g). $[\alpha]_D^{25}$ −13.0 (*c* 1.0, MeOH). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**4c**. TOF-MS calculated for $C_{16}H_{25}O_3N_2$: 293.1859; found: 293.1860.

*4.3.9. (R)-Leu-N-Bn-β-Ala·TFA, (R)-**4c**.* The general procedure was followed with 1.3 g (2.9 mmol) of (*R*)-**3c** to afford the desired product (*R*)-**4c** as a brownish oil in quantitative yield (1.2 g). $[\alpha]_D^{25}$ +11.5 (*c* 1.0, MeOH). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**4c**. TOF-MS calculated for $C_{16}H_{25}O_3N_2$: 293.1859. Found: 293.1863.

*4.3.10. (S,S)-Ile-N-Bn-β-Ala·TFA, (S,S)-**4d**.* The general procedure was followed with 1.2 g (2.7 mmol) of (*S*,*S*)-**3d** to afford the desired product (*S*,*S*)-**4d** as a brownish oil in quantitative yield (1.1 g). $[\alpha]_D^{25}$ −6.0 (*c* 1.0, MeOH). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 °C) δ (ppm): 0.87 (m, 3H, CH$_2$CH_3), 0.98 (d, 1H, *J*=6.9, *CHCH_3), 1.21 (m, 1H, CH_2CH$_3$), 1.53 (m, 1H, CH_2CH$_3$), 1.87 (m, 1H, *CHCH$_3$), 2.53 (m, 2H, CH_2CH$_2$N), 3.42 (m, 1H, CH$_2$CH_2N), 3.71 (m, 1H, CH$_2$CH_2N), 4.23 (m, 1H, *CH), 4.48 (m, 1H, CH_2Ph), 4.79 (d, 1H, *J*=15.9, CH_2Ph), 6.04 (br, 2H, NH_2), 7.32 (m, 5H, ArH); ^{13}C NMR (DMSO-d_6, 75.5 MHz, 120 °C) δ (ppm): 11.36 (CH$_2$CH_3), 15.31 (*CHCH_3), 23.74 (CH_2CH$_3$), 32.94 (CH_2CH$_2$N), 36.89 (*CHCH$_3$), 43.15 (CH$_2$CH_2N), 50.47 (CH_2Ph), 54.88 (*CH), 127.92 (Ar*C*), 128.16 (Ar*C*), 128.92 (Ar*C*), 137.31 (C*ipso*), 169.16 (*C*O*CH), 172.44 (*C*OCH$_2$). TOF-MS calculated for $C_{16}H_{25}O_3N_2$: 293.1859; found: 293.1860.

*4.3.11. (R,R)-Ile-N-Bn-β-Ala·TFA, (R,R)-**4d**.* The general procedure was followed with 0.484 g (1.1 mmol) of (*R*,*R*)-**3d** to afford the desired product (*R*,*R*)-**4d** as a brownish oil in quantitative yield (0.44 g). $[\alpha]_D^{25}$ +6.2 (*c* 1.0, MeOH). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (*S*,*S*)-**4d**. TOF-MS calculated for $C_{16}H_{25}O_3N_2$: 293.1859; found: 293.1860.

*4.3.12. (±)-Phe-N-Bn-β-Ala·TFA, (±)-**4e**.* The general procedure was followed with 3.0 g (6.2 mmol) of (±)-**3e** to afford the desired product (±)-**4e** as a brownish oil in quantitative yield (2.7 g). ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 2.45 (m, 2H, CH_2CH$_2$N), 3.33 (m, 1H, *CHCH_2Ph), 3.55 (m, 1H, *CHCH_2Ph), 4.02 (m, 1H, CH$_2$CH_2N), 4.29 (m, 1H, CH$_2$CH_2N), 4.48 (m, 1H, *CH), 4.57 (m, 2H, CH_2Ph), 7.24 (m, 10H, ArH), 8.30 (br, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 125.8 MHz) δ (ppm): 32.35 (CH_2CH$_2$N), 37.80 (*CHCH$_2$Ph), 42.31 (CH$_2$CH_2N), 48.13 (CH_2Ph), 50.77 (*CH), 127.87 (Ar*C*), 128.13 (Ar*C*), 128.39 (Ar*C*), 128.90 (Ar*C*), 129.16 (Ar*C*), 130.19 (Ar*C*), 134.84 (C*ipso*), 137.00 (C*ipso*), 169.10 (*C*O*CH), 172.98 (*C*OCH$_2$). IR (KBr, cm^{-1}): ν_{max} 3031, 1650, 1496, 1454, 1184, 1133, 721, 698. MS (20 eV): *m*/*z* 308, 281, 217, 207, 190, 120, 106, 91. TOF-MS calculated for $C_{19}H_{23}O_3N_2$: 327.1703; found: 327.1707.

*4.3.13. (S)-Phe-N-Bn-β-Ala·TFA, (S)-**4e**.* The general procedure was followed with 2.6 g (5.4 mmol) of (*S*)-**3e** to afford the desired product (*S*)-**4e** as a brownish oil in quantitative yield (2.4 g). $[\alpha]_D^{25}$ +19.4 (*c* 1.0, MeOH). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**4e**. TOF-MS calculated for $C_{19}H_{23}O_3N_2$: 327.1703; found: 327.1704.

*4.3.14. (R)-Phe-N-Bn-β-Ala·TFA, (R)-**4e**.* The general procedure was followed with 2.5 g (5.2 mmol) of (*R*)-**3e** to afford the desired product (*R*)-**4e** as a brownish oil in quantitative yield (2.3 g). $[\alpha]_D^{25}$ −17.0 (*c* 1.0, MeOH). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**4e**. TOF-MS calculated for $C_{19}H_{23}O_3N_2$: 327.1703; found: 327.1704.

*4.3.15. (±)-Phg-N-Bn-β-Ala·TFA, (±)-**4f**).* The general procedure was followed with 2.5 g (5.3 mmol) of (±)-**3f** to afford the desired product (±)-**4f** as a brownish oil in quantitative yield (2.3 g). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 °C) δ (ppm): 2.43 (m, 2H, CH_2CH$_2$N), 3.33 (m, 1H, CH$_2$CH_2N), 3.55 (m, 1H, CH$_2$CH_2N), 4.48 (m, 2H, CH_2Ph), 4.57 (m, 1H, *CH), 5.46 (s, 2H, NH_2), 7.44 (m, 10H, ArH); ^{13}C NMR (DMSO-d_6, 75.5 MHz, 120 °C) δ (ppm): 32.72 (CH_2CH$_2$N), 42.87 (CH$_2$CH_2N), 50.22 (CH_2Ph), 55.09 (*CH), 127.84 (Ar*C*), 128.83 (Ar*C*), 129.09 (Ar*C*), 129.58 (Ar*C*), 130.17 (Ar*C*), 133.16 (C*ipso*), 136.88 (C*ipso*), 167.93 (*C*O*CH), 172.28 (*C*OCH$_2$). IR (KBr, cm^{-1}): ν_{max} 3067,

1650, 1178, 1131, 720, 696. MS (20 eV): *m*/*z* 294, 266, 203, 189, 133, 106, 91, 57. TOF-MS calculated for $C_{18}H_{21}O_3N_2$: 313.1546; found: 313.1552.

*4.3.16. (S)-Phg-N-Bn-β-Ala·TFA, (S)-**4f**.* The general procedure was followed with 2.0 g (4.3 mmol) of (*S*)-**3f** to afford the desired product (*S*)-**4f** as a brownish oil in quantitative yield (1.8 g). $[\alpha]_D^{25}$ +21.0 (*c* 1.0, MeOH). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**4f**. TOF-MS calculated for $C_{18}H_{21}O_3N_2$: 313.1546; found: 313.1549.

*4.3.17. (R)-Phg-N-Bn-β-Ala·TFA, (R)-**4f**.* The general procedure was followed with 2.2 g (4.7 mmol) of (*R*)-**3f** to afford the desired product (*R*)-**4f** as a brownish oil in quantitative yield (2.0 g). $[\alpha]_D^{25}$ −20.0 (*c* 1.0, MeOH). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**4f**. TOF-MS calculated for $C_{18}H_{21}O_3N_2$: 313.1546; found: 313.1552.

4.4. Cyclization reaction—general procedure

In a flask provided with magnetic stirrer and condenser were placed the linear precursors **4a**–**f** in a concentration 0.01 M in toluene (1.1 mmol/108 mL) and triethylamine (3.23 mmol) and the resulting mixture was heated to reflux for 3 h. The reaction mixture was left stirring at room temperature for 1 h and was then treated with phenylphosphonic dichloride (1.61 mmol). The resulting mixture was heated to reflux for 18 h, the solvent was then removed in a rotary evaporator and the residue was dissolved in ethyl acetate (50 mL). The solid residues were filtered and the solution was concentrated under vacuum. The residue was purified on a silica gel column (EtOAc or CH_2Cl_2/MeOH, 98:2).

*4.4.1. (±)-1-Benzyl-3-methyl-1,4-diazepine-2,5-dione, (±)-**5a**.* The general procedure was followed with 0.7 g (1.9 mmol) of (±)-**4a** and the crude product was purified by flash chromatography using CH_2Cl_2/MeOH (98:2) as eluent, to give 0.37 g (82% yield) of the desired (±)-**5a** as a white solid, mp 173 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.43 (d, 3H, *J*=6.6, *CH*CH*$_3$*), 2.42 (ddd, 1H, *J*=5.3, 5.3, 12.9, C*H*$_2$CH$_2$N), 2.55 (m, 1H, C*H*$_2$CH$_2$N), 3.24 (ddd, 1H, *J*=3.4, 5.3, 10.4, CH$_2$C*H*$_2$N), 3.87 (ddd, 1H, *J*=3, 3.2, 12.9, CH$_2$C*H*$_2$N), 4.47 (m, 1H, *CH), 4.59 (d, 1H, *J*=14.6, C*H*$_2$Ph), 4.67 (d, 1H, *J*=14.6, C*H*$_2$Ph), 6.21 (br, 1H, N*H*), 7.27 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ (ppm): 16.97 (*CH*CH$_3$), 34.97 (*C*H$_2$CH$_2$N), 42.05 (CH$_2$*C*H$_2$N), 48.48 (*CH), 50.49 (*C*H$_2$Ph), 128.03 (Ar*C*), 128.35 (Ar*C*), 128.98 (Ar*C*), 136.83 (C*ipso*), 170.69 (*C*O*CH), 171.55 (*C*OCH$_2$). IR (KBr, cm^{-1}): ν_{max} 2931, 1649, 1440, 1393, 1210, 1080, 707. MS (20 eV): *m*/*z* 232 (M^+), 189, 141, 133, 118, 98, 91, 70, 44. Elemental Anal. Calcd for $C_{13}H_{16}O_2N_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.94; H, 7.18; N, 11.88.

*4.4.2. 1-Benzyl-3(S)-methyl-1,4-diazepine-2,5-dione, (S)-**5a**.* The general procedure was followed with 1.9 g (5.2 mmol) of (*S*)-**4a** and the crude product was purified by flash chromatography using CH_2Cl_2/MeOH (98:2) as eluent, to give 0.86 g (72% yield) of the desired (*S*)-**5a** as a white solid, mp 160–161 °C. $[\alpha]_D^{25}$ −4.2 (*c* 1.0, $CHCl_3$). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**5a**. Elemental Anal. Calcd for $C_{13}H_{16}O_2N_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.04; H, 7.23; N, 11.91.

*4.4.3. 1-Benzyl-3(R)-methyl-1,4-diazepine-2,5-dione, (R)-**5a**.* The general procedure was followed with 1.7 g (4.7 mmol) of (*R*)-**4a** and the crude product was purified by flash chromatography using CH_2Cl_2/MeOH (98:2) as eluent, to give 0.77 g (70% yield) of the desired (*R*)-**5a** as a white solid, mp 160–162 °C. $[\alpha]_D^{25}$ +4.4 (*c* 1.0, $CHCl_3$). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**5a**. Elemental Anal. Calcd for $C_{13}H_{16}O_2N_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.04; H, 7.23; N, 11.91.

*4.4.4. 1-Benzyl-3-isopropyl-1,4-diazepine-2,5-dione, (±)-**5b**.* The general procedure was followed with 0.94 g (2.4 mmol) of (±)-**4a** and the crude product was purified by flash chromatography using AcOEt to give 0.44 g (70% yield) of the desired (±)-**5a** as a white solid, mp 154–155 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.07 (d, 3H, *J*=6.7, *CHCH(C*H*$_3$)$_2$), 1.09 (d, 3H, *J*=6.7, *CHCH(C*H*$_3$)$_2$), 2.31 (ddd, 1H, *J*=6.8, 7.5, 13.5, CHC*H*(CH$_3$)$_2$), 2.45 (ddd, 1H, *J*=5.8, 5.9, 12, C*H*$_2$CH$_2$N), 2.56 (m, 1H, C*H*$_2$CH$_2$N), 3.28 (ddd, 1H, *J*=4.4, 5.4, 10.5, CH$_2$C*H*$_2$N), 3.80 (ddd, 1H, *J*=3.8, 3.9, 11.8, CH$_2$C*H*$_2$N), 3.96 (dd, 1H, *J*=4.1, 7.7, *CH), 4.59 (d, 1H, *J*=14.7, C*H*$_2$Ph), 4.66 (d, 1H, *J*=14.7, C*H*$_2$Ph), 5.97 (d, 1H, *J*=3.15, N*H*), 7.28 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ (ppm): 18.41 (*CHCH(*C*H$_3$)$_2$), 20.38 (*CHCH(*C*H$_3$)$_2$), 28.98 ((*CHC*H(CH$_3$)$_2$), 34.87 (*C*H$_2$CH$_2$N), 42.09 (CH$_2$*C*H$_2$N), 50.36 (*C*H$_2$Ph), 58.90 (*CH), 128.00 (Ar*C*), 128.31 (Ar*C*), 128.99 (Ar*C*), 136.95 (C*ipso*), 170.10 (*C*O*CH), 171.63 (*C*OCH$_2$). IR (KBr, cm^{-1}): ν_{max} 2912, 1655, 1387, 1207, 1154, 785, 696, 652. MS (20 eV): *m*/*z* 260 (M^+), 218, 190, 188, 169, 133, 73. Elemental Anal. Calcd for $C_{15}H_{20}O_2N_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.00; H, 7.74; N, 10.55.

*4.4.5. 1-Benzyl-3(S)-isopropyl-1,4-diazepine-2,5-dione, (S)-**5b**.* The general procedure was followed with 2.5 g (6.4 mmol) of (*S*)-**4b** and the crude product was purified by flash chromatography using EtOAc to give 1.25 g (77% yield) of the desired (*S*)-**5b** as a white solid, mp 151–152 °C. $[\alpha]_D^{25}$ −5.3 (*c* 1.0, $CHCl_3$). ^{1}H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**5b**. Elemental Anal. Calcd for $C_{15}H_{20}O_2N_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.00; H, 7.74; N, 10.55.

*4.4.6. 1-Benzyl-3(R)-isopropyl-1,4-diazepine-2,5-dione, (R)-**5b**.* The general procedure was followed with 2.1 g (5.4 mmol) of (*R*)-**4b** and the crude product was purified by flash chromatography using EtOAc to give 0.72 g (60% yield) of the desired (*R*)-**5b** as a white solid, mp 153 °C. $[\alpha]_D^{25}$ +5.0 (*c* 1.0, $CHCl_3$). ^{1}H, ^{13}C NMR spectra, and mass spectra were identical with those recorded for (**5b**). Elemental Anal. Calcd for $C_{15}H_{20}O_2N_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.25; H, 8.10; N, 10.96.

*4.4.7. (±)-1-Benzyl-3-isobutyl-1,4-diazepine-2,5-dione, (±)-**5c**.* The general procedure was followed with 2.3 g (5.7 mmol) of (±)-**4a** and the crude product was purified by flash chromatography using AcOEt to give 0.75 g (50% yield) of the desired (±)-**5a** as a white solid, mp 146–147 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.95 (d, 3H, *J*=6.5, *CHCH$_2$CH(C*H*$_3$)$_2$), 0.96 (d, 3H, *J*=6.5, *CHCH$_2$CH(C*H*$_3$)$_2$), 1.53 (m, 1H, CHCH$_2$C*H*(CH$_3$)$_2$), 1.75 (m, 1H, CHC*H*$_2$CH(CH$_3$)$_2$), 1.92 (m, 1H, CHC*H*$_2$CH(CH$_3$)$_2$), 2.42 (ddd, 1H, *J*=5.4, 5.5, 12.8, C*H*$_2$CH$_2$N), 2.57 (m, 1H, C*H*$_2$CH$_2$N), 3.26 (ddd, 1H, *J*=3.3, 5.5, 10.4, CH$_2$C*H*$_2$N), 3.91 (ddd, 1H, *J*=3.0, 3.2, 12.8, CH$_2$C*H*$_2$N), 4.36 (m, 1H, *CH), 4.61 (d, 1H, *J*=14.6, C*H*$_2$Ph), 4.65 (d, 1H, *J*=14.6, C*H*$_2$Ph), 5.85 (s, 1H, N*H*), 7.31 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ (ppm): 22.12 (*CHCH$_2$CH(*C*H$_3$)$_2$), 23.02 (*CHCH$_2$CH(*C*H$_3$)$_2$), 24.62 (*CHCH$_2$*C*H(CH$_3$)$_2$), 34.93 (*C*H$_2$CH$_2$N), 39.87 (*CHCH$_2$CH(CH$_3$)$_2$), 42.11 (CH$_2$*C*H$_2$N), 50.45 (*C*H$_2$Ph), 50.63 (*CH), 128.05 (Ar*C*), 128.35 (Ar*C*), 129.01 (Ar*C*), 136.89 (C*ipso*), 170.52 (*C*O*CH), 171.44 (*C*OCH$_2$). IR (KBr, cm^{-1}): ν_{max} 2951, 1655, 1434, 1391, 1202, 747, 701, 647. MS (20 eV): *m*/*z* 274 (M^+), 232, 218, 190, 188, 133, 86. Elemental Anal. Calcd for $C_{16}H_{22}O_2N_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.37; H, 8.29; N, 10.32.

*4.4.8. 1-Benzyl-3(S)-isobutyl-1,4-diazepine-2,5-dione, (S)-**5c**.* The general procedure was followed with 1.1 g (2.7 mmol) of (*S*)-**4c** and the crude product was purified by flash chromatography using

AcOEt to give 0.689 g (90% yield) of the desired (*S*)-**5c** as a white solid, mp 124–126 °C. $[\alpha]_D^{25}$ −7.6 (*c* 1.0, $CHCl_3$). ^1H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**5c**. Elemental Anal. Calcd for $C_{16}H_{22}O_2N_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.37; H, 8.29; N, 10.32.

*4.4.9. 1-Benzyl-3(R)-isobutyl-1,4-diazepine-2,5-dione, (R)-**5c**.* The general procedure was followed with 1.1 g (2.7 mmol) of (*R*)-**4c** and the crude product was purified by flash chromatography using AcOEt to give 0.689 g (90%% yield) of the desired (*S*)-**5c** as a white solid, mp 126–128 °C. $[\alpha]_D^{25}$ +7.5 (*c* 1.0, $CHCl_3$). ^1H and ^{13}C NMR spectra, and mass spectra were identical with those recorded for (±)-**5c**. Elemental Anal. Calcd for $C_{16}H_{22}O_2N_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.20; H, 8.28; N, 10.43.

*4.4.10. 1-Benzyl-3(S)-[1(S)-methylpropyl]-1,4-diazepine-2,5-dione, (S,S)-**5d**.* The general procedure was followed with 0.99 g (2.4 mmol) of (*S*,*S*)-**4d** and the crude product was purified by flash chromatography using EtOAc to give 0.52 g (78% yield) of the desired (*S*,*S*)-**5d** as a white solid, mp 110 °C. $[\alpha]_D^{25}$ −9.7 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.95 (t, 3H, *J*=7.3, 14.7, CH_2CH_3), 1.04 (d, 1H, *J*=6.8, *CHCH_3), 1.21 (m, 1H, CH_2CH_3), 1.71 (m, 1H, CH_2CH_3), 2.05 (m, 1H, *CHCH$_3$), 2.46 (ddd, 1H, *J*=5.8, 6.2, 11.6, CH_2CH_2N), 2.56 (m, 1H, CH_2CH_2N), 3.31 (m, 1H, CH_2CH_2N), 3.77 (ddd, 1H, *J*=4, 11.5, CH_2CH_2N), 4.05 (dd, 1H, *J*=3.9, 7.8, *CH), 4.56 (d, 1H, *J*=14.7, CH_2Ph), 4.67 (d, 1H, *J*=14.6, CH_2Ph), 6.16 (br, 1H, NH), 7.30 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ (ppm): 11.02 (CH_2CH_3), 16.32 (*CHCH$_3$), 24.92 (CH_2CH_3), 34.74 (CH_2CH_2N), 35.42 (*CHCH$_3$), 41.98 (CH_2CH_2N), 50.37 (CH_2Ph), 58.00 (*CH), 128.00 (ArC), 128.29 (ArC), 128.99 (ArC), 136.89 (Cipso), 170.07 (CO*CH), 171.50 ($COCH_2$). Elemental Anal. Calcd for $C_{16}H_{22}O_2N_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.90; H, 8.49; N, 10.57.

*4.4.11. 1-Benzyl-3(R)-[1(R)-methylpropyl]-1,4-diazepine-2,5-dione (R,R)-**5d**.* The general procedure was followed with 0.44 g (1.1 mmol) of (*R*,*R*)-**4d** and the crude product was purified by flash chromatography using EtOAc to give 0.177 g (60% yield) of the desired (*R*,*R*)-**5d** as a white solid, mp 111 °C. $[\alpha]_D^{25}$ +8.0 (*c* 1.0, $CHCl_3$). ^1H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (*S*,*S*)-**5d**. Elemental Anal. Calcd for $C_{16}H_{22}O_2N_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.90; H, 8.07; N, 10.53.

*4.4.12. (±)-1-Benzyl-3-benzyl-1,4-diazepine-2,5-dione, (±)-**5e**.* The general procedure was followed with 2.7 g (6.1 mmol) of (±)-**4e** and the crude product was purified by flash chromatography using EtOAc to give 0.756 g (40% yield) of the desired (±)-**5e** as a white solid, mp 114–115 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 2.40 (ddd, 1H, *J*=5.2, 5.2, 12.9, CH_2CH_2N), 2.49 (ddd, 1H, *J*=3.3, 6.6, 11.7, CH_2CH_2N), 2.92 (dd, 1H, *J*=5, 14, *CHCH_2Ph), 3.25 (ddd, 1H, *J*=3.4, 5.2, 10.7, CH_2CH_2N), 3.42 (dd, 1H, *J*=5, 14.6, *CHCH_2Ph), 3.88 (ddd, 1H, *J*=3.0, 3.1, 12.8, CH_2CH_2N), 4.59 (ddd, 1H, *J*=2.8, 4.3, 5.3, *CH), 4.66 (s, 2H, CH_2Ph), 5.83 (br, 1H, NH), 7.32 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ (ppm): 35.07 (CH_2CH_2N), 37.10 (*CHCH_2Ph), 42.01 (CH_2CH_2N), 50.59 (CH_2Ph), 53.96 (*CH), 127.46 (ArC), 128.12 (ArC), 128.40 (ArC), 129.03 (ArC), 129.19 (ArC), 129.36 (ArC), 136.29 (Cipso), 136.72 (Cipso), 169.98 (CO*CH), 171.23 ($COCH_2$). IR (KBr, cm^{-1}): ν_{max} 3300, 1646, 1494, 1382, 1353, 755, 704. MS (20 eV): *m*/*z* 308 (M^+), 217, 207, 190, 120, 91, 84. Elemental Anal. Calcd for $C_{19}H_{20}O_2N_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.34; H, 6.78; N, 9.30.

*4.4.13. 1-Benzyl-3(S)-benzyl-1,4-diazepine-2,5-dione, (S)-**5e**.* The general procedure was followed with 2.4 g (5.5 mmol) of (*S*)-**4e** and the crude product was purified by flash chromatography using EtOAc to give 0.68 g (40%% yield) of the desired (*S*)-**5e** as a white solid, mp 178 °C. $[\alpha]_D^{25}$ −27.3 (*c* 1.0, $CHCl_3$). ^1H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**5e**. Elemental Anal. Calcd for $C_{19}H_{20}O_2N_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.38; H, 6.79; N, 9.12.

*4.4.14. 1-Benzyl-3(R)-benzyl-1,4-diazepine-2,5-dione, (R)-**5e**.* The general procedure was followed with 2.3 g (5.2 mmol) of (*R*)-**4e** and the crude product was purified by flash chromatography using EtOAc to give 0.618 g (39% yield) of the desired (*R*)-**5e** as a white solid, mp 178 °C. $[\alpha]_D^{25}$ +25.9 (*c* 1.0, $CHCl_3$). ^1H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**5e**. Elemental Anal. Calcd for $C_{19}H_{20}O_2N_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.34; H, 6.78; N, 9.30.

*4.4.15. 1-Benzyl-3-phenyl-1,4-diazepine-2,5-dione, (±)-**5f**.* The general procedure was followed with 2.2 g (5.1 mmol) of (±)-**4f** and the crude product was purified by flash chromatography using EtOAcOEt to give 0.603 g (40% yield) of the desired (±)-**5e** as a white solid, mp 140 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 2.46 (m, 2H, CH_2CH_2N), 3.12 (m, 1H, CH_2CH_2N), 3.30 (ddd, 1H, *J*=4.6, 6.5, 9.2, CH_2CH_2N), 4.55 (d, 1H, *J*=14.6, CH_2Ph), 4.70 (d, 1H, *J*=14.7, CH_2Ph), 5.41 (d, 1H, *J*=6.5, *CH), 7.29 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ (ppm): 35.10 (CH_2CH_2N), 41.21 (CH_2CH_2N), 50.89 (CH_2Ph), 61.76 (*CH), 125.60 (ArC), 127.99 (ArC), 128.25 (ArC), 128.44 (ArC), 128.94 (ArC), 129.23 (ArC), 136.57 (Cipso), 137.31 (Cipso), 169.52 (CO*CH), 173.05 ($COCH_2$). IR (KBr, cm^{-1}): ν_{max} 3061, 1654, 1433, 1395, 733, 696. MS (20 eV): *m*/*z* 294 (M^+), 266, 203, 201, 189, 106, 91. Elemental Anal. Calcd for $C_{18}H_{18}O_2N_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.44; H, 6.39; N, 9.93.

*4.4.16. 1-Benzyl-3(S)-phenyl-1,4-diazepine-2,5-dione, (S)-**5f**.* The general procedure was followed with 1.8 g (4.2 mmol) of (*S*)-**4f** and the crude product was purified by flash chromatography using EtOAc to give 0.428 g (35% yield) of the desired (*S*)-**5f** as a white solid, mp 144 °C. $[\alpha]_D^{25}$ −21.0 (*c* 1.0, $CHCl_3$). ^1H and ^{13}C NMR spectra, IR, and mass spectra were identical with those recorded for (±)-**5f**. Elemental Anal. Calcd for $C_{18}H_{18}O_2N_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.29; H, 6.17; N, 9.79.

*4.4.17. 1-Benzyl-3(R)-phenyl-1,4-diazepine-2,5-dione, (R)-**5f**.* The general procedure was followed with 2.0 g (4.8 mmol) of (*S*,*S*)-**4d** and the crude product was purified by flash chromatography using EtOAc to give 0.537 g (38% yield) of the desired (*R*,*R*)-**5d** as a white solid, mp 143 °C. $[\alpha]_D^{25}$ +27.0 (*c* 1.0, $CHCl_3$). ^1H and ^{13}C NMR spectra, IR and mass spectra were identical with those recorded for (±)-**5f**. Elemental Anal. Calcd for $C_{18}H_{18}O_2N_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.17; H, 6.28; N, 9.79.

*4.4.18. (±)-tert-Butyl-4-benzyl-2-methyl-3,7-dioxo-1,4-diazepine-1-carboxylate, (±)-**6a**.* A stirred solution of cyclic dipeptide (±)-**5a** (0.39 g, 1.4 mmol) in 20 mL of DCM was cooled to 0 °C in an ice bath and treated with triethylamine (0.2 mL, 1.4 mmol) and DMAP (0.17 g, 1.4 mmol). Following 10 min of stirring was added Boc_2O (0.61 g, 2.8 mmol). The resulting mixture was stirred for 1 h at 0 °C and then allowed to warm to room temperature and continued stirring for 24 h, it was then washed with 1 N HCl and with water until neutral pH. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography using hexane/EtOAc (1:1) to give 0.5 g, (89% yield) of a white solid, mp 85–86 °C. 1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.50 (s, 9H, $C(CH_3)_3$), 1.66 (d, 3H, *J*=7.5, *CHCH_3), 2.78 (ddd, 1H, *J*=2.0, 6.5, 10.5, CH_2CH_2N), 2.85 (ddd, 1H, *J*=2.6, 5.9, 11.2, CH_2CH_2N), 3.26 (ddd, 1H, *J*=2.6, 6.6, 7.5, CH_2CH_2N), 3.65 (ddd, 1H, *J*=2.2, 2.7, 11.2, CH_2CH_2N), 4.31 (d, 1H, *J*=14.7, CH_2Ph), 4.91 (d, 1H, *J*=14.7, CH_2Ph), 5.21 (c, 1H, *J*=7.4, 14.9, *CH), 7.29 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ (ppm): 20.35 (*CHCH_3), 28.01 ($C(CH_3)_3$), 38.58 (CH_2CH_2N), 43.52 (CH_2CH_2N),

52.37 (CH_2Ph), 56.36 (*CH), 83.95 ($C(CH_3)_3$), 127.92 (Ar*C*), 128.14 (Ar*C*), 128.95 (Ar*C*), 136.47 (*Cipso*), 152.73 (*C*ON), 170.08 (*C*O*CH), 173.22 (*C*OCH$_2$). IR (KBr, cm^{-1}): ν_{max} 2980, 1715, 1630, 1251, 1151, 697. MS (20 eV): *m*/*z* 332 (M^+), 321, 274, 232, 191, 160, 141, 124, 106, 91, 57, 41. Elemental Anal. Calcd for $C_{18}H_{24}O_4N_2$: C, 65.04; H, 7.28; N, 8.43; found: C, 65.02; H, 7.39; N, 8.77.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.08.050.

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21. Crystal data for (*R*)-**5f**: $C_{18}H_{18}N_2O_2$, triclinic, space group *P*-1, *a*=6.9251(3) Å, *b*=8.1821(3) Å, *c*=14.1725(5) Å, *α*=103.682(2)°, *β*=92.338(2)°, *γ*=97.882(3)°, *V*=770.6 Å^3, crystal size: 0.12×0.25×0.55 mm^3, *R*1=0.0518, (*wR*2=0.1311). CCDC 849455 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.
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25. Crystal data for (±)-**6a**: $C_{18}H_{24}N_2O_4$, monoclinic, space group $P2(1)/c$, *a*=14.0998(4) Å, *b*=6.2825(2) Å, *c*=20.6293(7) Å, *α*=90°, *β*=98.7136(10)°, *γ*=90°, *V*=1806.293(98) Å^3, crystal size: 0.67×0.25×0.15 mm^3, *R*1=0.0617, (*wR*2=0.1388). CCDC 849456 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.
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