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Efficient construction of functionalized 5-carboxymethyl tetramic acids using *N*-Ac-L-aspartic anhydride as chiral building block

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ABSTRACT

A novel method for the synthesis of densely functionalized optically active 5-carboxymethyl tetramic acids is reported. The proposed strategy is focused on the synthesis of 3,3′-disubstituted pyrrolidine-2,4-diones as useful molecules for the synthesis of natural products. The proposed methodology has been established by X-ray diffraction structure analysis.

1. Introduction

The development of new methodologies for the construction of highly functionalized tetramic acids containing the pyrrolidine-2,4-dione structural motif, is of continuing interest.[1] The fascinating biology of naturally occurring tetramic acids and their derivatives, has resulted in several groups dedicating their efforts toward the synthesis and biological evaluation of these important molecules, and analogues thereof.

Representative examples of bioactive naturally occurring tetramic acids are (Fig. 1): reutericyclin(I) extracted from cell and culture filtrates of *Lactobacillus reuteri*, which inhibits the growth of salmonella and helicobacter,[2] ancorinosides(II) isolated from the marine sponge *Penares sollasi thiele* as inhibitors of membrane type 1 matrix metalloproteinase,[3] tenuazonic acid, produced by Alternaria spp., a biologically active compound with antitumor, antiviral and antibiotic activities,[4] and aurantoside B isolated from various marine sponges exhibits antifungal and cytotoxic activity.[5]

Construction of densely functionalized tetramic acids attract interest and the development of rapid and effective synthetic methodologies have been the focus of many research groups.[6]

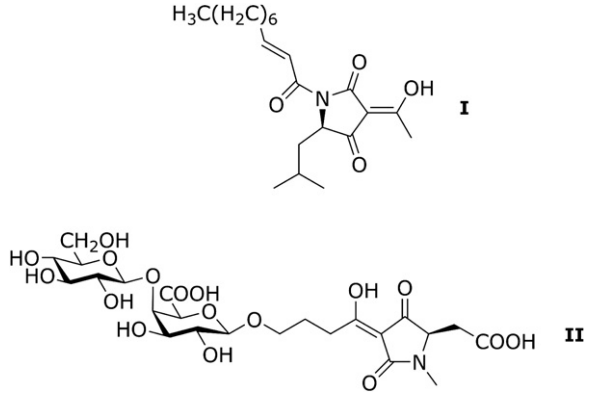

Figure 1. Natural occurring tetramic acids.

Recently an efficient stereocontrolled synthesis of various 3,3′-bisubstituted tetramic acids has been developed starting from 2,5-diketopiperazines, giving access to 2-substituted statins, or the synthesis of relevant lactam-constrained dipeptide mimetics.[7] Furthermore, the genes responsible for several tetramic acids and more modified relatives have been characterized.[8] Janda and co-workers demonstrated that *N*-(3-oxododecanoyl) homoserine lacton (AHLS) generates the 3-substituted-5-(2-hydroxyethyl) tetramic acid via an unusual Claisen-like condensation reaction.[9] Additionally the 3-acetyl pyrrolidine-2,4-dione heterocycle

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moiety has been shown to efficiently chelate a variety of metal cations.[10]

Furthermore, tetramic acids have been identified as a novel starting point for the synthesis of peptide analogues. Methodologies for the incorporation of pyrrolidine-2,4-diones into peptide chains, at the C- or N-terminus or in an intermediate position have been explored by Hosseini and co-workers.[11]

Consequently construction of densely functionalized tetramic acids containing a quaternary carbon center found within these naturally occurring molecules has proven to be a significant synthetic challenge.[12]

Despite the many diverse and creative approaches that have been used to assemble the pyrrolidinone nucleus a general synthesis for regioselective introduction of substituents at C-3 and C-5 is of great importance.

2. Results and discussion

During the course of our studies toward the development of a new methodology on the synthesis of pyrrolidine-2,4-diones, we have been interested in the possibility of developing a new approach to the synthesis and structure elucidation of tetramic acids bearing a polar substituent at the C-5 position[13] and a functionalized quaternary carbon at the C-3 position.

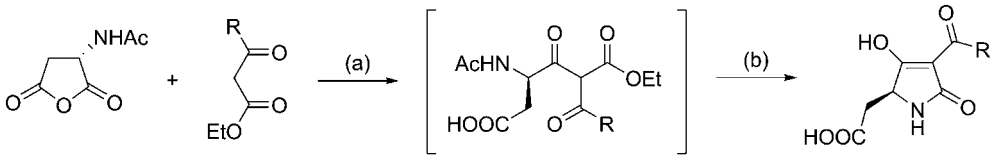
This paper described a new class of functionalized optically active tetramic acids designed and synthesized using the (*S*)-*N*-protected aspartic acid anhydride as a novel chiral starting point, as outlined in Scheme 1.

It is well known that *N*-protected aspartic acid anhydrides constitute useful intermediates in peptide synthesis. In these activated anhydrides the two carboxylic acid moieties can be opened regioselectively, depending on the experimental conditions.[14] The C-2 carbonyl function of *N*-aspartates is susceptible toward a nucleophilic attack and regioselective ring opening by alcohols,[15] amines,[16] and Grignard reagents.[14] To our knowledge, there has been no previous report concerning this nucleophilic attack by active methylene compounds.

Herein a new class of functionalized optically active tetramic acids were designed and synthesized using *N*-acetyl aspartic acid anhydride as the chiral synthon. The electron-withdrawing group activated the C-2 site, which was therefore preferentially attacked. The requisite (*S*)-*N*-acetyl aspartic acid anhydride was easily prepared from L-aspartic acid following a literature procedure.[17] The acetyl *N*-protecting group was found to be stable under the reaction conditions, as was the configuration at the C-2 stereogenic center.

The majority of natural products that contain the tetramic acid moiety have an acyl group at the C-3 position of the heterocyclic ring and their biological activity is essentially due to the presence of the pyrrolidin-2,4-dione ring, the carbonyl group of the C-3 acyl group, and the stereocenter at C-5. Owing to the importance of the naturally occurring 3-acyl tetramic acids,[6e] our initial investigations focused on the acylation of the appropriate β-ketoesters **2a**–**c** by the anhydride **1** (Scheme 1).

Under the proposed reaction conditions, 2 equiv of NaH were added to anhydrous THF followed by the addition of the β-ketoester

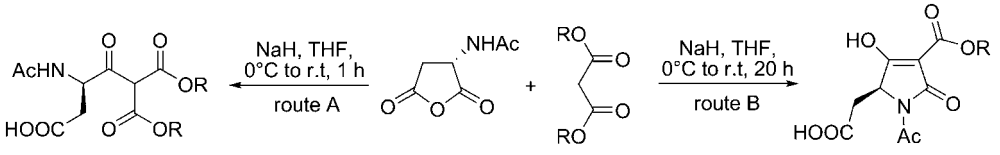


1 **2a** R=Me; **2b** R=Pr; **2c** R=Ph **3a** R=Me (**57%**); **3b** R=Pr (**64%**); **3c** R=Ph (**66%**)

Scheme 1. Reagents and conditions: (a) NaH, THF, 1 h at 0 °C to rt; (b) EtONa/EtOH, rt, overnight.

The requisite (*S*)-*N*-acetyl aspartic acid anhydride **1** was utilized as a convenient precursor for the introduction of the chiral C-5 carbon of the γ-lactam ring. This anhydride was found to react in a highly stereoselective manner at the hindered, more electron-deficient carbonyl at the C-2 site, with carbon nucleophiles derived from the anions of suitable β-ketoesters (**2a**–**c**, **4a**, **4b**) or appropriately substituted ethyl acetates (**7a**–**d**, **9a**–**f**) (Schemes 2–4).

2a–**c** (2 equiv). *N*-Acetyl aspartic acid anhydride **1**, (1 equiv) was then added and the mixture was stirred at room temperature for 1 h. After work-up (see Experimental section) a mixture was produced, which is based on the ^{1}H NMR spectrum, contained the C-acylation compound as the major product. Stirring the crude mixture in EtONa/EtOH at room temperature for 20 h provided 3-acyl-5-carboxymethyl tetramic acids **3a**–**c** in good yields (57–66%).

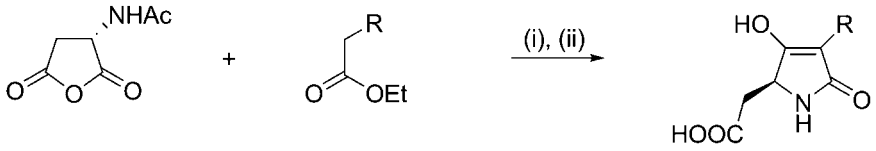


5a R=Me (**60%**) **1** **4a** R=Me; **4b** R=Et **6a** R=Me (**55%**); **6b** R=Et (**50%**)

Scheme 2. Reagents and conditions: the molar ratio of **1**:**4**: NaH is 1:2:2 for route A and 1:3:3 for route B.

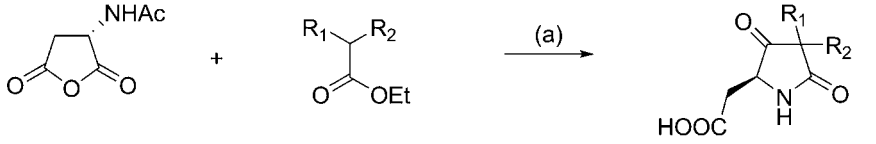
The proposed protocol allows simultaneous construction of the pyrrolidine-2,4-dione ring system with retention of the configuration at the C-5 position and the installation of a quaternary carbon at the C-3 position of the tetramic acid nucleus, which is a useful complement to the synthetic approaches to natural products.

Acylation of the malonate anions **4** (2 equiv) (Scheme 2) under the previous conditions, yielded the *N*-acetyl-3-alkoxycarbonyl-5-carboxymethyl tetramic acids **6a** and **6b**. When the reaction of **1** and **4a** with NaH (2 equiv) was quenched after 1 h, the intermediate **5a** was isolated in 60% yield.



1	**7a** R=Me	**8a** R=Me (**45%**)
	7b R=Ph	**8b** R=Ph (**65%**)
	7c R=4-OMe-Ph	**8c** R=4-OMe-Ph (**51%**)
	7d R=3-OMe-Ph	**8d** R=3-OMe-Ph (**42%**)

Scheme 3. Reagents and conditions: (i) LDA, THF, 1 h −78 °C, 1 h rt; (ii) EtONa/EtOH/benzene (1:1) 3 h reflux, 20 h rt.



1	**9a** R_1=R_2=Me	**10a** R_1=R_2=Me (**55%**)
	9b R_1=Me, R_2 =Et	**10b** R_1=Me, R_2 =Et (**70%**)
	9c R_1=Me, R_2=Pr	**10c** R_1=Me, R_2=Pr (**65%**)
	9d R_1=Me, R_2=Allyl	**10d** R_1=Me, R_2=Allyl (**60%**)
	9e R_1=Et, R_2=Ph	**10e** R_1=Et, R_2=Ph (**70%**)
	9f R_1=Me, R_2=Ph	**10f** R_1=Me, R_2=Ph (**30%**)

Scheme 4. Reagents and conditions: (a) LDA, THF, −78 °C, 1.5 h, to rt, 1.5 h.

The scope of the reaction was further evaluated using lithium enolates derived from appropriately substituted ethyl acetates as carbon nucleophiles; the corresponding 3-alkyl and 3-aryl substituted tetramic acids have been prepared in good yields, which can be regarded as useful key intermediates for the synthesis of natural products[18] (Scheme 3).

Initial acylation experiments were conducted at −78 °C using lithium base (LDA) in THF, followed by cyclization with EtONa/EtOH, benzene, to form the corresponding 3-alkyl and 3-aryl tetramic acids **8a**–**d**, in 45–65% yield.

The enantiomeric excess (ee) of the compounds **8b**–**d** has been determined by HPLC analysis, using a chiral stationary phase.[19] The results (92–96%, ee) indicate that our methodology leads to optically active final compounds, in which the stereochemical integrity of the 5-chiral center is retained to a great extent.

Having established a high efficient route to *N*-protected and NH– tetramic acids we turned our attention to the synthesis of 3,3-disubstituted tetramic acids (Scheme 4), which constitute interesting molecular scaffolds, though references concerning the synthesis of this kind of compounds are rather limited.[20] The 3,3-dimethyl-2,4-pyrrolidinedione moiety would be the characteristic heterocyclic core of the marine neurotoxin 'janolusimide', isolated from nudibranch mollusc *Janolus cristatus*.[21] Moreover, the synthesis of 3,3-disubstituted tetramic acids would provide useful information concerning the diastereoselectivity of the reaction.

We were gratified to find out that our methodology gives rise to the desired compounds in one step. As depicted in Scheme 4, the C-acylation of the apropriate lithium enolates, derived from disubstituted ethyl acetates **9a**–**f**, using the *N*-acetyl-aspartic anhydride **1** as acylating agent provided the 3,3-disubstituted tetramic acids **10a**–**f**, in good yields (60–70%). Under the proposed reaction conditions, we obtained the deacetylated tetramic acids directly, and no deacetylation step was required.

Careful analysis of the ^{1}H NMR spectra indicated that tetramic acids **10b**–**f** exist as mixtures of two diastereomers, as can be deduced from the double signals appearing for each of the protons on the nitrogen atom and at C-5 position of the ring. The diastereomeric ratio was determined to be approximately 70:30 from the integration of either of these signals.

At this point it is important to notice that the nucleophilic attack of active lithium enolates occurs in a highly regioselective manner on the α-carbonyl of the *N*-aspartate, thus providing the desired compounds in good yields. This regioselectivity is probably the result of the following reasons: firstly, the electron withdrawing effect of the *N*-acetyl group activates the α-carbonyl carbon and directs the attack of the nucleophile exclusively to the α-position. In addition, in the non-polar solvent (THF) used for the acylation reaction, the intramolecular hydrogen bond between the hydrogen of the amine group and the α-carbonyl is favored, rendering the α-carbonyl carbon more susceptible for nucleophilic attack.[16]

The carboxymethyl functionality at position 5 of the heterocyclic ring could be further modified to enable access to tetramic acids analogues bearing a variety of substituents on this position.

The X-ray structure[22] of compound **10d** was carried out to confirm the structure in the solid state. The molecular structure and numbering scheme are shown in Figure 2.

There is some double bond character evident in the N (1)–C (1) bond (1.3235 Å) compared to N (1)–C (8) bond (1.4566 Å), and the O (1)–C (1) bond is distinctly longer than the conventional carbonyl distance for O (2)–C (7) (1.2428 Å and 1.208 Å), respectively.

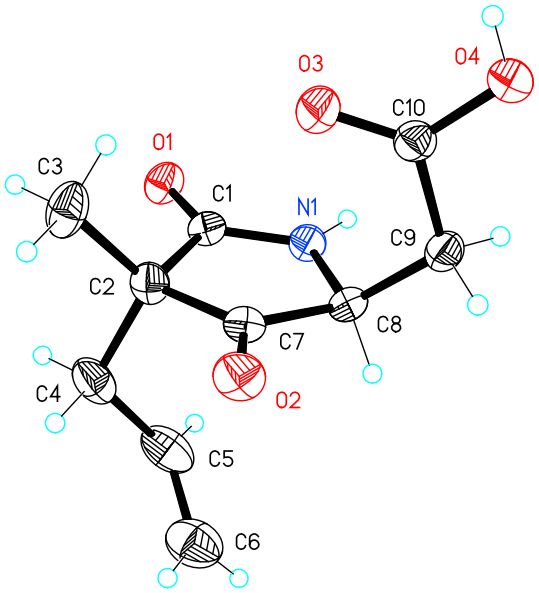


Figure 2. Molecular structure of **10d**. Thermal ellipsoids drawn at the 50% probability level.

3. Conclusions

N-Acetyl aspartic acid anhydride proved to be an excellent acylating agent for *C*-nucleophiles. In all instances ring opening was regioselective, occurring at position 2 of the anhydride ring. The scope of our methodology has been investigated using various nucleophiles and leads to the synthesis of tetramic acids bearing a wide variety of substituents at position 3.

4. Experimental section

4.1. General

Mps were determined on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. High resolution mass spectra were obtained in the Department of Chemistry & Biochemistry of University of Notre Dame on a ESI instrument. IR spectra were recorded by using the attenuated total reflection (ATR) method on a FTIR Bruker Tensor 27 in the Institute of Organic and Pharmaceutical Chemistry of National Hellenic Foundation. The NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz on a Varian Gemini-2000 300 MHz spectrometer; chemical shifts are quoted in parts per million (s=singlet, d=doublet, dd=doublet of douplet, t=triplet, pt=pseudotriplet, q=quartet, m=multiplet, br=broad); *J* values are given in hertz. Elemental analyses were obtained on a Euro EA3000 Series Euro Vector CHNS Elemental Analyzer. All commercially available starting materials were used without further purification. Commercially available THF was dried prior to use by refluxing over Na. All other solvents (puriss quality) were used without further purification. Compounds **7c**, **7d**, **9e**, **9f** were synthesized by following the well established literature procedures.[23] *N*-Acetyl aspartic acid anhydride (**1**) was synthesized according to the literature procedure.[17] Column chromatography was performed with silica gel 60 (230–400 mesh with eluents given in parentheses).

4.2. Synthesis

*4.2.1. General procedure for the preparation of compounds (**3a–c**).* The appropriate active methylene compound (**2**) (10 mmol) was added dropwise to a suspension of NaH (60%, 0.6 g, 10 mmol) in THF (30 mL) and the mixture was stirred at 0 °C for 30–40 min under nitrogen. (*S*)-*N*-Acetyl-L-aspartic anhydride (**1**) (0.79 g, 5 mmol) in THF (5 mL) was added then by syringe, and the reaction mixture was stirred at room temperature for 1 h, under nitrogen. Water (10 mL) was added to the reaction and the THF evaporated in vacuo. The aqueous layer was then washed with Et_2O (20 mL), acidified with HCl 10% to pH=1–2 in an ice-water bath, and then extracted with AcOEt (3×30 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated under reduced pressure, dried in vacuo to give the C-acylation intermediate as an oily product. After 1–2 h drying in vacuo the appropriate C-acylation product was added to a solution of sodium ethoxide [prepared by the addition of sodium (12.5 mmol) in absolute ethanol (44 mL)] and the resulting solution was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was treated with water (10 mL), washed with Et_2O (20 mL), and acidified with HCl 10% to pH=1–2 in an ice-water bath, to give the corresponding (**3**) as solid products, which were dried in vacuo over P_2O_5 for 2–3 h. Otherwise (**2**) was isolated by extraction of aqueous layer with ethyl acetate (3×30 mL), the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure, dried in vacuo to give a solid, after trituration with methanol/diethylether.

*4.2.1.1. (S)-3-Acetyl-5-carboxymethyl tetramic acid (**3a**).* Starting from anhydride (**1**) and using ethyl acetoacetate (10.0 mmol, 1.3 g) the title compound was obtained as a white solid (0.57 g, 57%). Mp: 157–159 °C (lit., mp 168 °C).[24] $[\alpha]_D^{20}$ −14.7 (*c* 0.2, methanol). IR (ATR): 3214, 3054, 1703, 1655, 1610 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.35 (3H, s), 2.58 (1H, dd, *J*=16.8, 6.6 Hz), 2.65 (1H, dd, *J*=16.8, 4.8 Hz), 4.07 (1H, pt), 8.79 (1H, br s), 10.37 (1H, br s), 12.40 (1H, br s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.6, 35.7, 58.1, 101.5, 171.2, 174.6, 184.3, 194.8. Anal. Calcd for $C_8H_9NO_5$: C, 48.25; H, 4.55; N, 7.03. Found: C, 48.01; H, 4.28; N, 6.84.

*4.2.1.2. (S)-3-Butanoyl-5-carboxymethyl tetramic acid (**3b**)* Starting from anhydride (**1**) and using ethyl butanoylacetate (10.0 mmol, 1.58 g) the title compound was obtained as a white solid (0.73 g, 64%). Mp: 161–163 °C. $[\alpha]_D^{20}$ −57.1 (*c* 0.2, methanol). IR (ATR): 3205, 3055, 1704, 1655, 1606 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.89 (3H, t, *J*=7.2 Hz), 1.53–1.66 (2H, m), 2.56/2.66 (2H, 2dd, *J*=16.8, 6.3, 17.1, 4.5 Hz), 2.72 (2H, t, *J*=7.2 Hz), 4.06 (1H, pt), 8.86 (1H, br s), 11.25 (1H, br s) 12.36 (1H, br s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.5, 18.8, 34.2, 35.7, 58.2, 101.1, 171.2, 175.3, 187.6, 194.5. Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.16. Found: C, 52.52; H, 5.51; N, 6.00.

*4.2.1.3. (S)-3-Benzoyl-5-carboxymethyl tetramic acid (**3c**)* Starting from anhydride (**1**) and using ethyl benzoylacetate (10.0 mmol, 1.92 g) the title compound was obtained as a white solid (0.86 g, 66%). Mp: 202–204 °C. $[\alpha]_D^{20}$ −122.2 (*c* 0.5, methanol). IR (ATR): 3207, 3058, 1701, 1663, 1605, 1595 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.62/2.72 (2H, 2dd, *J*=16.8,6.0 Hz, *J*=16.8,4.5 Hz), 4.14 (1H, pt), 7.53 (2H, t, *J*=7.5 Hz), 7.64 (1H, t, *J*=7.5 Hz), 8.11 (2H, d, *J*=7.5 Hz), 9.22 (1H, br s), 11.72 (2H, br s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.8, 57.7, 99.8, 128.1, 129.1, 132.5, 133.3, 171.3, 176.8, 180.3, 192.4. Anal. Calcd for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.24; N, 5.36. Found: C, 59.52; H, 4.02; N, 5.14.

*4.2.2. General procedure for the preparation of compounds (**5a**, **6a**, **6b**).* The appropriate active methylene compound **4** (10 mmol) was added dropwise to a suspension of NaH (60%, 0.9 g, 15 mmol) in THF (30 mL) and the mixture was stirred at 0 °C for 30–40 min under nitrogen. (*S*)-*N*-Acetyl-L-aspartic anhydride (**1**) (0.79 g, 5 mmol) in THF (5 mL) was added then by syringe, and the reaction mixture was stirred at room temperature for 20 h. The same work up was followed as for **3** to give the corresponding products **6a**, **6b** in an

oily form. After trituration with MeOH/Et_2O/PE the precipitated solids were collected by filtration and dried in vacuo over P_2O_5 for 2–3 h.

*4.2.2.1. (S)-3-Acetamido-6-methoxy-5-(methoxycarbonyl)-4,6-dioxohexanoic acid (**5a**).* The title compound was afforded according to the modified procedure for (**6a**, **6b**), so after the addition of anhydride (**1**) the reaction mixture was stirred for only 1 h and then quenched [dimethyl malonate (10.0 mmol, 1.32 g) and sodium hydride (10 mmol, 0.6 g, 60% in oil) was used]. The C-acylation intermediate **5a** was solidified by treating of the oily crude reaction mixture with Et_2O and then refrigerated for several hours. The title compound was obtained as a white solid (0.87 g, 60%). Mp: 273–275 °C. $[\alpha]_D^{20}$ −83.6 (*c* 0.35, methanol). IR (ATR): 3420, 3378, 1764, 1737, 1701, 1641, 1512 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.86 (3H, s), 2.56 (1H, dd, *J*=16.8, 7.2 Hz), 2.73 (1H, dd, *J*=16.8, 5.4 Hz), 3.68/3.69 (6H, 2s), 4.70 (1H, m), 4.98 (1H, s), 8.55 (1H, br d, *J*=8.1 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.1, 35.0, 52.96, 53.01, 54.6, 61.3, 164.6, 164.7, 170.1, 171.6, 198.4. Anal. Calcd for $C_{11}H_{15}NO_8$: 45.68; H, 5.23; N, 4.84. Found: 45.46; H, 5.04; N, 4.62.

*4.2.2.2. (S)-1-Acetyl-5-carboxymethyl-3-methoxycarbonyl tetramic acid (**6a**).* Starting from anhydride (**1**) and using dimethyl malonate (10.0 mmol, 1.32 g) the title compound was obtained as a white solid (0.71 g, 55%). Mp: 168–170 °C. $[\alpha]_D^{20}$ +48.3 (*c* 0.2, methanol). Mp: 111–113 °C. IR (ATR): 3177, 1722, 1688, 1614 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.37 (3H, s), 2.80/2.88 (2H, 2dd, *J*=15.9, 3.6 Hz, *J*=15.9, 5.7 Hz), 3.65 (3H, s), 4.65 (1H, dd, *J*=5.7, 3.6 Hz), 10.29 (2H, br s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.0, 34.2, 50.6, 55.2, 96.3, 162.2, 166.5, 168.9, 170.5, 184.0. Anal. Calcd for $C_{10}H_{11}NO_7$: C, 46.70; H, 4.31; N, 5.45. Found: C, 46.48; H, 4.12; N, 5.22.

*4.2.2.3. (S)-1-Acetyl-5-carboxymethyl-3-ethoxycarbonyl tetramic acid (**6b**).* Starting from anhydride (**1**) and using diethyl malonate (10.0 mmol, 1.6 g) the title compound was obtained as a white solid (0.68 g, 50%). Mp: 115–117 °C. $[\alpha]_D^{20}$ +48.3 (*c* 0.2, methanol). IR (ATR): 3215, 1735, 1691, 1663, 1608 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.22 (3H, t, *J*=6.9 Hz), 2.37 (3H, s), 2.80/2.89 (2H, 2dd, *J*=16.2, 3.6, 16.2, 6.0 Hz), 4.15 (2H, m), 4.66 (1H, dd, *J*=5.7, 3.6 Hz), 8.37 (2H, br s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.3, 25.0, 34.1, 55.1, 59.2, 96.7, 161.9, 166.3, 168.9, 170.5, 183.7. Anal. Calcd for $C_{11}H_{13}NO_7$: C, 48.71; H, 4.83; N, 5.16. Found: C, 48.49; H, 4.61; N, 5.01.

*4.2.3. General procedure for the preparation of compounds (**8a–d**).* A solution of the appropriate aryl or alkylacetates (**7**) (8 mmol) in THF (4 mL) was added dropwise via a syringe over a period of 10 min to a solution of lithium diisopropylamide (LDA) 2.0 M solution in THF/hexane/ethylbenzene (8 mmol, 4 mL) in THF (20 mL) at −78 °C under nitrogen. The mixture was stirred for 45 min, then (*S*)-*N*-acetyl-L-aspartic anhydride (**1**) (0.42 g, 2.67 mmol) in THF (4 mL) was added by cannula over 10 min. The reaction mixture was stirred for 1 h at −78 °C and 1 h at room temperature, quenched with water (10 mL), and the THF evaporated in vacuo. The resulting aqueous layer was then washed with Et_2O (20 mL) and acidified with HCl 10% to pH=1–2 in an ice-water bath, and then extracted with AcOEt (3×30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to give the C-acylation intermediates as oily products. After 1–2 h drying in vacuo the appropriate C-acylation product was added to a solution of sodium ethoxide [prepared by the addition of sodium (6.65 mmol) to a solution of absolute EtOH/anhydrous benzene 1:1 (46 mL)] and the resulting solution was refluxed for 3 h and then stirred for 20 h at room temperature. The solvents were concentrated and the residue was treated with water (10 mL), washed with Et_2O (20 mL) and acidified with HCl 10% to pH=1–2 in an ice-water bath. Compounds (**8a–d**) were isolated by extraction of the aqueous layer with AcOEt (3×30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to give after trituration with methanol/diethylether the final products (**8a–d**), which were dried in vacuo over P_2O_5 for 2–3 h.

*4.2.3.1. (S)-5-Carboxymethyl-3-methyl tetramic acid (**8a**)* Starting from anhydride (**1**) and using ethyl propionate (8.0 mmol, 0.82 g) the title compound was obtained as a gummy solid (0.21 g, 45%). Mp: 171–173 °C. $[\alpha]_D^{20}$ +25.9 (*c* 0.2, methanol). IR (ATR): 3408, 1715, 1687, 1640 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.52 (3H, s), 2.16 (1H, dd, *J*=16.2, 8.7 Hz), 2.70 (1H, dd, *J*=16.2, 3.6 Hz), 4.07 (1H, pt), 7.28 (1H, br s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 6.1, 37.7, 52.4, 100.3, 167.9, 172.0, 174.6. Anal. Calcd for $C_7H_9NO_4$: C, 49.12; H, 5.30; N, 8.18. Found: 48.95; H, 5.14; N, 8.01.

*4.2.3.2. (S)-5-Carboxymethyl-3-Phenyltetramic acid (**8b**)* Starting from anhydride (**1**) and using ethyl phenylacetate (8.0 mmol, 1.31 g) the title compound was obtained as a white solid (0.41 g, 65%). Mp: 222–224 °C. $[\alpha]_D^{20}$ −52.1 (*c* 0.2, methanol), ee 92%. IR (ATR): 3402, 3061, 1720, 1643, 1596 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.29 (1H, dd, *J*=16.2,9.3 Hz), 2.95 (1H, dd, *J*=16.2,3.0 Hz), 4.28 (1H, dd, *J*=9.3, 3.0 Hz), 7.16 (1H, t, *J*=7.5 Hz), 7.31 (2H, t, *J*=7.8 Hz), 7.59 (1H, br s), 7.93 (2H, d, *J*=7.5 Hz), 11.58/12.37 (2H, 2br s) ^{13}C NMR (75 MHz, DMSO-d_6): δ 37.8, 52.1, 103.6, 125.8, 127.2, 127.7, 132.2, 170.0, 172.0, 172.8. Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.62; H, 4.52; N, 5.79.

*4.2.3.3. (S)-5-Carboxymethyl-3-(4-methoxyphenyl)tetramic acid (**8c**).* Starting from anhydride (**1**) and using ethyl 2-(4-methoxyphenyl)acetate (8.0 mmol, 1.55 g) the title compound was obtained as a light beige solid (0.36 g, 51%). Mp: 220–222 °C. $[\alpha]_D^{20}$ −30.6 (*c* 0.2, methanol). IR (ATR): 3408, 1723, 1699, 1655, 1590 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.25 (1H, dd, *J*=16.2, 9.3 Hz), 2.94 (1H, dd, *J*=16.2, 3.0 Hz), 3.74 (3H, s), 4.25 (1H, dd, *J*=9.3, 3.0 Hz), 6.89 (2H, d, *J*=9.0 Hz), 7.56 (1H, br s), 7.88 (2H, d, *J*=9.0 Hz), 11.30 (1H, br s), 12.45 (1H, br s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 37.8, 52.0, 55.0, 103.3, 113.0, 124.6, 128.2, 134.5, 157.2, 168.4, 172.0, 172.9. Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.15; H, 4.81; N, 5.14.

*4.2.3.4. (S)-5-Carboxymethyl-3-(3-methoxyphenyl)tetramic acid (**8d**).* Starting from anhydride (**1**) and using ethyl 2-(3-methoxyphenyl)acetate (8.0 mmol, 1.55 g) the title compound was obtained as a light beige solid (0.29 g, 42%). Mp: 207–209 °C. $[\alpha]_D^{20}$ −70.8 (*c* 0.2, methanol). IR (ATR): 3307, 1720, 1647, 1609, 1575 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 2.29 (1H, dd, *J*=16.2, 9.3 Hz), 2.93 (1H, dd, *J*=16.2, 3.3 Hz), 3.73 (3H, s), 4.28 (1H, dd, *J*=9.3, 3.3 Hz), 6.73–6.83 (1H, m), 7.21 (1H, t, *J*=8.1 Hz), 7.54–7.59 (2H, m), 11.76/12.03 (2H, 2br s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 37.8, 52.0, 54.8, 103.2, 111.2, 112.6, 119.6, 128.6, 133.5, 158.7, 170.5, 172.0, 172.7. Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.11; H, 4.79; N, 5.17.

*4.2.4. General procedure for the preparation of 3,3-disubstituted carboxymethyltetramic acids (**10a–h**).* A solution of the appropriate disubstituted acetates (**9**) (8 mmol) in THF (4 mL) was added dropwise via a syringe over a period of 10 min to a solution of lithium diisopropylamide (LDA) 2.0 M solution in THF/hexane/ethylbenzene (8 mmol, 4 mL) in THF (20 mL) at −78 °C under nitrogen. The mixture was stirred for 45 min, then (*S*)-*N*-acetyl-L-aspartic anhydride (**1**) (0.42 g, 2.67 mmol) in THF (4 mL) was added by cannula over 10 min. The reaction mixture was stirred for 90 min at −78 °C and 90 min at room temperature, quenched with water (10 mL), and the THF evaporated in vacuo. The same work up was followed as for (**8**) to give the corresponding products (**10e–f**),

in an oily form, which were purified by column chromatography on silica gel with dichloromethane/MeOH/AcOH.

*4.2.4.1. (S)-5-Carboxymethyl-3,3-dimethyltetramic acid (**10a**)* Starting from anhydride (**1**) and using ethyl isobutyrate (8.0 mmol, 0.93 g) the title compound was obtained as a white solid (0.27 g, 55%) after purification by column chromatography [dichloromethane/methanol/acetic acid (94:4:2)] and trituration with diethylether/petroleum ether. Mp: 286–288 °C. $[\alpha]_D^{20}$ +37.0 (*c* 0.1, methanol). IR (ATR): 3323, 1768, 1701, 1652 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.10 (6H, s), 2.64 (1H, dd, *J*=17.7, 4.2 Hz), 2.81 (1H, dd, *J*=17.4, 4.2 Hz), 4.23 (1H, pt), 8.23 (1H, br s), 12.41 (1H, br s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.8, 22.4, 35.6, 46.0, 56.5, 171.4, 176.9, 214.6. Anal. Calcd for $C_8H_{11}O_4N$: C, 51.89; H, 5.99; N, 7.56. Found: C, 52.06; H, 6.11; N, 7.69. ESI-HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_8H_{11}NNaO_4$ 208.0580, found 208.0569.

*4.2.4.2. (S)-5-Carboxymethyl-3-ethyl-3-methyltetramic acid (**10b**).* Starting from anhydride (**1**) and using ethyl 2-methylbutanoate (8.0 mmol, 1.05 g) the title compound was obtained as a colorless oil (0.37 g, 70%), after purification by column chromatography [dichloromethane/methanol/acetic acid (94:4:2)] as a mixture of two diastereomers (69:31). IR (ATR): 3315, 1758, 1701, 1639 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$/DMSO-d_6): δ 0.70/0.76 (3H, 2 t, *J*=7.2 Hz), 1.12/1.13 (3H, 2s), 1.58–1.66 (2H, m), 2.33/2.58 (0.31/0.69H, 2dd, *J*=17.1, 10.2/17.1, 7.2 Hz), 2.79 (1H, dd, *J*=17.1,3.6 Hz), 4.01/4.23 (0.69/0.31H, 2dd, *J*=3.6, 7.2/10.2, 3.6 Hz), 7.68/7.75 (1H, 2br s), 10.37 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6): δ 8.8, 9.5, 18.5, 20.4, 27.5, 29.9, 35.9, 36.2, 51.5, 51.6, 57.7, 58.6, 172.4, 172.8, 177.8, 178.4, 212.9, 213.3. ESI-HRMS: *m*/*z* $[M+H]^+$ calcd for $C_9H_{14}NO_4$ 200.0917, found 200.0909.

*4.2.4.3. (S)-5-Carboxymethyl-3-methyl-3-propyltetramic acid (**10c**).* Starting from anhydride (**1**) and using ethyl 2-methylpentanoate (8.0 mmol, 1.15 g) the title compound was obtained as a colorless oil (0.37 g, 65%), after purification by column chromatography [dichloromethane/methanol/acetic acid (94:4:2)] as a mixture of two diastereomers (81:19). IR (ATR): 3318, 1758, 1702, 1643 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.81 (3H, t, *J*=7.2 Hz), 1.09–1.27 (5H, m), 1.43–1.53 (2H, m), 2.57–2.68 (1.19H, m), 2.79 (0.81H, dd, *J*=17.7, 4.2 Hz), 4.09/4.33 (0.81/0.19H, 2pt), 8.33/8.43 (0.81/0.19H, 2br s), 12.54 (1H, br s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1/14.4, 17.2/17.6, 18.2/20.6, 35.7/35.9, 49.8/50.2, 57.0/57.8, 171.1, 175.9/176.3, 214.6/214.9. ESI-HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{10}H_{16}NO_4$ 214.1074, found 214.1066.

*4.2.4.4. (S)-3-allyl-5-Carboxymethyl-3-methyltetramic acid (**10d**).* Starting from anhydride (**1**) and using ethyl 2-methylpent-4-enoate (8.0 mmol, 1.14 g) the title compound was obtained as a colorless oil (0.34 g, 60%), after purification by column chromatography (dichloromethane/methanol/acetic acid (94:4:2)) as a mixture of two diastereomers (79:21). Crystalization occures with petroleum ether/drops MeOH in order to give colorless crystals. IR (ATR): 3191, 1771, 1728, 1660, 1640 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.10 (3H, s), 2.17–2.30 (2H, m), 2.55–2.67 (1.24H, m), 2.81 (0.76H, dd, *J*=17.4, 3.9 Hz), 3.98/4.30 (0.76/0.24H, 2pt), 5.02–5.07 (2H, m), 5.57–5.82 (1H, m), 8.34/8.43 (0.76/0.24H, 2br s), 12.59 (1H, br s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 17.7/19.9, 35.6/35.9, 37.8/40.9, 49.4/50.3, 57.0/57.79, 118.6/119.2, 132.1/133.2, 171.2/171.3, 175.6/175.7, 213.7/214.0. ESI-HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{10}H_{14}NO_4$ 212.0917, found 212.0919. X-ray data were collected at 150(2) K on a Bruker Apex II CCD diffractometer. The structure was solved by direct methods and refined on F^2 using all the reflections.[22] All the non-hydrogen atoms were refined using anisotropic atomic displacement parameters and hydrogen atoms were inserted at calculated positions using a riding model. $C_{10}H_{13}NO_4$, monoclinic, *Pc*, *a*=6.7116(6), *b*=9.5530(8), *c*=8.4485(7) Å, β=102.183(1)°, *V*=529.48(8) $Å^3$, *T*=150(2) K, λ=0.71073 Å, *Z*=2, 5344 reflections measured, 2578 unique (R_{int}=0.0202), *wR2*=0.0776 (all data), *R*1=0.313 ($I>2\sigma(I)$). Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 740987. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

*4.2.4.5. (S)-5-Carboxymethyl-3-ethyl-3-phenyltetramic acid (**10e**).* Starting from anhydride (**1**) and using ethyl 2-methylbutanoate (8.0 mmol, 1.15 g) the title compound was obtained as a colorless oil (0.37 g, 70%), after purification by column chromatography [dichloromethane/methanol/acetic acid (94:4:2)] as a mixture of two diastereomers (51:49). IR (ATR): 3247, 1769, 1697, 1658 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.87/0.91 (3H, 2 t, *J*=7.2 Hz), 2.03–2.27 (2H, m), 2.55 (0.49H, dd, *J*=17.4, 10.2 Hz), 2.87 (0.51H, dd, *J*=17.4, 3.0 Hz), 2.87 (0.51H, dd, *J*=17.4, 3.0 Hz), 4.24–4.32 (1H, m), 7.27–7.44 (5H, m), 8.48/8.54 (0.51/0.49H, 2br s), 11.26 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.6/10.0, 28.7/30.1, 35.4/37.3, 57.9/59.2, 60.2/60.9, 126.5/126.6, 128.1/128.3, 129.1/129.2, 135.2/135.6, 174.2/174.4, 176.8/177.1, 208.5/209.3. ESI-HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{14}H_{16}NO_4$ 262.1074, found 262.1056.

*4.2.4.6. (S)-5-Carboxymethyl-3-methyl-3-phenyltetramic acid (**10f**).* Starting from anhydride (**1**) and using ethyl 2-phenylpropanoate (8.0 mmol, 1.43 g) the title compound was obtained as a colorless oil (0.20 g, 30%), after purification by column chromatography [dichloromethane/methanol/acetic acid (94:4:2)] as a mixture of two diastereomers (81:19). IR (ATR): 3196, 1768, 1732, 1685, 1654 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.51/1.54 (3H, 2s), 2.60 (0.19H, pt), 2.73/2.88 (1.82H, 2dd, *J*=17.7, 3.6 Hz, *J*=17.7, 3.6 Hz), 4.27/4.48 (0.81/0.19H, 2pt), 7.25–7.39 (5H, m), 8.62/8.73 (0.81/0.19H, 2br s), 12.65 (1H, br s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.3, 35.3, 54.7, 57.3, 126.1, 127.5, 128.9, 137.9, 171.2, 174.8, 211.5. ESI-HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{13}H_{14}NO_4$ 248.0917, found 248.0893.

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2010.03.083.

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