Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 3955–3963

TETRAHEDRON: *ASYMMETRY*

Total synthesis of 3,4-dihydroxyprolines, D-*threo*-L-norvaline and (2*S*,3*R*,4*R*)-2-amino-3,4-dihydroxytetrahydrofuran-2-carboxylic acid methyl ester

Raquel G. Soengas, Juan C. Estévez and Ramón J. Estévez*

Departamento de Química Orgánica, Universidade de Santiago, 15782 Santiago de Compostela, Spain

Received 13 September 2003; accepted 1 October 2003

Abstract—The Henry reaction between D-glyceraldehyde and ethyl nitroacetate allowed the practical development of a diastereoselective synthesis of 3,4,5-trihydroxy-2-nitropentanoic acid esters, which were reduced to polyoxamic acids, which were used in a new diastereoselective synthesis of 3,4-dihydroxyprolines and new enantioselective syntheses of D-*threo*-L-norvaline and (2*S*,3*R*,4*R*)-2-amino-3,4-dihydroxytetrahydrofuran-2-carboxylic acid methyl ester.

1. Introduction

The Henry reaction, or nitroaldol reaction, couples a carbonyl compound and a nitroalkane bearing an α hydrogen atom, thereby creating an α-nitroalkanol. It is a powerful tool for the construction of C–C bonds, and can result in the formation of one or two stereogenic centres.[1] Following the condensation reaction, the nitro group can be subjected to a diverse range of chemical transformations, including reduction to an amino group or oxidation to the corresponding ketone (the Nef reaction).[2]

Nitroacetic acid esters are a class of nitroalkanes that have received considerable attention due to their special chemical properties.[3] The presence of an active methylene group makes these esters particularly efficient in the formation of carbon–carbon bonds. For example, they readily execute nucleophilic attack on a wide range of electrophiles, including alkyl halides, carbonyl compounds and Michael acceptors. Accordingly, they are convenient starting materials for the synthesis of 2-nitroalkanoic acids. Thus, methyl nitroacetate has thereby proved to be a versatile equivalent of glycine for the preparation of non-natural α-amino acids.[4] Somewhat surprisingly, the preparation of α-amino acids by the Henry reaction of sugars with alkyl nitroacetates has received very little attention.[5]

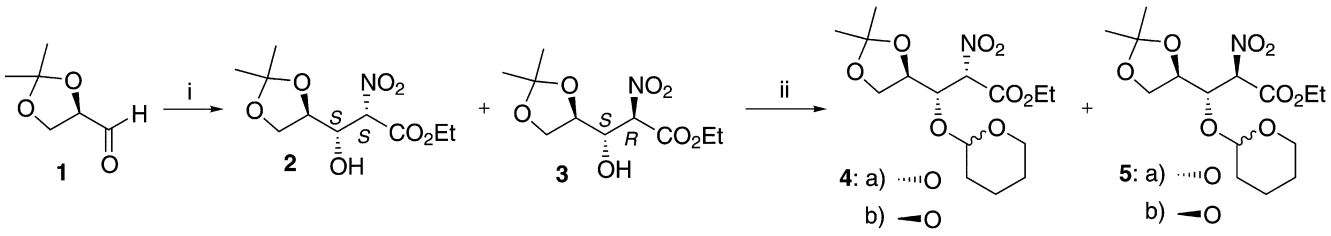
As part of a broader programme on the synthesis and synthetic applications of nitroalkanoic acids derived from sugars,[6] we describe herein practical conditions for the Henry reaction between D-glyceraldehyde and ethyl nitroacetate, which gives 2-nitro-3,4,5-trihydroxypentanoic acids. We also describe the reduction of these products to polyoxamic acids, and the use of the latter in a new diastereoselective synthesis of 3,4-dihydroxyprolines **14** and **15** and new enantioselective syntheses of D-*threo*-L-norvaline **19** and (2*S*,3*R*,4*R*)-2-amino-3,4-dihydroxytetrahydrofuran-2-carboxylic acid methyl ester **25**.

2. Results and discussion

Condensation of D-glyceraldehyde **1**[7] with ethyl nitroacetate under typical Henry reaction conditions gave a 45% yield the data of which showed it to be an unstable 6:5 mixture of pentanoic acid ester epimers **2** and **3** (Scheme 1). The ^{1}H NMR spectrum of this mixture included a multiplet between 1.33 and 1.44 ppm due to the methyl groups of the ethyl ester moieties, and the IR spectrum showed bands at 3502 cm^{-1} (due to the hydroxyl group), at 1753 cm^{-1} (the carbonyl signal) and at 1565 and 1375 cm^{-1} (two typical nitro group bands). The stereochemistry of **2** and **3** were tentatively elucidated by reasoning analogous to that applied to a similar, previously reported reaction:[7] the (*S*)-configuration of the two nitroaldols C_3 epimers is explained in terms of preferential attack by the nucleo-

* Corresponding author. Tel.: +34-981-563100; fax: +34-981-591014; e-mail: qorjec@usc.es

0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2003.10.005



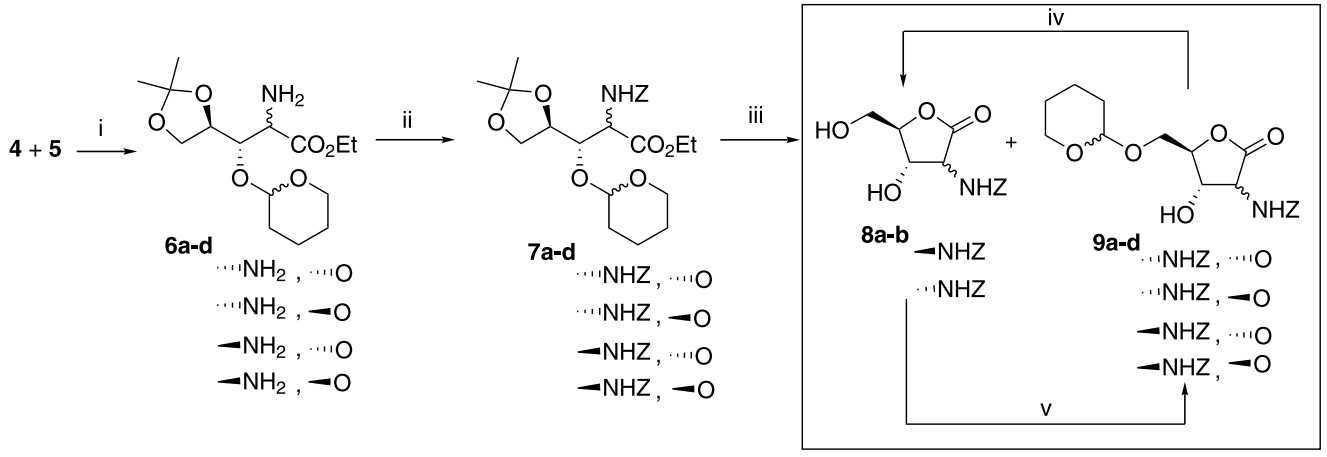
Scheme 1. *Reagents and conditions*: (i) Ethyl nitroacetate/KF/isopropanol; (ii) DHP/PPTS/CH_2Cl_2.

phile at the *re* face of the aldehyde and the preferred conformation of the latter.

To avoid the easy retro-Henry reaction we decided to protect the free OH group of compounds **2** and **3** as soon as this mixture was isolated. After several unsuccessful attempts at protection with benzyl trichloroacetimidate in an acidic medium, reaction of the mixture **2**+**3** with DHP and pyridinium *p*-toluenesulfonate gave an 80% yield of the expected mixture of alkanoic acid esters, which comprised the epimeric pairs **4a**+**4b** and **5a**+**5b**. The IR spectrum of this mixture contained the typical nitro bands at 1562 and 1374 cm^{-1}, but not the free OH of the starting compounds. Attempts to separate compounds **4** and **5** failed, both the chromatographic fractions that were isolated seeming to consist of both **4** and **5**; both fractions gave a mixture of compounds **2** and **3** upon treatment with pyridinium *p*-toluenesulfonate to remove the THP protecting group.

Catalytic hydrogenation of the mixture **4**+**5** gave the expected mixture of polyoxamic acid esters **6a–d** (Scheme 2). The success of the reaction was evidenced by the IR spectrum, in which the nitro bands had been replaced by a band at 3391 cm^{-1}, due to the NH_2 group. The four components of this mixture were separated by column chromatography, and it was planned to convert each amino acid ester into the corresponding furolactone in order to establish its configuration. However, following protection of the amino group of **6a** as its benzyloxycarbonyl derivative (by treatment with benzyloxycarbonylchloride and sodium carbonate) and reaction of the resulting compound **7a** with trifluoroacetic acid (to remove the THP and acetonide groups), subsequent lactonization gave a crude product that when purified by column chromatography afforded a mixture of the two epimeric lactones **8a** and **8b** (28% yield) and a mixture of the four diastereomeric lactones **9a–d** (42% yield). The same result was obtained on starting from **6b**, **6c** and **6d**. This unexpected outcome implies that three processes accompany lactonization: epimerization at the stereogenic centre bearing the NHZ group,[8] deprotection of the OH group at C_3 and transfer of the protecting group to the less hindered OH group at position C_5. Since treatment of the mixture of **8a** and **8b** with DHP and *p*-TsOH under the same conditions as for **2**+**3** led to the mixture **9a–d**, and treatment of the mixture of **9a–d** with pyridinium *p*-toluenesulfonate gave **8a**+**8b**, it seems like that **9a–d** are formed from compound **7a** via **8a** and **8b**.

In view of these results, in subsequent experiments the mixture of polyoxamic acid esters **6a–d** was transformed directly, and in better yield, into the above mixture of lactones **8a**, **8b** and **9a–d**. Reaction of this mixture with pyridinium *p*-toluenesulfonate gave a quantitative yield of the mixture **8a**+**8b**, from which a



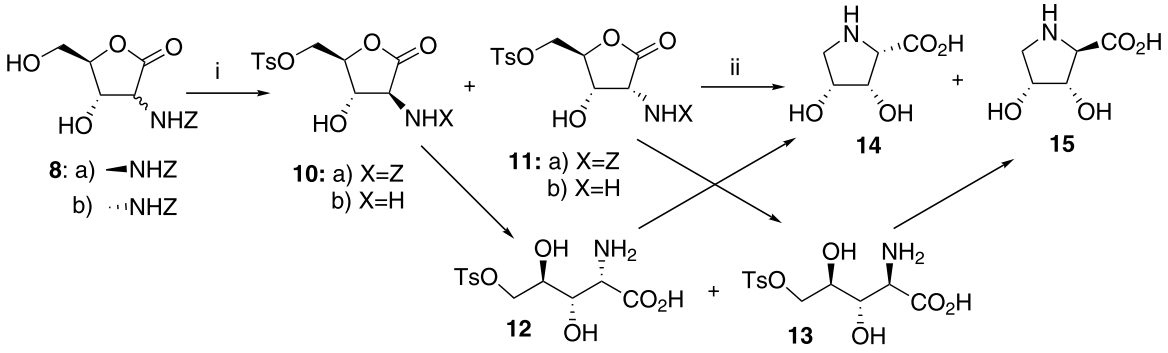
Scheme 2. *Reagents and conditions*: (i) H_2/Raney-Ni/methanol; (ii) BnOCOCl/$NaHCO_3$/ethyl acetate; (iii) TFA/H_2O/THF; (iv) PPTS/ethanol, 50°C; (v) DHP/PPTS/CH_2Cl_2.

small amount of the major component, **8a**, was isolated by column chromatography and tentatively identified on the basis of its spectroscopic properties.

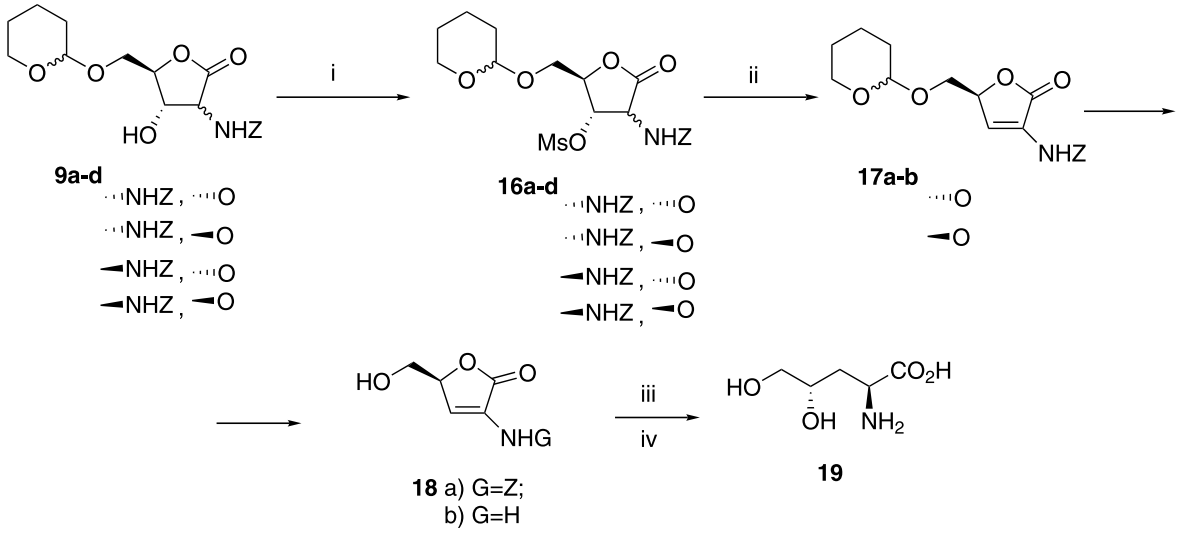
Via lactones **8a** and **8b** it was possible to transform polyoxamic acids **6** into 3,4-dihydroxyprolines **14** and **15**,[9] members of a family that include compounds with inhibitory activity,[10] anti-HIV activity,[11] immunostimulatory properties,[12] or the ability to induce secondary structures in peptides.[13] In an initial attempt to transform pure lactone **8a** into **14** via **10a** and **10b**, selective tosylation of the C_5 OH group by reaction with *p*-toluenesulfonyl chloride in pyridine gave a mixture of lactones **10a** and **11a** as a result of epimerization at position C_2 (Scheme 3). The mixture **10a**+**11a** was also obtained, albeit in better yield, starting from the mixture **8a**+**8b**. Removal of the benzyloxycarbonyl group of **10a**+**11a** by catalytic hydrogenation in the presence of hydrochloric acid, followed by treatment of the resulting mixture, **10b**+**11b**, with aqueous barium hydroxide, afforded a mixture of 3,4-dihydroxyprolines **14**[14] and **15** in 68% yield.[15] Since lactone **11b** cannot be converted directly into the corresponding proline **15** (its stereochemistry prevents internal displacement of the OTs group by the amino group), we deduce that this transformation must have involved the opening of **10b** and **11b** to polyoxamic acids **12** and **13** by the action of barium hydroxide, followed by ring-closing intramolecular displacement of the OTs group by the NH_2 group. Compounds **14** and **15** were not separated, but their separation has been described previously following their preparation by a different method.[16]

As a second application of the derivatives of polyoxamic acids **6**, we converted the mixture **9a–d** into D-*threo*-L-norvaline[17] **19** (Scheme 4), an abundant non-proteogenic natural amino acid that has been used as a key precursor in the synthesis of clavalanine,[18] a potent β-lactam antibiotic isolated[19] from *Streptomyces clavuligerus*, and has previously been synthetized from D-glucose and D-ribose.[20]

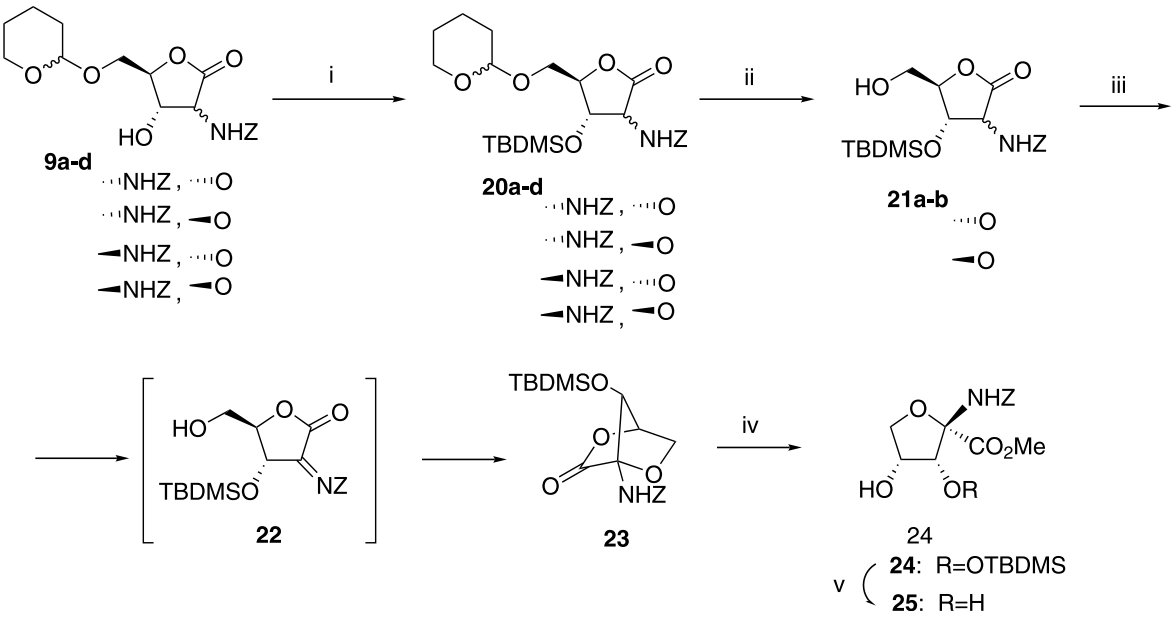
Treatment of **9a–d** with methanesulfonyl chloride in pyridine resulted in the formation of a mixture of *O*-mesyl derivatives **16a–d**, which upon treatment with PPTS in ethanol gave **17a**+**17b** through elimination of MsOH and formation of the carbon–carbon double bond. Removal of the benzyloxycarbonyl protecting group provided lactone **18a**, which was transformed into the target compound **19** in 63% yield stereoselective reduction of the carbon–carbon double bond and subsequent treatment of the resulting lactone, **18b**, with barium hydroxide and Amberlite 120-IR.[20b]



Scheme 3. *Reagents and conditions*: (i) TsCl/pyridine; (ii) a. H_2/Pd–C, HCl, b. $Ba(OH)_2$, Amberlite 120-IR.



Scheme 4. *Reagents and conditions*: (i) MsCl, pyridine; (ii) PPTS, ethanol; (iii) H_2/Pd–C, acetic acid; (iv) $Ba(OH)_2$.



Scheme 5. *Reagents and conditions*: (i) TBDMSiCl, imidazole, DMF; (ii) PPTS, ethanol; (iii) NBS, acetonitrile; (iv) HCl (1% in methanol); (v) Bu_4NF, THF.

We also transformed **9a**–**d** into furan α-amino acid **25** (Scheme 5). Although a number of sugar α-amino acids of this kind the amino and carboxylate groups at the anomeric position, have been incorporated into peptides and/or converted into spirodiketopiperazine derivatives or hydantoins such as the natural herbicide hydantocidin,[22,23] **25** is the only member of this class with no substituents at C4.[21]

Following the efficient protection of the free OH group of **9a**–**d** by treatment with *t*-butyldimethylsilyl chloride and imidazole, the THP group of the resulting lactones, **20a**–**d**, was efficiently removed with pyridinium *p*-toluenesulfonate in ethanol, giving a mixture of lactones **21a** and **21b** in 75% yield. Reaction of this mixture with NBS in acetonitrile then gave a 42% yield of the bicyclic lactone **23**, probably through oxidation of **21** to the imino intermediate **22** followed by intramolecular attack by the free OH group on the carbon–nitrogen double bond.[24] Finally, **23** was opened with methanol and sodium carbonate, and the resulting aminoester **24** was transformed into amino acid **25** by removal of the silyl protecting group.

3. Conclusion

In conclusion, new synthetic applications have been developed for D-glyceraldehyde, which has proved to be a valuable chiral synthon that can be used an alternative to tartaric, malic and lactic acids in the preparation of optically active naturally occurring compounds.[25] The applications developed include the first practical synthesis of nitroalkanoic acids and their transformation into polyoxamic acids; a new transformation of these latter into 3,4-dihydroxyprolines; and novel total syntheses of norvaline **19** and amino acid **25**. Work is now in progress on a more efficient synthesis of nitroalkanoic acids using synthetic equivalents of ethyl nitroacetate that can stabilize the corresponding Henry adducts and allow better stereochemical results to be obtained. Transformation of nitroalkanoic acids into derivatives other than amino acids by exploiting the wide reactivity of nitro groups is also under investigation.[2]

4. Experimental

Melting points were determined using a Kofler Thermogerate apparatus and are uncorrected. Specific rotations were recorded on a JASCO DIP-370 optical polarimeter. Infrared spectra were recorded on a MIDAC FTIR spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker WM-300 apparatus or a Bruker AMX-500, using deuterochloroform solutions containing tetramethylsilane as internal standard. Mass spectra were obtained on a Kratos MS 50 TC mass spectrometer. Elemental analyses were obtained from the Elemental Analysis Service at the University of Santiago de Compostela. Thin layer chromatography (tlc) was performed using Merck GF-254 type 60 silica gel and ethyl acetate/hexane mixtures as eluants; the tlc spots were visualized with Hanesian mixture. Column chromatography was carried out using Merck type 9385 silica gel. Solvents were purified as per Ref. 26. Solutions of extracts in organic solvents were dried with anhydrous sodium sulfate.

4.1. (3*S*)-3-{(4*R*)-2,2-Dimethyl-[1,3]dioxolan-4-yl}-3-hydroxy-2-nitropropionic acid ethyl ester 2+3

Ethyl nitroacetate (1.9 mL, 16.8 mmol) and potassium fluoride (0.80 g, 13.8 mmol) were added to a solution of

D-glyceraldehyde derivative **1** (2 g, 15.3 mmol) in isopropanol (80 mL) and the resulting mixture was stirred at room temperature for 24 h. The solvent was evaporated in vacuo, the resulting residue dissolved in ethyl ether (100 mL), and the solution was washed with water (20 mL), dried and evaporated to dryness. The resulting oil was purified by flash column chromatography (ethyl acetate/hexane 2:7) to give a 6:5 mixture of nitropropionic acid ethyl esters **2**+**3** (0.89 g, 45%), which showed the following spectroscopic properties: ν_{max} (NaCl, cm^{-1}): 3502 (–OH); 1753 (–C=O); 1565, 1375 ($–NO_2$). δ_H (300 MHz, $CDCl_3$): 1.33–1.44 (m, 18H, 4×–CH_3, 2×–$OCH_2C\underline{H}_3$); 4.02–4.43 (m, 12H); 5.48 (d, 1H, $J_{2,3}$ 1.2 Hz, H-2); 5.49 (d, 1H, $J_{2,3}$ 2.4 Hz, H-2). δ_C (75.3 MHz, $CDCl_3$): 13.83, 13.86 (2×q, 2×–CH_3); 24.81, 24.88 (2×q, 2×–CH_3); 26.77, 26.88 (2×q, 2×–CH_3); 63.34, 63.49 (2×t, 2×–CH_2–); 67.15, 67.32 (2×t, 2×–CH_2–); 72.36, 72.87 (2×d, 2×–CH–); 74.66 (2×d, 2×–CH–); 87.87, 88.08 (2×d, –CH–); 110.35, 110.43 (2×s, 2×–C–); 163.01, 163.27 (2×s, 2×–C=O). m/z (%): 248 (M^+–15, 42); 218 (2); 142 (9); 101 (100). HRMS: calcd for $C_9H_{14}NO_7$ (M^+) 248.0770; found 248.0766. $\Delta m = 4\times10^{-4}$.

4.2. (3*S*)-3-{(4*R*)-2,2-Dimethyl-[1,3]dioxolan-4-yl}-2-nitro-3-(tetrahydropyran-2-yloxy)propionic acid ethyl ester 4+5

DHP (1.9 mL, 20.8 mmol) and PPTS (0.42 g, 1.67 mmol) were added to a solution of 2-nitropropionic acid ethyl esters **2**+**3** (2.18 g, 8.28 mmol) in dry dichloromethane (70 mL) and the resulting mixture was stirred at room temperature under argon for 14 h. Ethyl ether (90 mL) was then added and the mixture was washed with saturated aqueous sodium chloride solution (90 mL), dried and evaporated in vacuo. Flash column chromatography (ethyl acetate/hexane 2:7) of the resulting residue gave two diastereomeric mixtures of pentanoic acid ethyl esters (**4**+**5**) (2.32 g, 80%) (mixture 1 and mixture 2), which showed the following spectroscopic properties.

4.2.1. Spectroscopic data for mixture 1. ν_{max} (NaCl, cm^{-1}): 1742 (–C=O); 1562, 1374 ($–NO_2$). δ_H (300 MHz, $CDCl_3$): 1.30–1.76 (m, 30H, 6×–CH_3, 6×–CH_2–OTHP); 3.51–3.58 (m, 2H, –OTHP); 3.84–3.92 (m, 2H, –OTHP); 4.10–4.36 (m, 10H); 4.43–4.51 (m, 2H); 4.69 (dd, 1H, $J_{3,4}$ 3.0 Hz, $J_{4,5}$ 5.5 Hz, H-4); 4.86 (dd, 1H, $J_{3,4}$ 2.5 Hz, $J_{4,5}$ 5.9 Hz, H-4); 5.48 (d, 1H, $J_{2,3}$ 5.4 Hz, H-2); 5.63 (d, 1H, $J_{2,3}$ 2.1 Hz, H-2). δ_C (75.3 MHz, $CDCl_3$): 13.80, 14.01 (2×q, 2×–CH_3); 20.08, 20.26 (2×t, 2×–CH_2–); 24.93 (2×t, 2×–CH_3); 25.04 (2×d, 2×–CH_2–) 26.36, 26.74 (2×q, 2×–CH_3); 30.77, 30.85 (2×t, 2×–CH_2–); 62.85, 62.99, 63.96, 64.19, 67.44, 67.60 (6×t, 6×–CH_2–); 74.55, 75.19, 77.24, 77.65, 88.74, 89.07 (6×d, 6×–CH–); 100.50, 101.54 (2×d, 2×–CH–); 109.96, 110.03 (2×s, 2×–C–); 162.65, 162.86 (2×s, 2×–C=O). m/z (%): 332 (M^+–15, 1.7); 248 (5); 158 (5); 101 (51); 85 (100).

4.2.2. Spectroscopic data for mixture 2. ν_{max} (NaCl, cm^{-1}): 1742 (–C=O); 1562, 1374 ($–NO_2$). δ_H (300 MHz, $CDCl_3$): 1.29–1.72 (m, 30H, 6×–CH_3, 6×–CH_2–OTHP); 3.41–3.55 (m, 2H, –OTHP); 3.74–4.35 (m, 12H); 4.49–4.62 (m, 1H); 4.72, 4.79 (2×s, 2H); 5.42 (d, 1H, $J_{2,3}$ 5.5 Hz, H-2); 5.75 (d, 1H, $J_{2,3}$ 3.8 Hz, H-2). δ_C (75.3 MHz, $CDCl_3$): 13.80, 13.85 (2×q, 2×–CH_3); 19.30, 19.42 (2×t, 2×–CH_2); 24.82 (2×q, 2×–CH_3); 24.93, 24.98 (2×t, 2×–CH_2–); 26.27, 26.42 (2×t, 2×–CH_3); 30.58, 30.67 (2×t, 2×–CH_2–); 62.89, 62.99, 63.15, 63.22, 66.55, 66.58 (6×t, 6×–CH_2–); 74.40, 74.57, 77.32, 78.20, 89.11, 89.33 (6×d, 6×–CH–); 100.71, 101.80 (2×d, 2×–CH–); 109.67, 109.92 (2×s, 2×–C–); 162.47, 162.69 (2×s, 2×–C=O). m/z (%): 332 (M^+–15, 1.7); 248 (5); 158 (5); 101 (51); 85 (100).

4.3. (3*S*)-2-Amino-3-{(4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl}-3-(tetrahydropyran-2-yloxy)propionic acid ethyl ester 6a–d

Raney nickel (50% in water) (0.5 mL) was added to a deoxygenated solution of propionic acid ethyl esters **4**+**5** (2.14 g, 6.18 mmol) in methanol (150 mL) and the suspension was stirred at room temperature under a hydrogen atmosphere for 5 h. The reaction mixture was then filtered through a Celite plug, which was eluted with methanol. The filtrate was evaporated in vacuo to give a mixture of polyoxamic acid ethyl esters **6a**–**d** as a clear gum. The mixture was used without purification.

4.3.1. Spectroscopic data for the mixture 6a–d. ν_{max} (NaCl, cm^{-1}): 3391 ($–NH_2$); 1731 (–C=O). m/z (%, CI): 318 [$(M+H)^+$, 23]; 316 [$(M-H)^+$, 1.2]; 302 (35); 244 (69); 218 (100). HRMS: calcd for $C_{15}H_{27}NO_6$ $(M+H)^+$ 318.1995; found 318.1999.

Careful flash column chromatography (CH_2Cl_2/methanol 98:2) of a small fraction of the mixture **6a**–**d** led to the isolation of small pure fractions of amino acid esters **6a**, **6b**, **6c** and **6d**, which showed the following spectroscopic data.

4.3.2. Amino acid ester 6a. $[\alpha]_D^{22} = +89.4$ (*c* 1.8, chloroform). δ_H (300 MHz, $CDCl_3$): 1.28 (t, 3H, *J* 7.1 Hz, –$OCH_2C\underline{H}_3$); 1.33, 1.42 (2×s, 6H, 2×–CH_3); 1.45–1.75 (m, 6H, 3×–CH_2–OTHP); 3.06 (bs, 2H, $–NH_2$); 3.39–3.44 (m, 1H); 3.83 (s, 1H); 3.85 (s, 1H); 4.06–4.22 (m, 6H); 4.40 (s, 1H). δ_C (75.3 MHz, $CDCl_3$): 14.21 (q, –CH_3); 20.19, 25.06 (2×t, 2×–CH_2–); 25.14, 26.93 (2×q, 2×–CH_3); 30.97 (t, –CH_2–); 54.74 (d, –CH–); 61.33, 63.08, 67.46 (3×t, 3×–CH_2–); 74.44, 79.36 (2×d, 2×–CH–); 100.18 (d, –CH–); 109.43 (s, –C–); 174.05 (s, –C=O).

4.3.3. Amino acid ester 6b. $[\alpha]_D^{24} = +6.5$ (*c* 1.0, chloroform). δ_H (300 MHz, $CDCl_3$): 1.24–1.28 (m, 6H, 2×–CH_3); 1.32 (s, 3H, –CH_3); 1.42–1.72 (m, 6H, 3×–CH_2–OTHP); 3.11 (bs, 2H, $–NH_2$); 3.48–3.51 (m, 1H); 3.83–4.00 (m, 2H); 4.03–4.25 (m, 6H); 4.69 (s, 1H). δ_C (75.3 MHz, $CDCl_3$): 14.11 (q, –CH_3); 20.05 (t, –CH_2–); 25.09 (q, –CH_3); 25.14 (t, –CH_2–); 26.34 (q, –CH_3); 30.93 (t, –CH_2–); 55.24 (d, –CH–); 61.18, 63.61, 67.72 (3×t, 3×–CH_2–); 73.75, 78.95 (2×d, 2×–CH–); 98.06 (d, –CH–); 109.38 (s, –C–); 171.72 (s, –C=O).

4.3.4. Amino acid ester 6c. $[\alpha]_D^{24} = -17.7$ (*c* 1.5, acetone). δ_H (300 MHz, $CDCl_3$): 1.21–1.72 (m, 15H, 3×–CH_3, 3×–CH_2–OTHP); 3.32 (bs, 2H, –NH_2); 3.29–3.33 (m, 1H); 3.60 (s, 1H); 4.70–4.23 (m, 7H); 4.53 (s, 1H). δ_C (75.3 MHz, $CDCl_3$): 14.11 (q, –CH_3); 20.39, 24.96 (2×t, 2×–CH_2–); 25.22, 26.79 (2×q, 2×–CH_3); 30.93 (t, –CH_2–); 55.29 (d, –CH–); 61.10, 63.72, 66.49 (3×t, 3×–CH_2–); 75.77, 79.60 (2×d, 2×–CH–); 101.42 (d, –CH–); 108.96 (s, –C–); 174.03 (s, –C=O).

4.3.5. Amino acid ester 6d. $[\alpha]_D^{24} = -48.9$ (*c* 1.6, chloroform). δ_H (300 MHz, $CDCl_3$): 1.25 (t, 3H, *J* 7.2 Hz, –OCH_2CH_3); 1.28, 1.33 (2×s, 6H, 2×–CH_3); 1.48–1.75 (m, 6H, 3×–CH_2–OTHP); 2.40 (bs, 2H, –NH_2); 3.48–3.52 (m, 1H); 3.81–4.26 (m, 8H); 4.65 (s, 1H). δ_C (75.3 MHz, $CDCl_3$): 14.13 (q, –CH_3); 20.14, 25.09 (2×t, 2×–CH_2–); 25.11, 26.45 (2×q, 2×–CH_3); 31.03 (t, –CH_2–); 56.36 (d, –CH–); 61.00, 63.74, 66.55 (2×t, 3×–CH_2–); 74.58, 81.80 (2×d, 2×–CH–); 101.67 (d, –CH–); 109.03 (s, –C–); 172.21 (s, –C=O).

4.4. (3*S*)-2-Benzyloxycarbonylamino-3-{(4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl}-3-(tetrahydropyran-2-yloxy)propionic acid ethyl ester 7a–d

Saturated sodium bicarbonate solution (38 mL) was added to a solution of polyoxamic acid ethyl esters **6a**–**d** in ethyl acetate (90 mL). The solution was then cooled to 0°C, benzyl chloroformate (1.3 mL, 9.27 mmol) was added and the reaction was stirred at room temperature for 2 h. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (3×80 mL). The combined organic layers were washed with saturated sodium chloride solution (100 mL), dried and concentrated to dryness. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:4) to give a mixture 2-benzyloxycarbonylamino pentanoic acid ethyl esters **7a**–**d** (2.56 g, 92%) as a yellow oil, which showed the following spectroscopic properties: ν_{max} (NaCl, cm^{-1}): 3040 (–NH–); 1748, 1709 (2×–C=O). δ_H (300 MHz, $CDCl_3$): 1.22–1.75 (m, 15H, 3×–CH_3, 3×–CH_2–OTHP); 3.53–3.57 (m, 1H, –OTHP); 3.75–4.40 (m, 7H); 5.14, 5.15 (2×s, 2H, –CH_2Ph); 7.34–7.38 (m, 5H, 5×ArH). *m*/*z* (%): 352 (M^+–99, 0.5); 266 (2); 237 (9); 176 (6); 131 (4); 91 (100); 85 (88).

4.5. (4*S*,5*R*)-(4-Hydroxy-5-hydroxymethyl-2-oxo-tetrahydrofuran-3-yl)carbamic acid benzyl esters 8a–b and (4*S*,5*R*)-[4-hydroxy-2-oxo-5-(tetrahydropyran-2-yloxymethyl)tetrahydrofuran-3-yl]carbamic acid benzyl esters 9a–d

A solution of 2-benzyloxycarbonylaminopentanoic acid ethyl esters **7a**–**d** (1.75 g, 3.87 mmol) in a mixture of THF/trifluoroacetic acid/water 6:6:1 was stirred at room temperature for 3 h. The mixture was evaporated in vacuo, coevaporated with toluene (3×6 mL) and the resulting residue was purified by flash column chromatography (ethyl acetate/hexane 1:1 and then dichloromethane/methanol 10:0.6) to give a mixture of lactones **8a**–**b** (0.3 g, 28%) and a mixture of 5-(tetrahydropyran-2-yloxymethyl)lactones **9a**–**d** (0.59 g, 42%).

4.5.1. Spectroscopic data for compound 8a. ν_{max} (NaCl, cm^{-1}): 3399 (–OH, –NH–); 1776 (C=O); 1703 (C=O). δ_H (250 MHz, MeOD): 3.70, 3.72 (2×s, 2H); 4.28–4.32 (m, 2H); 4.80 (d, 1H, $J_{2,3}$ 5.7 Hz, H-2); 5.05 (s, 2H, –OCH_2Ph); 7.23–7.29 (m, 5H, 5×Ar–H). δ_C (75.4 MHz, MeOD): 55.87 (d, –CH–); 62.55, 68.21 (2×t, 2×–CH_2–); 70.68 (d, –CH–); 73.03 (d, –CH–); 129.17, 129.25, 129.67 (5×d, 5×–CH–); 138.19 (s, –C–); 159.06 (s, C=O); 177.12 (s, C=O). *m*/*z* (%, CI): 282 [$(M+H)^+$, 10]; 264 (13); 238 (21); 91 (100). HRMS (FAB): calcd for $C_{13}H_{15}NO_6$, 281.0899. Found, 281.0897. $\Delta m = 2\times10^{-4}$.

4.5.2. Spectroscopic data for the diastereoisomeric mixture 9a–d. ν_{max} (NaCl, cm^{-1}): 3397 (–OH, –NH–); 1767 (C=O); 1709 (C=O). δ_H (300 MHz, $CDCl_3$): 1.26–1.75 (m, 12H, 6×–CH_2–OTHP); 3.52–4.47 (m, 12H); 4.67–4.78 (m, 4H); 5.16 (s, 4H, 2×–OCH_2Ph); 5.69 (bs, 2H, 2×–NH–); 7.38 (s, 10H, 10×Ar-H). δ_C (75.3 MHz, $CDCl_3$): 19.01, 19.14, 25.05, 25.22, 30.19, 30.22 (6×t, 6×–CH_2–); 59.48 (2×d, 2×–CH–); 62.02, 62.15, 64.34, 65.50, 67.70, 67.90 (6×t, 6×–CH_2–); 74.04, 74.33 (2×d, 2×–CH–); 81.45, 81.56 (2×d, 2×–CH–); 98.97 (2×d, 2×–CH–); 128.21, 128.57, 128.68 (5×d, 5×Ar-H); 135.42 (2×s, 2×–C–); 171.04, 171.14 (2×s, 2×–C=O). *m*/*z* (%, FAB): 366 [$(M+H)^+$, 25]; 282 (100). HRMS (FAB): calcd for $C_{18}H_{24}NO_7$ $(M+H)^+$, 366.1553. found, 366.1561. $\Delta m = 8\times10^{-4}$.

4.6. (4*S*,5*R*)-(4-Hydroxy-5-hydroxymethyl-2-oxo-tetrahydrofuran-3-yl)carbamic acid benzyl ester 8a–b

A solution of lactones **9a**–**d** (0.14 g, 0.39 mmol) and pyridinium *p*-toluenesulfonate (0.02 g, 0.08 mmol) in ethanol (13 mL) was heated at 50°C for 10 h. The ethanol was evaporated and the residue submitted to flash column chromatography (dichloromethane/methanol, 95:5) to give lactones **8a**–**b** (44 mg, 40%) as a clear gum.

4.7. (4*S*,5*R*)-[4-Hydroxy-2-oxo-5-(tetrahydropyran-2-yloxymethyl)tetrahydrofuran-3-yl]carbamic acid benzyl esters 9a–b

PPTS (36 mg, 0.14 mmol) and DHP (0.05 mL, 0.52 mmol) were added to a solution of lactones **8a**–**b** (0.10 g, 0.35 mmol) in dichloromethane (3 mL). The mixture was stirred at room temperature for 3 d, concentrated to dryness and the residue was submitted to flash column chromatography (hexane/ethyl acetate 1:1 and then dichloromethane/methanol 95:5) to give a mixture of lactones **9a**–**d** (49 mg, 89% calculated on the basis of recovered starting material).

4.8. (4*S*,5*R*)-Toluene-4-sulfonic acid 4-benzyloxycarbonylamino-3-hydroxy-5-oxo-tetrahydrofuran-2-yl methyl ester 10a+11a

A mixture of lactones **8a**–**b** (0.31 g, 1.09 mmol) and molecular sieves (0.65 g) in dry pyridine (5 mL) was cooled to –20°C and tosyl chloride (0.23 g, 1.20 mmol) was added. The resulting mixture was stirred at –20°C for 20 h and then filtered through Celite. The filtrate was concentrated to dryness, dissolved in

dichloromethane (30 mL) and the solution washed with saturated aqueous copper sulfate (30 mL). The aqueous phase was extracted with dichloromethane (2×20 mL) and the combined organic layers were washed with water (2×20 mL), dried, filtered and evaporated in vacuo. The residue was submitted to flash column chromatography (ethyl acetate/hexane 4:5) to give an epimeric mixture of lactones **10a**+**11a** (0.32 g, 70%). ν_{max} (NaCl, cm^{-1}): 1769, 1737 (2×–C=O). δ_H (300 MHz, $CDCl_3$): 2.04, 2.44 (2×s, 6H, 2×–CH_3); 4.07–4.73 (m, 8H); 5.12 (s, 4H, 2×–OCH_2Ph); 5.56–5.70 (m, 2H, 2×H-2); 7.33–7.79 (m, 14H, 14×Ar-H) δ_C (75.3 MHz, $CDCl_3$): 21.36 (2×q, 2×–CH_3); 53.39, 58.29 (2×s, 2×–CH–); 66.81, 67.31, 67.85 (4×t, 4×–CH_2–); 68.41, 72.06, 78.62, 82.71 (4×d, 4×–CH–); 128.00, 128.06, 129.84, 129.95 (8×d, 8×–CH–); 131.27, 131.59 (2×s, 2×–C–); 135.39, 135.53 (2×s, 2×–C–); 145.28, 145.48 (2×s, 2×–C–); 156.57, 156.77 (2×s, 2×C=O); 170.83, 173.57 (2×s, 2×–C=O). m/z (%, CI): 436 [$(M+H)^+$, 6]; 392 (14); 173 (100); 91 (79). HRMS (CI): $C_{20}H_{22}NO_8S$ $(M+H)^+$, calcd 436.1066; found 436.1066.

4.9. (2*S*,3*S*,4*R*)-3,4-Dihydroxypyrrolidine-2-carboxylic acid 14 and (2*R*,3*S*,4*R*)-3,4-dihydroxypyrrolidine-2-carboxylic acid 15

Pd/C (10%) (13 mg) and concentrated hydrochloric acid solution (2 drops) were added to a deoxygenated solution of lactones **10a**+**11a** (0.13 g, 0.31 mmol) in dioxane/water (1:1) (4 mL). The resulting mixture was stirred at room temperature under hydrogen (1 atm.) for 3 h. The reaction mixture was filtered through Celite, the filtrate was evaporated to dryness and the residue dissolved in water (10 mL). Barium hydroxide (0.16 g) was added and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was acidified with Amberlite 120-IR up to pH 1, stirred at room temperature for 24 h, filtered and the resin was washed with water until the filtrate was inactive to the addition of aqueous silver nitrate solution. The resin was stirred with a solution of ammonium hydroxide 1 N (30 mL) for 3 h, filtered and the filtrate evaporated to dryness to give an epimeric mixture of 3,4-dihydroxyprolines **14** and **15** (31 mg, 68%) as an amorphous solid. ν_{max} (NaCl, cm^{-1}): 3326, 3249, 3131 (–OH);1623 (–C=O). δ_H (250 MHz, D_2O): 3.07–3.12 (m, 2H, 2×H-5); 3.36–4.54 (m, 2H, 2×H-5′); 3.76 (d, 1H, $J_{2,3}$ 5.0 Hz, H-2); 4.02 (d, 1H, $J_{2,3}$ 2.0 Hz, H-2); 4.18–4.33 (m, 4H, 2×H-3, 2×H-4). δ_C (62.8 MHz, D_2O): 49.52, 51.14 (2×t, 2×–CH_2–); 66.98, 67.20 (2×d, 2×–CH–); 72.80, 73.44 (2×d, 2×–CH–); 73.13, 77.01 (2×d, 2×–CH–); 173.48, 175.80 (2×s, 2×–C=O). m/z (%, FAB): 148 [$(M+H)^+$, 3]; 132 (2); 114 (7).

4.10. (3*E*,5*S*)-[2-Oxo-5-(tetrahydropyran-2-yloxymethyl)-2,5-dihydrofuran-3-yl]carbamic acid benzyl ester 17a–b

Methanesulfonyl chloride (0.16 mL, 1.91 mmol) was added to a solution of lactones **9a**–**d** (0.35 g, 0.96 mmol) in dry pyridine (4 mL) and the resulting mixture was stirred at 0°C under argon for 2 h. The pyridine was evaporated to dryness, the residue was dissolved in dichloromethane (20 mL) and the solution was washed with saturated aqueous copper sulfate (20 mL). The aqueous phase was extracted with dichloromethane (2×20 mL) and the combined organic layers were washed with saturated aqueous copper sulfate (1×20 mL) and water (2×20 mL), dried, filtered and evaporated in vacuo. The residue was submitted to flash column chromatography (ethyl acetate/hexane 1:3) to give lactones **17a**–**b** (0.28 g, 83% yield) as a clear oil. ν_{max} (NaCl): 1769, 1737 (2×C=O). δ_H (250 MHz, $CDCl_3$): 1.43–1.80 (m, 12H); 3.49–3.97 (m, 8H); 4.63–4.68 (m, 2H); 5.18 (s, 2H); 5.20 (s, 4H, 2×–OCH_2Ph); 7.12, 7.14 (2×bs, 4H, 2×H-3, 2×–NH–); 7.32–7.38 (m, 10H, 10×Ar–H). δ_C (62.8 MHz, $CDCl_3$): 18.73, 18.79, 25.09, 30.00, 30.04 (6×t, 6×–CH_2–); 61.70, 61.80, 67.09, 67.59, 67.69 (6×t, 6×–CH_2–); 80.16, 80.80 (2×d, 2×–CH–); 98.60, 98.78 (2×d, 2×–CH–); 123.38, 123.97 (2×–CH–); 126.79, 126.94 (2×–CH–); 128.05, 128.39, 128.48 (10×d, 10×–CH–); 135.19 (2×s, 2×–C–); 152.90 (2×s, 2×C=O); 168.77, 168.83 (2×s, 2×C=O). m/z (%): 347 (M^+, 2); 245 (1); 233 (3); 91 (69); 85 (100).

4.11. (3*E*,5*S*)-(5-Hydroxymethyl-2-oxo-2,5-dihydrofuran-3-yl)carbamic acid benzyl ester 18a

A solution of lactones **17a**–**b** (0.24 g, 0.68 mmol) and pyridinium *p*-toluenesulfonate (34 mg, 0.14 mmol) in ethanol (23 mL) was heated at 50°C for 9 h. The solvent was evaporated to dryness and the resulting residue was submitted to flash column chromatography (ethyl acetate/hexane 4:5) to give lactone **18a** (0.16 g, 86%) as a white solid. Mp 109–113°C (ethyl acetate). $[\alpha]_D^{23} = +21.4$ (*c* 1.0, methanol). ν_{max} (NaCl, cm^{-1}): 3422 (–OH); 1765, 1736 (–C=O). δ_H (500 MHz, MeOD): 3.69 (dd, 1H, $J_{6,6'}$ 12.3 Hz, $J_{5,6}$ 4.8 Hz, H-6); 3.89 (dd, 1H, $J_{6,6'}$ 12.3 Hz, $J_{5,6'}$ 3.5 Hz, H-6′); 5.11–5.13 (m, 1H, H-5); 5.24 (s, 2H, –OCH_2Ph); 7.16 (bs, 1H, H-4); 7.35–7.48 (m, 5H, H–Ph). δ_C (75.4 MHz, MeOD); 63.43, 68.48 (2×–CH_2–); 83.87 (C-5); 126.08 (C-4); 129.37, 129.49, 129.75 (5×–CH–, C-3); 135.77 (–CPh); 155.70 (–NH–C=O); 170.89 (C=O). m/z (%, CI): 264 [$(M+H)^+$, 4]; 263 (M^+, 0.2); 220 (5); 188 (2); 91 (100). Anal. calcd for $C_{13}H_{13}NO_5$: C, 59.31; H: 4.98; N, 5.32. Found: C, 58.96; H: 4.72; N, 5.16.

4.12. (2*S*,4*S*)-2-Amino-4,5-dihydroxypentanoic acid 19

Pd/C (10%) (10 mg) was added over a deoxygenated solution of lactone **18a** (82 mg, 0.31 mmol) in acetic acid (3 mL) and the resulting mixture was stirred at room temperature under hydrogen (1 atm.) for 12 h. The reaction was filtered through Celite, the filtrate was evaporated to dryness, the residue was dissolved in water (10 mL) and barium hydroxide (0.16 g) was added. The resulting mixture was stirred at room temperature for 3 h, acidified to pH 1 with Amberlite 120-IR, stirred at room temperature for 24 h and filtered. The resin was washed with water until the filtrate was inactive to the addition of aqueous silver nitrate solution. The residue was stirred with a 1N solution of ammonium hydroxide (30 mL) for 3 h, filtered and the filtrate evaporated to dryness to give pentanoic acid **19** (29 mg, 63%) as an amorphous solid.

$[\alpha]_D^{23} = -19.5$ (*c* 1.7, water). ν_{max} (NaCl): 3449 (–OH); 2536 (COO–H), 1627 (–C=O). δ_H (250 MHz, D_2O): 1.83–1.87 (m, 2H); 3.33–3.49 (m, 2H); 3.69–3.79 (m, 2H). δ_C (62.8 MHz, D_2O); 33.14 ($-CH_2-$); 53.09 (–CH–); 65.79 ($-CH_2-$); 69.39 (–CH–); 175.32 ($-CO_2H$). *m*/*z* (%, FAB): 150 [$(M+H)^+$, 4], 185 (glycerol, 100).

4.13. (4*S*,5*R*)-[4-(*tert*-Butyldimethylsilanyloxy)-2-oxo-5-(tetrahydropyran-2-yloxymethyl)tetrahydrofuran-3-yl]-carbamic acid benzyl esters 20a–d

tert-Butyldimethylsilyl chloride (1.08 g, 7.15 mmol) was added to a solution of lactones **9a**–**d** (0.76 g, 2.1 mmol) and imidazole (0.76 g, 11.19 mmol) in dry DMF (20 mL). and the mixture was stirred at room temperature for 60 h. The solvent was removed in vacuo and the residue was dissolved in chloroform (100 mL), washed with water (2×60 mL) and with saturated aqueous sodium chloride (60 mL). The organic layer was dried with magnesium sulfate, filtered and evaporated in vacuo. The residue was purified by flash column chromatography (ethyl acetate/hexane, 2:9) to give a mixture of diastereomeric lactones **20a**–**d** (0.79 mg, 80%) as clear gum. ν_{max} (NaCl): 1726 (C=O). δ_H (300 MHz, $CDCl_3$): 0.06, 0.07 (2×s, 6H, $-SiMe_2$), 0.88 (s, 9H, –Si′Bu), 1.59–1.76 (m, 6H, 3×–CH_2–OTHP), 3.52–4.04 (m, 4H), 4.32–4.71 (m, 3H), 4.91–5.41 (s, 3H, $-OCH_2Ph$), 7.36 (s, 5H, 5×Ar–H).

4.14. (4*S*,5*R*)-[4-(*tert*-Butyldimethylsilanyloxy)-5-hydroxymethyl-2-oxo-tetrahydrofuran-3-yl]carbamic acid benzyl esters 21a–b

A solution of lactones **20a**–**d** (0.35 g, 0.74 mmol) and pyridinium *p*-toluenesulfonate (40 mg, 0.15 mmol) in ethanol (25 mL) was heated at 50°C for 10 h. The solvent was removed in vacuo and the resulting residue was dissolved in dichloromethane (40 mL). The solution was washed with saturated aqueous sodium chloride (1×25 mL) and water (1×15 mL). The organic layer was dried, filtered and evaporated in vacuo. The residue was submitted to flash column chromatography (ethyl acetate/hexane 4:9) to give an epimeric mixture of lactones **21a**–**b** (0.22 g, 75%) as a gum. $[\alpha]_D^{26} = -2.0$ (*c* 1.7, methanol). ν_{max} (NaCl): 3444, 3363 (–OH, –NH–), 1788 (C=O), 1710 (–C=O). δ_H (300 MHz, $CDCl_3$): 0.03, 0.05 (2×s, 6H, $-SiMe_2$), 0.87 (s, 9H, –Si′Bu), 3.18 (bs, 1H, –OH), 3.79–3.93 (m, 2H, H-5, H-5′), 4.38 (s, 1H), 4.50 (d, 1H, *J* 4.7 Hz), 4.90–4.95 (m, 1H, H-2), 5.12, 5.15 (2×s, 2H, $-OCH_2Ph$), 5.33 (d, 1H, $J_{2,NH}$ 8.9 Hz –NH–), 7.35 (s, 5H, 5×Ar–H). δ_C (300 MHz, $CDCl_3$); −5.14, −4.99 (2×c, 2×–CH_3, $-SiMe_2$), 25.59 (q, 3×CH_3, –Si′Bu), 54.06 (d, –CH–), 61.67, 67.44 (2×t, 2×–CH_2–), 70.63 (d, –CH–), 86.88 (d, –CH–), 128.13, 128.24, 128.59 (3×d, 5×–CH–, 5×Ar–H), 135.94 (2×s, 2×–C–), 156.24 (s, –C=O), 174.50 (s, –C=O). *m*/*z* (%): 338 (M^+–57, 4); 294 (1); 230 (2); 108 (2); 91 (100). *m*/*z* (FAB,%): 396 (M^++H, 27), 379 (12), 352 (100). HRMS: calcd for $C_{19}H_{30}NO_6Si$ $(M+H)^+$ 396.1842; found 396.1847. $\Delta m = 5\times10^{-4}$.

4.15. (1*S*,4*R*,7*R*)-[7-(*tert*-Butyldimethylsilanyloxy)-6-oxo-2,5-dioxabicyclo[2.2.1]hept-1-yl]carbamic acid benzyl ester 23

A solution of lactones **21a**–**b** (0.22 mg, 0.55 mmol) in acetonitrile (45 mL) was deoxygenated by bubbling argon through for 10 min. Ammonium acetate (0.22 mg, 1.65 mmol) and *N*-bromosuccinimide (0.26 g, 0.48 mmol) were added. The reaction mixture was stirred at room temperature under argon for 24 h and filtered through a Celite plug. The filtrate was dried and evaporated in vacuo. The residue was submitted to flash column chromatography (ethyl acetate/hexane 1:5) to give the bicyclic lactone **23** (91 mg, 42%) as an amorphous solid. $[\alpha]_D^{23} = -44.4$ (*c* 0.9, chloroform). ν_{max} (NaCl): 3344 (–NH); 1799 (C=O), 1740 (C=O). δ_H (500 MHz, $CDCl_3$): 0.02, 0.09 (2×s, 6H, $-SiMe_2$), 0.83 (s, 9H, –Si′Bu), 3.87 (d, 1H, $J_{3,3'}$ 9.2 Hz, H-3), 4.27–4.29 (m, 1H, H-3′), 4.75 (s, 1H, H_7), 5.09–5.18 (m, 3H, H_4 and $-CH_2$–Ph), 5.89 (bs, 1H, –NH), 7.32–7.37 (s, 5H, 5×Ar–H). δ_C (300 MHz, $CDCl_3$); −4.75, −5.25 (2×q, 2×–CH_3, $-SiMe_2$), 25.36 (q, 3×CH_3, –Si′Bu), 54.06 (d, –CH–), 61.67, 67.44 (2×t, 2×–CH_2–), 70.63 (d, –CH–), 86.88 (d, C-2), 128.13, 128.24, 128.59 (3×d, 5×–CH–, HC–Ph), 135.94 (s, 2×–CPh), 156.24 (s, –C=O), 174.50 (s, –C=O). *m*/*z* (%, CI): 394 [$(M+H)^+$, 0.2]; 350 (0.3), 205 (1), 149 (4), 119 (3), 91 (100). HRMS (CI): $C_{19}H_{27}NO_6Si$ $(M+H)^+$, calcd 394.1686; found 394.1687.

4.16. (2*S*,3*R*,4*R*)-2-Benzyloxycarbonylamino-3-(*tert*-butyldimethylsilanyloxy)-4-hydroxytetrahydrofuran-2-carboxylic acid methyl ester 24

A mixture of acetyl chloride (0.05 mL) and methanol (5 mL) was stirred at room temperature for 20 min. The resulting solution was added to lactone **23** (71 mg, 0.18 mmol) and the mixture was stirred at room temperature overnight. The clear solution was neutralized with solid sodium bicarbonate, preabsorbed onto silica gel and purified by flash column chromatography (ethyl acetate/hexane 1:3) to give amino acid derivative **24** (39 mg, 51%) as a yellow oil. $[\alpha]_D^{21} = -30.4$ (*c* 1.6, chloroform). ν_{max} (NaCl): 3431 (–OH), 1785, 1735 (2×–C=O). δ_H (400 MHz, $CDCl_3$): 0.06, 0.10 (2×s, 6H, $-SiMe_2$), 0.83 (s, 9H, –Si′Bu), 3.35 (s, 3H, –OMe), 3.84–3.87 (m, 2H, H-5, H-5′), 4.33–4.34 (m, 1H, H-4), 4.45 (d, 1H, $J_{3,4}$ 2.2 Hz, H-3), 5.06–5.14 (m, 2H, $-OCH_2Ph$), 5.65 (bs, 1H, –NH), 7.30–7.34 (m, 5H, Ar–H). δ_C (300 MHz, $CDCl_3$); (50.2 MHz, Cl_3CD): −5.21, −4.72 ($-SiMe_2$), 17.76 [–Si**C**$(CH_3)_3$] 17.76 [–SiC(**C**$H_3)_3$], 51.38 ($-OCH_3$), 61.46, 67.38 (2×–CH_2–), 73.00 (–CH–), 86.01 (C-2), 86.87 (–CH–), 128.30, 128.41, 128.60 (5×–CH–, Ar–C), 135.57 (–C–, Ar–C), 153.95, 169.81 (2×C=O). *m*/*z* (%, FAB): 426 [$(M+H)^+$, 100], 395 (25), 394 (61), 350 (71). HRMS (FAB): calcd for $C_{20}H_{32}NO_7Si$ $(M+H)^+$: 426.1948. Found: 426.1944.

4.17. (2*S*,3*R*,4*R*)-2-Benzyloxycarbonylamino-3,4-dihydroxytetrahydrofuran-2-carboxylic acid methyl ester 25

A 1 M solution of Bu_4NF in THF (1 mL, 1 mmol) was added over a solution of amino acid ester **24** (30 mg,

0.07 mmol) in dry THF (10 mL) and the resulting solution was stirred at room temperature for 12 h. The reaction mixture was evaporated in vacuo and the residue submitted to flash column chromatography (ethyl acetate/hexane 1:1), to give (2*S*,3*R*,4*R*)-2-benzyloxycarbonylamino-3,4-dihydroxytetrahydrofuran-2-carboxylic acid methyl ester **25** (20 mg, 91% yield) as a clear gum. $[\alpha]_D^{20} = -12.4$ (*c* 1, chloroform). ν_{max} (NaCl): 3405 (–OH), 1789, 1732 (2×–C=O). δ_H (400 MHz, $CDCl_3$): 3.41 (s, 3H, –OMe), 3.85–3.87 (m, 2H, H-5, H-5′), 4.31–4.34 (m, 1H, H-4), 4.53 (d, 1H, $J_{3,4}$ 2.1 Hz, H-3), 5.06–5.14 (m, 2H, $-OCH_2Ph$), 5.65 (bs, 1H, –NH), 7.30–7.34 (m, 5H, Ar–H). HRMS (FAB): calculated for $C_{14}H_{17}NO_7$ $(M+H)^+$: 312.1083. Found: 312.1079.

Acknowledgements

Special thanks are due to Professor G. W. J. Fleet for helpful discussions on this chemistry. We also thank the Xunta de Galicia and the Spanish Ministry of Science and Technology for financial support, and the latter for a grant to Raquel G. Soengas.

References

1. (a) Henry, C. R. *Acad. Sci. Paris* **1895**, *120*, 1265; (b) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915; (c) Noboru, O. In *The Nitro Group in Organic Synthesis*; Chapter 2. Organic Nitro Chemistry Series; Feuer, H., Ed.; Wiley-VCH: New York, 2001.
2. (a) Pinnick, H. W. *Org. React.* **1990**, *38*, 655; (b) McMurry, J. E.; Melton, J.; Padgett, H. *J. Org. Chem.* **1974**, *39*, 259; (c) McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367; (d) Olah, G. A.; Gupta, B. G. B. *Synthesis* **1980**, 44; (e) Crosslay, M. J.; Crumbie, R. L.; Fung, Y. M.; Potter, J. J.; Pegler, M. A. *Tetrahedron Lett.* **1987**, *28*, 2883.
3. For reviews, see: (a) Schipchandler, M. T. *Synthesis* **1979**, 666; (b) Shvekhgeimer, M. G. A. *Russ. Chem. Rev.* **1998**, *67*, 35; (c) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1; (d) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833.
4. (a) Kaji, E.; Zen, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 337; (b) Shipchandler, M. T. *Synthesis* **1979**, 666; (c) Dauzonne, D.; Royer, R. *Synthesis* **1987**, 399; (d) Baldwin, J. E.; Haber, S. B.; Hoskins, C.; Kruse, L. I. *J. Org. Chem.* **1977**, *42*, 1239; (e) Lalonde, J. L.; Bergbreiter, D. E.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 2323; (f) Keller, E.; Veldman, N.; Spek, A. L.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3403; (g) Fornicola, R. S.; Oblinger, E.; Montgomery, J. *J. Org. Chem.* **1998**, *63*, 3528; (h) Versleijen, J. P. G.; van Leusen, A. M.; Feringa, B. L. *Tetrahedron Lett.* **1999**, *40*, 5803; (i) Fornicola, R. S.; Montgomery, J. *Tetrahedron Lett.* **1999**, *40*, 8387.
5. Borrachero, P.; Dianez, M. J.; Estrada, M. D.; Gomez-Guillen, M.; Gomez-Sanchez, A.; Lopez-Castro, A.; Perez-Garrido, S. *Carbohydr. Res.* **1995**, *271*, 79.
6. Soengas, R. G.; Estévez, J. C.; Estévez, R. J.; Maestro, M. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1653.
7. Le Cocq, J.; Ballou, C. E. *Biochemistry* **1964**, *3*, 976.
8. Bock, K.; Lundt, I.; Pedersen, C. *Carbohydr. Res.* **1981**, *90*, 17.
9. Hudson, C. B.; Roberston, A. V.; Simpson, R. J. *Aust. J. Chem.* **1968**, *21*, 769.
10. (a) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199; (b) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182.
11. Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W. *FEBS Lett.* **1988**, *237*, 128.
12. Kayakiri, H.; Nakamura, K.; Tagase, S.; Setoi, H.; Uchida, I.; Terano, H.; Hashimoto, M.; Tada, T.; Koga, S. *Chem. Pharm. Bull.* **1991**, *39*, 2807.
13. For a recent use of 3,4-dihydroxyprolines as building blocks in peptide synthesis, see: Weir, C. A.; Taylor, C. M. *J. Org. Chem.* **1999**, *64*, 1554.
14. Baird, P. D.; Dho, J. C.; Fleet, G. W. J.; Peach, J. M.; Prout, K.; Smith, P. W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1785.
15. Fuji, M.; Miura, T.; Kajimoto, Y. I. *Synlett* **2000**, 1046.
16. Lindblad, W. J.; Diegelmann, R. F. *J. Chromatogr.* **1984**, *315*, 447.
17. (a) Fowden, L. *Nature* **1966**, *209*, 807; (b) Matzinger, P.; Catalformo, P.; Eugster, C. H. *Helv. Chim. Acta* **1972**, *55*, 1478.
18. (a) Pruess, D. L.; Kellet, M. *J. Antibiot.* **1983**, *36*, 208; (b) Muller, J. C.; Toome, V.; Pruess, D. L.; Blount, J. F.; Weigele, M. *J. Antibiot.* **1983**, *36*, 217.
19. Reading, C.; Cole, M. *Antimicrob. Agents Chemother.* **1977**, *11*, 852.
20. (a) DeBernardo, S.; Tengi, J. T.; Sasso, G. J.; Weigele, M. *J. Org. Chem.* **1985**, *50*, 3457; (b) Ariza, J.; Díaz, M.; Font, J.; Ortuño, R. M. *Tetrahedron* **1993**, *49*, 1315.
21. Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4395 and references cited therein.
22. For the isolation of hydantocidin, see: (a) Harumayha, H.; Kinoshita, T.; Takayama, T.; Kondo, M.; Nakajima, M.; Haneishi, T. *J. Chem. Soc., Perkins Trans. 1* **1991**, 1637; (b) Nakajima, M.; Itoi, K.; Takamatsu, Y.; Kinoshita, T.; Okasaki, T.; Kawakubo, K.; Shindou, M.; Honma, T.; Tohjigamori, M.; Haneishi T. *J. Antibiot.* **1991**, *44*, 293.
23. For the previous synthesis of amino acid **25**, see: Hanessian, S.; Sancéau, J. Y.; Chemla, P. *Tetrahedron* **1995**, *51*, 6669.
24. (a) Burton, J. W.; Son, J. C.; Fairbanks, A. J.; Choi, S.; Taylor, H.; Watkin, D. J.; Winchester, B. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1993**, *34*, 6119; (b) Estevez, J. C.; Burton, J. W.; Estevez, R. J.; Ardon, H.; Wormald, M. R.; Dwek, R. A.; Brown, D.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2137.
25. Ghosh, A. K.; Koltun, E. S.; Bilcer, G. *Synthesis* **2001**, 1281.
26. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1988.