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One-pot synthesis of poly-substituted tetramic acids for the preparation of putative turn mimics

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ABSTRACT

A one-pot synthesis of poly-substituted tetramic acids and of their six-membered ring analogs have been obtained in one step by reaction of *N*-Boc dipeptides, activated as their *O*-succinimidyl esters (Boc-AA-AA-OSu), with the sodium anion of dibenzyl malonate. The adducts spontaneously cyclize to form five or six-member rings. To check whether this class of compounds may be used to promote reverse-turn conformations, one adduct was further derivatized. The formation of a hydrogen bond between the NH–Boc and the carbonyl at C2 of the heterocycle is highlighted, upon analysis of the product by IR, ^{1}H NMR, and MD techniques, thus suggesting that these compounds are good candidates to promote reverse-turn conformations or other secondary structures and may be used for the formation of new foldamers.

1. Introduction

Naturally occurring tetramic acids (pyrrolidin-2,4-dione) have attracted a great deal of interest because many natural compounds containing these heterocycles exhibit interesting biological activities,[1] such as dolastatin 15[2] and althiomycin.[3] HSAF (Fig. 1) was isolated from *Lysobacter enzymogenes*, a bacterium used in the biological control of fungal diseases of plants.[4] Furthermore the natural products tenuazonic acid,[5] melophlins,[6] and reutericyclin[7] are representative examples of the structurally diverse family of acyl-tetramic acids. Finally sintokamides A–E, 1,5-disubstituted tetramic acids, are the first natural products reported to selectively block transactivation of the N terminus of the androgen receptor in prostate cancer cells.[8]

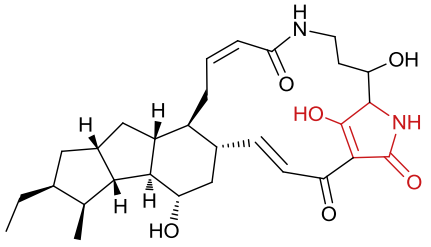

Fig. 1. Chemical structure of HSAF, the tetramic acid moiety is highlighted in red.

Tetramic acids are very polar and scarcely reactive and may be prepared with several methods. The most simple one is the activation of a Boc-protected amino acid with EDC, condensation with Meldrum's acid, and finally cyclization to give the Boc-protected pyrrolidine-2,4-diones. The following N-deprotection may be accomplished with TFA treatment giving the parent pyrrolidine-2,4-diones.[9] Another straightforward method is the condensation of methyl (*E*)-4-chloro-3-methoxy-2-butenoate with a 2-amino alcohol in the presence of triethylamine.[10]

The functionalization of these heterocycles is often a difficult task, due to their low reactivity and to the equilibrium between the ketonic and enolic form, although they may react with several classes of compounds. In many natural compounds, the tetramic acid moiety is present as a 3-acyl derivative or, less commonly, as a 4-*O*-alkyl ether derivative (Fig. 2).

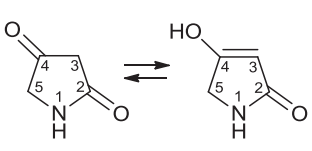

Fig. 2. Chemical structure of tetramic acid. The equilibrium between the two forms is shown.

Some synthetic methods have been reported. For instance the 3-acylation of tetramic acids was performed via O-acylation with

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carboxylic acids followed by acyl migration.[11] Another approach is the reaction of tetramic acids with the ylide Ph_3PCCO, that affords exclusively the corresponding 3-acylylidenetetramic acids. These were amenable to Wittig olefinations with aliphatic, aromatic, saturated and unsaturated aldehydes after deprotonation with KO^{t}Bu.[12] Very interesting are the studies reported by Tønder et al.[13] who have developed a straightforward strategy for the synthesis of *N*-acylates, *O*-alkylated pyrrolidin-2-ones by functionalization of tetramic acids, that leads to the formation of dipeptidomimetics comprising a pyrrolidinone and a protected amino acid. They have also reported an optimized two-step reductive amination procedure, which provides a small library of pyrrolidinone-containing dipeptide analogs. Another interesting approach to the synthesis of *N*-Boc 5-substituted tetramic acids is the cyclization of *N*-hydroxysuccinimide esters of Boc-protected α-amino acids.[14] The desired products have been obtained in two steps, by coupling of the α-amino acid derivatives with an alkyl malonate in the presence of NaH, with the formation of γ-amino-β-oxoalkanoates, that in turn cyclize under basic conditions to give the desired compounds.

We have become interested in the synthesis and in the derivatization of 1-acyl 3-carboxy tetramic acids, as they are constrained amino acid mimetics, contain an endocyclic carbonyl group and may be functionalized in several ways, thus they be may applied to the formation of pseudopeptide foldamers.[15] We have studied foldamers containing imide moieties, where the nitrogen atom is connected to an endocyclic and an exocyclic carbonyl, which tend to adopt always the trans conformation.[16] As a consequence of this locally constrained disposition effect, these imide-type oligomers are forced to fold in ordered conformations, such as PPII helixes,[17] β-band ribbon spirals,[18] β-sheets,[19] and β- or γ-turns.[20]

1-Acyl 3-carboxy tetramic acids are constrained β-amino acids, where the carbonyl unit is placed between the two functions, thus it forces the two carbonyls in the trans conformation, following the same effect that we have observed for the 4-carboxy-oxazolidin-2-ones (Fig. 3). As a consequence of this disposition, this scaffold may behave as a reverse-turn mimic, if it is introduced in the middle of a polypeptide chain, or it may promote the formation of new foldamers, if it is introduced in more complex structures. Although many examples of nonpeptidic reverse-turn surrogates have been reported, it is still challenging to find a new type of nonpeptidic scaffold that can adopt a highly populated reverse-turn conformation in solution[21] and that may be regarded as constrained pseudo-β-prolines.

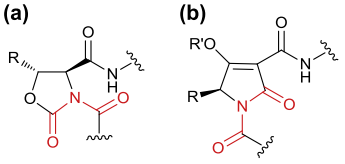
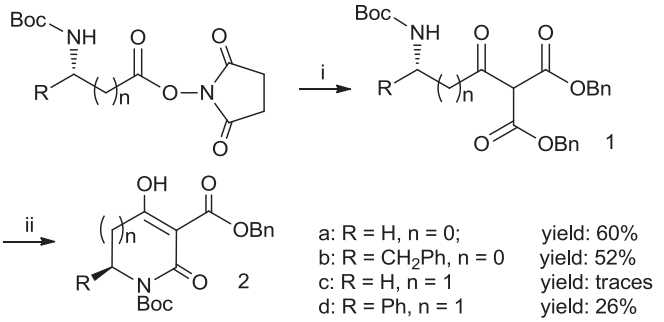


Fig. 3. (a) Preferential conformation of 4-carboxy-oxazolidin-2-ones and (b) possible preferential conformation of 1-acyl 3-carboxy tetramic acids.

2. Results and discussion

2.1. Synthesis of the heterocycles

We report here a one-pot synthesis of poly-substituted tetramic acids (4-hydroxy-2-oxo-1*H*-pyrrole-1,3(2*H*,5*H*)-dicarboxylates) and of the corresponding six-membered rings (4-hydroxy-2-oxo-5,6-dihydropyridine-1,3(2*H*)-dicarboxylates) starting from benzyl malonate and *N*-hydroxysuccinimide esters of Boc-protected amino acids (Scheme 1). As a first attempt, we utilized the protocol described by Igglessi-Markopoulou et al.[14a] that allows to obtain γ-amino β-oxo acids by reaction of *N*-hydroxysuccinimide esters of Boc-protected amino acids with alkyl malonate.



Scheme 1. Reagents and conditions: (i) $Na^{+\bullet-}CH(CO_2Bn)_2$ (1.5 equiv), dry THF, 30 min at 0 °C then 2h at rt; (ii) 2 M NaOH (166 equiv), BnOH, 2 h, rt.

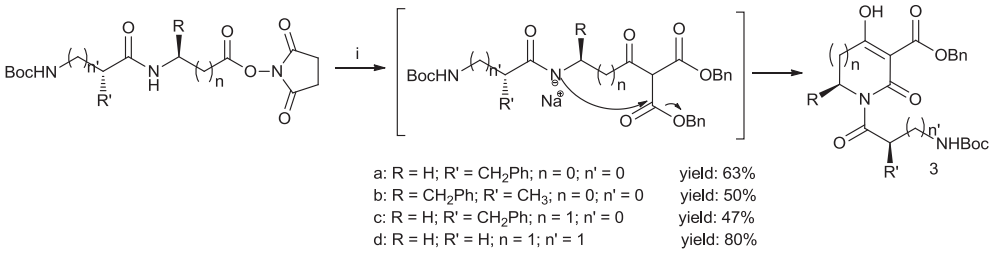
As the final scope is the formation of a free carboxy unit, the reaction was performed with benzyl malonate, as the benzyl unit may be removed easily by hydrogenolysis. So benzyl malonate was treated with NaH in dry THF, followed by the *N*-hydroxysuccinimide esters, to afford the desired γ-amino β-oxo benzyl esters **1a**–**d** in high yield. This reaction allows to obtain the desired compound **1**, starting from both α- and β-amino acids (Scheme 1). The following cyclization was performed in benzyl alcohol and aqueous 2 M NaOH. While satisfactory yields were obtained for the synthesis of both 4-hydroxy-2-oxo-1*H*-pyrrole-1,3(2*H*,5*H*)-dicarboxylates **2a** and **2b** (60% and 52%, respectively), the synthesis of 4-hydroxy-2-oxo-5,6-dihydropyridine-1,3(2*H*)-dicarboxylates **2c** and **2d** afforded very unsatisfactory results, as **2c** was obtained only in traces from **1c** and **2d** in 26% yield from **1d**. No racemization occurred in the formation of **2b** (after analysis with HPLC equipped with a chiral column AD, *n*-hexane/*iso*-propanol 8:2, flow: 0.5 mL/min), probably due to the mild reaction conditions.

Then **2a** was deprotected from the Boc moiety by reaction with trifluoroacetic acid in dry dichloromethane, for further derivatizations. The desired product was obtained in high yield. Unfortunately, the following N-acylation reaction, performed with standard coupling conditions (HBTU or HATU, in the presence of tertiary amines) was totally unsuccessful, as the heterocyclic nitrogen of this compound is very unreactive. In effect, this reaction has been previously reported only in hard conditions,[13a] by reaction with a lithium base (*n*-BuLi or LiHMDS), followed by addition of an activated ester (Fmoc-AA-OPfp) at −50 °C.

To overcome this problem, we reversed the step order, making the coupling before the cyclization (Scheme 2). Thus four dipeptides were prepared containing both α- and β-amino acids, in both positions. Then the carboxy moieties were activated as the corresponding *N*-hydroxysuccinimide esters and treated with the sodium anion of the benzyl malonate to obtain the corresponding γ-amino β-oxo acids, as previously reported in Scheme 1. Much to our surprise, the expected products were not obtained, as the reaction proceeded directly to the formation of the heterocyclic rings. The reaction yield was further optimized with the addition of 2.5 equiv of base. No epimerization of **3b** was observed by ^{1}H NMR and HPLC analysis (chiral column AD, *n*-hexane/*iso*-propanol 8:2, flow: 0.5 mL/min).

The different behavior between Boc-AA-OSu and Boc-AA-AA-OSu may be ascribed to the secondary amide involved in the cyclization, that is, more acidic than the carbamate involved in the cyclization of Boc-AA-OSu. The heterocycles **3a**–**d** are obtained in good to high yield and can be further derivatized simply by removing the Boc or benzyl ester protecting groups.

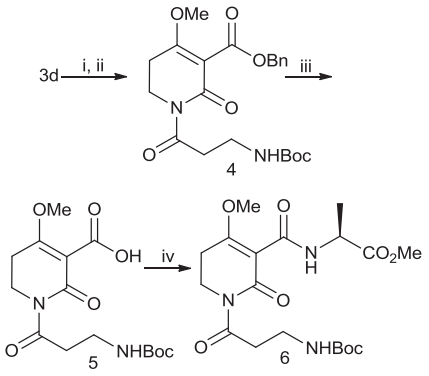
Finally, the achiral **3d** was further derivatized to check if this new class of compounds may be utilized to promote the formation of reverse-turn mimics, as they may be considered as a mimic of the Gly-Pro moiety, that is, often present in the β-turn motifs.[22] Thus we replaced the OBn group with H-Ala-OMe that contains the small



Scheme 2. Reagents and conditions: (i) $Na^{+\bullet-}CH(CO_2Bn)_2$ (1.5 equiv), dry THF, 16 h, rt.

methyl ester. Of course, if a longer peptide chain has to be introduced, benzyl-protected amino acids are preferred.

After hydrogenolysis of the benzyl ester with H_2 and Pd/C, the acid was coupled with H-Ala-OMe, but the coupling reaction produced only a mixture of products, probably due to the free hydroxyl group, that was then protected by methylation of the Li anion with (trimethylsilyl)diazomethane (Scheme 3).[13a] The product **4** was obtained in good yield and the deprotected by reaction with H_2 and Pd/C to form the free acid **5**, that was coupled with H-Ala-OMe in the presence of HBTU and Et_3N. The derivative **6** was obtained in high yield after purification.



Scheme 3. Reagents and conditions: (i) LiHMDS (1.1 equiv), dry THF, 10 min, rt (ii) (trimethylsilyl)diazomethane (8 equiv), dry THF, 3 h, rt (iii) H_2, Pd/C, MeOH, 6 h, rt; (iv) HCl·H-Ala-OMe (1 equiv), HBTU (1.1 equiv), Et_3N (3 equiv), CH_3CN, 2 h, rt.

2.2. Conformational analysis of 6

Information on the preferred conformation of the compound **6** in solution was obtained by FT-IR and ^1H NMR techniques. The FT-IR absorption spectrum of **6** was obtained as 3 mM solution in methylene chloride, as at this concentration self-aggregation is usually unimportant (Fig. 4). The IR spectrum of **6** shows the presence of a non-hydrogen-bonded amide N–H bands (3438, above 3400 cm^{-1}) and of a large band located at 3327 cm^{-1}, that suggests that an equilibrium takes place, involving a hydrogen-bonded amide protons bands.

The in-solution conformation of **6** was investigated also by ^1H NMR spectroscopy and MD simulations; NMR analyses were conducted using standard techniques at 400 MHz in $CDCl_3$. The ^1H NMR analysis of **6** revealed a single set of sharp resonances, indicating conformational homogeneity or a fast equilibrium between conformers.

To verify the IR outcome and to check, which hydrogen-bonded amide proton is involved in the equilibrium, some ^1H NMR spectra of **6** have been recorded, as a function of the addition of increasing amounts of DMSO-d_6, to check the dependence of NH proton chemical shifts from DMSO-d_6 (Fig. 5a);[23] this solvent is a strong hydrogen-bonding acceptor and, if it is bound to a free NH proton, it will be expected to dramatically move its chemical shift downfield.

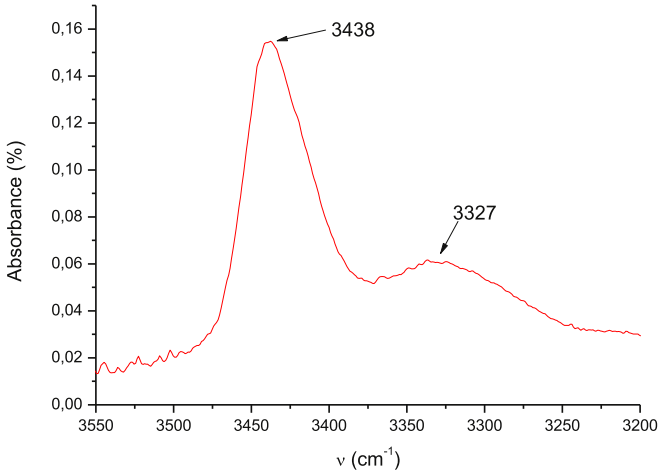


Fig. 4. FT-IR absorption spectrum in the N–H stretching region for 3 mM concentration samples of **6** in pure CH_2Cl_2 at room temperature.

The titration of the NH bonds shows that NH–Ala is poorly bonded ($\Delta\delta$=0.68 ppm), while the NH–Boc is an equilibrium between a hydrogen-bonded and an open conformation ($\Delta\delta$=0.48 ppm). A strong hydrogen-bonded conformation would require a lower $\Delta\delta$ outcome ($\Delta\delta \leq 0.15$ ppm).

Some more information have been obtained, by recoding the ^1H NMR spectrum of a 10 mM sample of **6** in $CDCl_3$ at different temperature, to check the dependence of the NH proton from the temperature (Fig. 5b).

This test points out the presence of hydrogen-bonded amide protons, as in $CDCl_3$ a small temperature coefficient ($\leq$3 ppb/K in absolute value) indicates the presence of a hydrogen-bonded amide proton,[24] while protons, which participate to an equilibrium between hydrogen-bonded and non-hydrogen-bonded state show a larger temperature coefficient. In DMSO-d_6 the temperature coefficients can be bigger, so that a hydrogen-bonded amide proton can have a value of −4 ppb/K or smaller in absolute value. The analysis of the variation of the NH chemical shift with the temperature furnish a result, that is, in agreement both with the titration and with the IR spectrum, because a $\Delta\delta$ of −6.0 ppb/K for NH–Ala shows that no hydrogen bond is formed, while −3.0 ppb/K for NH–Boc suggests the formation of a weak hydrogen bond.

To have more information on the in-solution preferred conformation, **6** was further analyzed by 2D ROESY experiments performed on a 10 mM solution of **6** in $CDCl_3$ (mixing time 0.500 s). Several cross peaks were obtained (see Supplementary data), the most interesting ones (Fig. 6, red arrows) are the cross peak between the β-AlaNH and the methylene at the C5 of the heterocycle, and the cross peak between the CH_α–Ala and the Boc group. This cross peak shows that one chain lays nearby to the other, thus suggesting that this molecule is a good candidate for the formation of a reverse-turn motif.

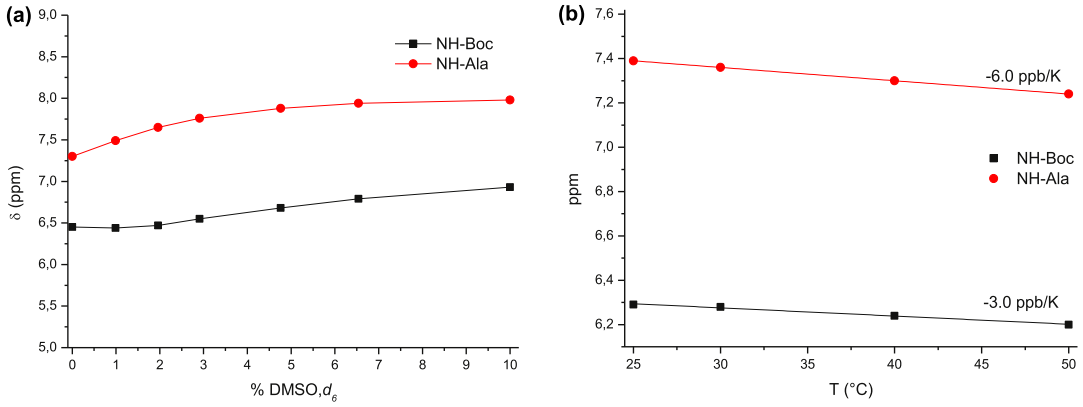


Fig. 5. (a) Variation of NH proton chemical shift (ppm) of **6** as a function of increasing percentages of DMSO-d_6 to the $CDCl_3$ solution (v/v) (concentration: 3 mM); (b) variation of NH proton chemical shift (ppm) of **6** as a function the temperature (°C) for 10 mM samples measured in $CDCl_3$.

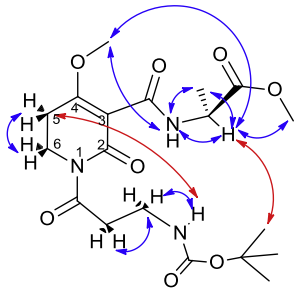


Fig. 6. NOE enhancements as gathered from the ROESY analysis spectrum of **6** (10 mM solution in $CDCl_3$, mixing time 0.500 s).

Furthermore a strong signal was observed between the NH—Ala and the OMe heterocyclic group and two weaker signals between CH_α—Ala and CO_2Me and CH_α—Ala and OMe.

MD simulations[25] furnished some more hints on the preferred in-solution conformation of **6**.[26] Structures consistent with the spectroscopic analyses were obtained by restrained MD simulations, using the distances derived from ROESY as constraints, and minimized with AMBER force field (see Supplementary data).[27] To investigate the dynamic behavior of **6**, two structures **a** and **b** were analyzed by unrestrained MD for 500 ns. The analysis of the trajectories did not manifest the conversion of one conformation into the other.

The simulation of the more stable structure revealed a strong propensity to maintain the folded conformations, with the occurrence of an explicit H-bond between β-AlaNH and the heterocyclic C=O, in agreement to the IR and ^{1}H NMR results (Fig. 7).

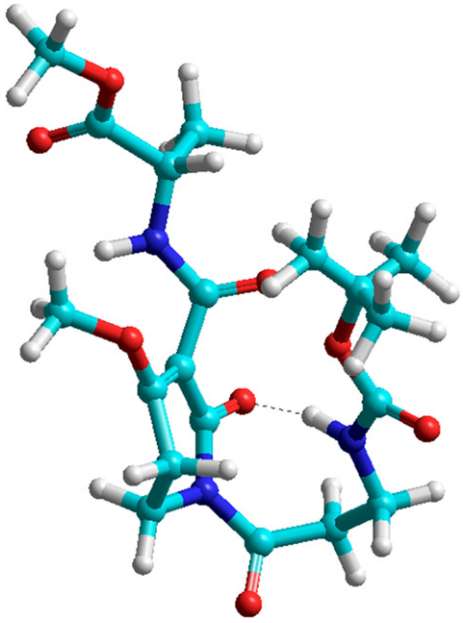


Fig. 7. Representative low-energy structure of **6** obtained by unrestrained MD simulation, performed on the lower-energy structure consistent with ROESY analysis, calculated by restrained MD.

3. Conclusions

We have reported a one-pot synthesis of poly-substituted tetramic acids and of their six-membered ring analogs. The key step is the reaction of *N*-Boc dipeptides activated as their *O*-succinimidyl esters (Boc-AA-AA-OSu) with the sodium anion of dibenzyl malonate, that spontaneously cyclize to five or six-member rings. This new class of compounds may be prepared in multigram scale.

To check if they may be used to promote reverse-turn conformations, achiral **3d** was further derivatized at the C-terminal position with the small H-L-Ala-OMe group. The product **6** was analyzed by means of IR, ^{1}H NMR, and MD techniques that all suggest the formation of a hydrogen bond between the β-AlaNH and the carbonyl at C2 of the heterocycle. Further studies are currently ongoing on more complex structures containing poly-substituted tetramic acids or their six-membered ring analogs to check if they are able to promote the formation of new foldamers.

4. Experimental

4.1. Materials and instrumentation

The melting points of the compounds under investigation were determined in open capillaries and are uncorrected. High quality infrared spectra (64 scans) were obtained at 2 cm^{-1} resolution using a 1 mm NaCl solution cell and an FT-infrared spectrometer. All spectra were obtained in 3 mM solutions in dry CH_2Cl_2 at 297 K or as 1% solid mixture with dry KBr. All compounds were dried in vacuo and all the sample preparations were performed in a nitrogen atmosphere. Routine NMR spectra were recorded with spectrometers at 600, 400 or 300 MHz (^{1}H NMR) and at 150, 100 or 75 MHz (^{13}C NMR). The measurements were carried out in $CDCl_3$ and in DMSO-d_6. The proton signals were assigned by gCOSY spectra. Chemical shifts are reported in δ values relative to the solvent ($CDCl_3$ or DMSO-d_6) peak. 2D spectra were recorded in the phase sensitive mode and processed using a 90°-shifted, squared sine-bell apodization. 2D ROESY experiments were recorded with a 5000 ms mixing time with a proton spectral width of 4032.3 Hz.

4.2. Synthesis and characterization

4.2.1. General method for the derivatives ***1***. To a stirred solution of NaH (60% in mineral oil, 1.4 mmol, 55 mg) in dry THF (3 mL) was added benzyl malonate (1.05 mmol, 0.27 g) at 0 °C and the mixture was stirred 30 min. Then Boc-Xaa-*O*-Succinimide (0.7 mmol) was added in one portion at 0 °C and the mixture was stirred for 2 h at room temperature. Then THF was removed under reduced pressure and replaced with ethyl acetate. The mixture was washed with water (2×30 mL), dried over sodium sulfate and concentrated in vacuo. The product was obtained pure after silica gel chromatography (cyclohexane/ethyl acetate 8:2 as eluant).

4.2.1.1. Benzyl 1-tert-butoxycarbonylamino-2-benzoxycarbonyl-3-oxobutanoate ***1a***. Yield: 75%; mp=99 °C; IR (CH_2Cl_2, 3 mM): ν 3446, 1752, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$; keto/enol, 50:50): δ 1.36 (s, 9H, ^{t}Bu), 3.39 (s, 0.5H, $CH(CO)_3$, keto), 4.07 (d, J=4.0 Hz, 1H, CH_2, keto), 4.17 (d, J=4.0 Hz, 1H, CH_2, enol), 4.99 (br s, 1H, NH), 5.10–5.27 (m, 4H, 2× OCH_2Ph), 7.16–7.32 (m, 10H, 2× Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3, 41.5, 49.9, 67.2, 68.2, 128.0, 128.3, 128.4, 128.5, 128.6, 134.5, 135.1, 168.8, 166.2.

4.2.1.2. (S)-Benzyl 5-phenyl-4-tert-butoxycarbonylamino-2-benzoxycarbonyl-2-benzoxycarbonyl-3-oxopentanoate ***1b***. Yield: 73%; mp=167 °C; $[\alpha]_D^{25}$ +23.4 (*c* 0.15, $CHCl_3$); IR (CH_2Cl_2, 3 mM): ν 3436, 1761, 1720, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 9H, ^{t}Bu), 2.97–3.06 (m, 1H, C*H*HCH), 3.07–3.17 (m, 1H, CH*H*CH), 3.40 (s, 1H, $CH(CO)_3$), 4.46–4.59 (m, 1H, C*H*CH_2), 4.98 (br s, 1H, NH), 5.10 (s, 4H, 2× OCH_2Ph), 7.08–7.39 (m, 15H, 3× Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.7, 25.4, 28.3, 33.4, 49.8, 128.0, 128.3, 128.4, 128.6, 129.1, 129.2, 129.4, 135.2, 166.2.

4.2.1.3. Benzyl 4-tert-butoxycarbonylamino-2-benzoxycarbonyl-3-oxopentanoate ***1c***. Yield: 80%; mp=141 °C; IR (CH_2Cl_2, 3 mM): ν 3514, 3451, 1816, 1787, 1744, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 9H, ^{t}Bu), 2.71–2.87 (m, 2H, $NHCH_2CH_2$), 3.50 (s, 1H, $CH(CO)_3$), 3.27–3.53 (m, 2H, $NHCH_2CH_2$), 4.96 (br s, 1H, NH), 5.10–5.35 (m, 4H, 2× OCH_2Ph), 7.15–7.59 (m, 10H, 2× Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3, 30.9, 34.4, 41.5, 67.3, 128.3, 128.4, 128.6, 135.2, 166.2.

4.2.1.4. (S)-Benzyl 5-phenyl-5-tert-butoxycarbonylamino-2-benzoxycarbonyl-2-benzoxycarbonyl-3-oxopentanoate ***1d***. Yield: 76%; mp=101 °C; $[\alpha]_D^{25}$ −19.4 (*c* 0.55, $CHCl_3$); IR (CH_2Cl_2, 3 mM): ν 3436, 3362, 1761, 1708, 1646, 1601 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9H, ^{t}Bu), 2.83–3.09 (m, 1H, CH*H*), 3.10–3.32 (m, 1H, C*H*H), 4.97–5.34 (m, 5H, 2× OCH_2Ph+C*H*CH_2), 5.74 (br s, 1H, NH), 7.01–7.45 (m, 10H, 2× Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3, 40.9, 41.5, 67.3, 67.4, 100.9, 125.9, 126.1, 127.3, 128.1, 128.3, 128.3, 128.5, 135.2, 155.1, 166.1, 170.8, 180.9.

4.2.2. General method for the preparation of 4-hydroxy-2-oxo-1H-pyrrole-1,3(2H,5H)-dicarboxylates or 4-hydroxy-2-oxo-5,6-dihydropyridine-1,3(2H)-dicarboxylates ***2***. To a stirred solution of compound **1a**–**d** (0.12 mmol) in benzyl alcohol (1 mL) was added 2 M NaOH (20 mmol, 1 mL) and the mixture was stirred at room temperature for 2 h. Then water was removed under reduced pressure and the product was obtained pure after silica gel chromatography (cyclohexane/ethyl acetate 1:9 → pure ethyl acetate as eluant) to remove benzyl alcohol and by-products.

4.2.2.1. Benzyl 1-tert-butyl 4-hydroxy-2-oxo-1H-pyrrole-1,3(2H,5H)-dicarboxylates ***2a***. Yield: 60%; mp=190 °C; (CH_2Cl_2, 3 mM): ν 3595, 1752, 1650, 1605 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 1.55 (s, 9H, ^{t}Bu), 3.83 (s, 2H, CH_2), 5.27 (s, 2H, OCH_2–Ph), 7.22–7.49 (m, 5H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 30.9, 56.2, 67.6, 131.0, 131.1, 131.8, 193.5. Anal. Calcd for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 60.21; H, 5.79; N, 4.23.

4.2.2.2. (S)-3-Benzyl 1-tert-butyl 5-benzyl-4-hydroxy-2-oxo-1H-pyrrole-1,3(2H,5H)-dicarboxylates ***2b***. Yield: 52%; mp=101 °C; $[\alpha]_D^{25}$ −32.0 (*c* 1.0, CH_3OH); (CH_2Cl_2, 3 mM): ν 1736, 1677, 1640 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 1.56 (s, 9H, ^{t}Bu), 3.10–3.31 (m, 2H, CH_2–Ph), 4.14 (s, 1H, C*H*CH_2), 5.09 (s, 2H, OCH_2–Ph), 6.89–7.06 (m, 5H, Ph), 7.17–7.35 (m, 5H, Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 24.2, 28.2, 28.5, 30.7, 36.0, 64.7, 126.2, 126.9, 127.5, 127.9, 129.6. Anal. Calcd for $C_{24}H_{25}NO_6$: C, 68.07; H, 5.95; N, 3.31. Found: C, 68.01; H, 5.92; N, 3.33.

4.2.2.3. (R)-3-Benzyl 1-tert-butyl 4-hydroxy-2-oxo-6-phenyl-5,6-dihydropyridine-1,3(2H)-dicarboxylate ***2d***. Yield: 26%; mp=110 °C; $[\alpha]_D^{25}$ −27.9 (*c* 0.4, $CHCl_3$); IR (CH_2Cl_2, 3 mM): ν 3491, 3437, 3325, 1748, 1711 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 1.29 (s, 9H, ^{t}Bu), 2.56–2.62 (m, 2H, C*H*$_2$CH), 4.87–4.98 (m, 1H, CH_2C*H*), 5.08 (s, 2H, OCH_2–Ph), 7.06–7.32 (m, 10H, 2× Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.9, 28.2, 29.7, 41.4, 51.2, 67.3, 80.0, 126.1, 127.3, 128.3, 128.6, 141.4, 155.6, 176.0. Anal. Calcd for $C_{24}H_{25}NO_6$: C, 68.07; H, 5.95; N, 3.31. Found: C, 68.10; H, 5.97; N, 3.29.

4.2.3. General method for the preparation of compounds ***3***. To a stirred solution of NaH (60% in mineral oil, 1.75 mmol, 69 mg) in dry THF (3 mL) was added benzyl malonate (1.05 mmol, 0.27 g) at 0 °C and the mixture was stirred 30 min. Then Boc-AA-AA-*O*-Succinimide (0.7 mmol) was added in one portion at 0 °C and the mixture was stirred for 16 h at room temperature. Then THF was removed under reduced pressure and replaced with ethyl acetate. The mixture was washed with water (2×30 mL), dried over sodium sulfate and concentrated in vacuo. The product was obtained pure after silica gel chromatography (cyclohexane/ethyl acetate 1:9 → pure ethyl acetate as eluant).

4.2.3.1. (S)-Benzyl 1-(2-((tert-butoxycarbonyl)amino)-3-phenylpropanoyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate ***3a***. Yield: 63%; mp=159 °C; $[\alpha]_D^{25}$ +45.4 (*c* 0.6, $CHCl_3$); IR (CH_2Cl_2, 3 mM): ν 3427, 3364, 1702, 1675, 1645 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 1.23 (s, 9H, ^{t}Bu), 2.49–2.67 (m, 1H, C*H*H–Ph), 3.06–3.16 (m, 1H, CH*H*–Ph), 3.73 (AB, 2H, J=10.0 Hz, CH_2), 5.16 (s, 2H, OCH_2–Ph), 6.95–7.50 (m, 10H, 2× Ph); ^{13}C NMR (100 MHz, CD_3OD): δ 24.6, 24.8, 27.0, 27.2, 37.9, 50.9, 55.4, 63.7, 79.0, 126.0, 127.0, 127.2, 127.7, 127.8, 129.2, 137.3, 137.7. Anal. Calcd for $C_{26}H_{28}N_2O_7$: C, 64.99; H, 5.87; N, 5.83. Found: C, 65.03; H, 5.89; N, 5.80.

4.2.3.2. (S)-Benzyl 5-benzyl-1-((S)-2-((tert-butoxycarbonyl)amino) propanoyl)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate ***3b***. Yield: 50%; mp=140 °C; $[\alpha]_D^{25}$ −54.5 (*c* 0.6, $CHCl_3$); IR (CH_2Cl_2, 3 mM): ν 3425, 3357, 1718, 1679, 1650 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.11 (d, 1H, J=8 Hz, CHC*H*$_3$), 1.39 (s, 9H, ^{t}Bu), 3.20–3.31 (m, 2H, CH_2–Ph), 3.40 (S, 1H, C*H*CH_2), 5.00 (s, 2H, OCH_2–Ph), 5.20–5.30 (m, 1H, C*H*CH_3), 6.95–7.37 (m, 10H, 2× Ph); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.8, 28.2, 34.2, 49.5, 62.4, 77.7, 125.9, 126.8, 127.1, 127.5, 128.1, 128.3, 128.9, 129.7, 130.0, 136.1, 137.9, 155.0, 173.5. Anal. Calcd for $C_{27}H_{30}N_2O_7$: C, 65.57; H, 6.11; N, 5.66. Found: C, 65.54; H, 6.08; N, 5.70.

4.2.3.3. (S)-Benzyl 1-(2-((tert-butoxycarbonyl)amino)-3-phenylpropanoyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate ***3c***. Yield: 47%; mp=119 °C; $[\alpha]_D^{25}$ +4.9 (*c* 1.4, $CHCl_3$); IR (CH_2Cl_2, 3 mM): ν 3424, 3315, 1749, 1726, 1667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 9H, ^{t}Bu), 1.82–1.91 (m, 1H, NCH_2CHH), 2.19–2.31 (m, 1H, NCH_2CHH), 2.92 (S, 2H, CH_2–Ph), 3.40 (S, 1H, NCH_2CH_2), 4.51 (s, 1H, C*H*CH_2), 5.09 (s, 2H, CH_2–Ph), 5.43 (br s, 1H,

NH), 6.99–7.55 (m, 10H, 2× Ph); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.8, 25.5, 28.2, 33.6, 39.1, 41.6, 49.3, 67.3, 68.7, 126.9, 128.3, 128.4, 128.5, 128.6, 128.7, 129.3, 135.2, 136.6, 157.4, 161.2, 171.5. Anal. Calcd for $C_{27}H_{30}N_2O_7$: C, 65.57; H, 6.11; N, 5.66. Found: C, 65.59; H, 6.14; N, 5.68.

4.2.3.4. Benzyl 1-(3-((tert-butoxycarbonyl)amino)propanoyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate ***3d***. Yield: 80%; mp=180 °C; IR (CH_2Cl_2, 3 mM): ν 3441, 3314, 1750, 1734, 1704, 1670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 9H, ^{t}Bu), 2.16–2.33 (m, 2H, COC*H*$_2$CH$_2$), 2.44–2.49 (m, 1H, NCH$_2$C*H*H), 2.71–2.76 (m, 1H, NCH$_2$CH*H*), 3.22–3.35 (m, 2H, COCH$_2$C*H*$_2$), 3.36–3.49 (m, 2H, NC*H*$_2$CH$_2$), 5.01–5.32 (m, 2H, OCH$_2$–Ph), 6.07–6.31 (m, 1H, NH), 6.94–7.38 (m, 10H, 2× Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 21.0, 24.9, 28.3, 33.9, 36.2, 36.8, 41.5, 60.4, 67.4, 68.2, 79.2, 128.0, 128.3, 128.4, 128.5, 128.6, 128.7, 135.2, 156.0, 164.1, 166.2, 171.4. Anal. Calcd for $C_{21}H_{26}N_2O_7$: C, 60.28; H, 6.26; N, 6.69. Found: C, 60.31; H, 6.74; N, 6.66.

4.2.3.5. Benzyl 1-(3-((tert-butoxycarbonyl)amino)propanoyl)-4-methoxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate ***4***. To a solution of compound **3d** (0.2 mmol, 70 mg) in dry THF (10 mL) was added LiHMDS (1 M solution in THF, 0.24 mmol, 0.24 mL) under nitrogen atmosphere, then the mixture was stirred at room temperature for 10 min and (trimethylsilyl)diazomethane (2 M solution in diethyl ether, 2.0 mmol, 1 mL) was added and the mixture was further stirred for 3 h at room temperature. Then the volatiles were removed under reduced pressure and replaced with ethyl acetate. The mixture was washed with 1 N aqueous HCl, dried over sodium sulfate and concentrated in vacuo. Cyclohexane was added to the residue and the mixture was sonicated for 20 min. The product **4** was obtained pure after concentration of the cyclohexane mother liquid in 50% yield (37 mg) as a waxy solid. IR (CH_2Cl_2, 3 mM): ν 3444, 1749, 1733, 1708, 1672 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 9H, ^{t}Bu), 2.29 (t, 2H, J=6.4 Hz, MeO–C–C*H*$_2$–CH$_2$–N), 2.46 (t, 2H, J=6.0 Hz, C*H*$_2$–CH$_2$–NHBoc), 3.31 (t, 2H, J=6.4 Hz, MeO–C–CH$_2$–C*H*$_2$–N), 3.63 (s, 1H, OMe), 3.44 (q, 2H, J=6.0 Hz, CH$_2$–C*H*$_2$–NHBoc), 5.10 (s, 2H, OC*H*$_2$Ph), 6.19 (br s, 1H, NH), 7.20–7.30 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.9, 27.4, 32.8, 33.8, 40.6, 66.3, 114.3, 119.2, 127.3, 127.4, 127.6, 128.5, 134.2, 155.1, 165.3.

4.2.3.6. 1-(3-((tert-Butoxycarbonyl)amino)propanoyl)-4-methoxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylic acid ***5***. Compound **4** (0.1 mmol, 37 mg) was dissolved in MeOH (5 mL) under nitrogen. Pd/C (3 mg, 10% w/w) was added under nitrogen. Vacuum was created inside the flask using the vacuum line. The flask was then filled with hydrogen using a balloon (1 atm). The solution was stirred for 16 h under a hydrogen atmosphere. The product was obtained pure in quantitative yield (30 g) after filtration through a Celite pad using ethyl acetate and concentration in vacuo. ^{1}H NMR (400 MHz, CD_3OD): δ 1.43 (s, 9H, ^{t}Bu), 2.34 (t, 2H, J=6.8 Hz, MeO–C–C*H*$_2$–CH$_2$–N), 2.53 (t, 2H, J=6.8 Hz, C*H*$_2$–CH$_2$–NHBoc), 3.28 (t, 2H, J=6.8 Hz, MeO–C–CH$_2$–C*H*$_2$–N), 3.43 (t, 2H, J=6.8 Hz, CH$_2$–C*H*$_2$–NHBoc), 3.67 (s, 3H, OMe), 4.51 (s, 1H, C*H*CH$_2$).

4.2.3.7. (S)-Methyl 2-(1-(3-((tert-butoxycarbonyl)amino)propanoyl)-4-methoxy-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxamido) propanoate ***6***. A solution of compound **5** (0.1 mmol, 30 mg) was dissolved in dry acetonitrile (5 mL) together with HBTU (0.11 mmol, 40 mg). Then a solution of HCl·H-L-Ala-OMe (0.1 mmol, 15 mg) and Et$_3$N (0.3 mmol, 40 μL,) in dry acetonitrile (2 mL) was added dropwise to the mixture. The solution was stirred for 50 min under nitrogen atmosphere, then acetonitrile was removed under reduced pressure and replaced with ethyl acetate. The mixture was washed with water, dried over sodium sulfate and concentrated in vacuo. The product **5** was obtained pure after silica gel chromatography (cyclohexane/ethyl acetate 1:1→2:8 as eluant) in 70% (21 mg) overall yield. $[\alpha]_D^{25}$ −9.0 (*c* 0.1, $CHCl_3$); IR (CH_2Cl_2, 3 mM): ν 3436, 3334, 1736, 1709, 1671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9H, ^{t}Bu), 1.42 (d, 3H, J=6.0 Hz, Me–Ala), 2.37 (t, 2H, J=6.4 Hz, C^{5}H$_2$), 2.53 (t, 2H, J=6.0 Hz, C$_\alpha$H$_2$–βAla), 3.37 (t, 2H, J=6.4 Hz, C^{6}H$_2$), 3.51 (q, 2H, J=6.0 Hz, C$_\beta$H$_2$–βAla), 3.26 and 3.68 (s, 1H, OMe), 3.73 (s, 1H, COOMe), 4.55 (dq, 1H, J=6.8 Hz, C$_\alpha$H–Ala), 6.35 (br s, 1H, NH–βAla), 7.42 (d, 1H, J=6.8 Hz, NH–Ala); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 28.4, 33.7, 34.9, 36.3, 42.3, 48.3, 51.8, 52.5, 112.5, 114.9, 156.2, 166.8, 171.6, 172.9, 173.0. Anal. Calcd for $C_{19}H_{29}N_3O_8$: C, 53.39; H, 6.84; N, 9.83. Found: C, 53.42; H, 6.85; N, 9.85.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.11.006.

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