From *N*-triisopropylsilylpyrrole to an optically active C-4 substituted pyroglutamic acid: total synthesis of penmacric acid†

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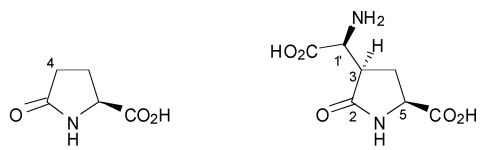
The stereoselective synthesis of penmacric acid, an optically active C-4 substituted pyroglutamic acid, has been efficiently achieved through an unusual 11-step sequence starting from simple *N*-triisopropylsilylpyrrole. The key-steps are the initial addition of the pyrrole nucleus onto a chiral nitrone and the obtention of the pyroglutamic acid moiety by reductive hydrogenation of the pyrrole followed by oxidation of the corresponding pyrrolidine into pyrrolidinone.

Introduction

(*S*)-(−)-Pyroglutamic acid, also called 5-oxo-L-proline, is an intriguing optically active γ-lactam obtained by the thermal dehydration of L-glutamic acid (Fig. 1). The scaffold of pyroglutamic acid is present in many conformationally restrained peptides as well as peptidomimetics.[1] Therefore, the development of new methods for the synthesis of substituted analogues of this molecule is of great concern. Consequently, within the past decades, research efforts towards stereoselective access to this class of compounds have been made. For example, the preparation of C-4 substituted analogues often involves the use of a protected pyroglutamic acid derivative as the chiral template.[2] The key step consists either in stereocontrolled alkylation,[3] or halogenation of the lactam enolate or of the corresponding silyl enol ether.[3b,4] The resulting molecules are also useful intermediates in the synthesis of C-4 substituted L-glutamic acid[5] as well as L-proline analogues.[2,6] In the latter case, the reductive conversion of the pyrrolidinone into a pyrrolidine is usually achieved using boranes,[7] or through a two-step sequence *via* a hemiaminal species.[8]



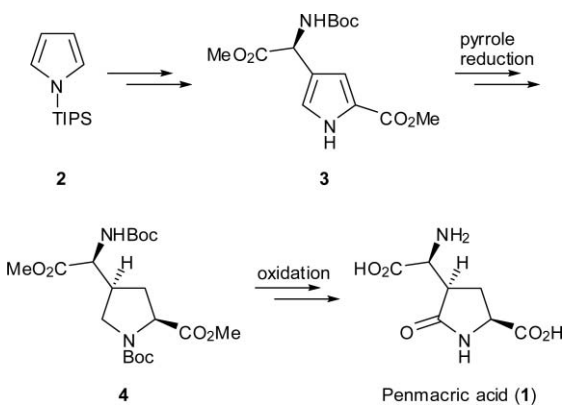
(*S*)-(−)-Pyroglutamic acid Penmacric acid (**1**)

Fig. 1 Pyroglutamic frameworks.

However, the preparation of C-4 substituted chiral pyroglutamic acids from pyrrolic frameworks is not well documented despite its potential usefulness.

Following our works in the field of the total synthesis of pyrrole containing natural products,[9] we then decided to explore this synthetic area. Our attention was particularly focused on the synthesis of penmacric acid (**1**) (Fig. 1). This compound was first isolated simultaneously by two independent teams from the seeds of the leguminous tree *Pentaclethra macrophylla*, also known as the "oil bean tree" that could be found in several western African countries.[10,11] The seeds' extracts are both used in the local food[12] and as anti-inflammatories in the traditional medicines.[13] The structure of this compound is based on a chiral pyroglutamic acid skeleton bearing a glycine substituent at the C-4 position. Its absolute configuration was established to be (3*R*,5*S*,1′*S*) through crystallographic, spectroscopic and optical studies.[14,15] To date, only two research teams have described their works towards the synthesis of title compound **1**. The synthesis of this compound was first attempted by Moloney and co-workers in 2003, but the authors were not able to reach the target molecule **1**.[16] In 2007, Naito and co-workers described the first total synthesis of **1** in 12 steps (5.4% overall yield) as well as the synthesis of the C-1′ epimer (3.0% overall yield).[17] None of these strategies involved the use of a functionalized pyrrole backbone as the key intermediate.

Our present strategy towards penmacric acid (**1**) implies first some selective transformations of the *N*-triisopropylsilylpyrrole **2** into the appropriate 2,4-disubstituted pyrrole **3** bearing a stereogenic center on the C-4 position. Then, a sequence involving the reduction of the pyrrole ring[18] followed by the oxidation of the chiral pyrrolidine **4** would give access to the target molecule **1** (Scheme 1).



Scheme 1 Proposed strategy.

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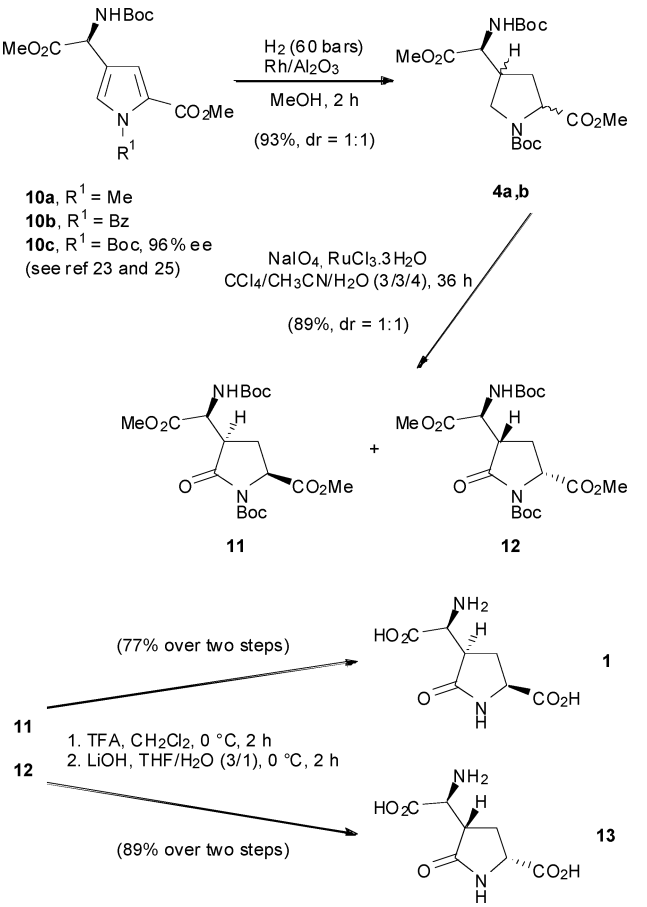
Results and discussion

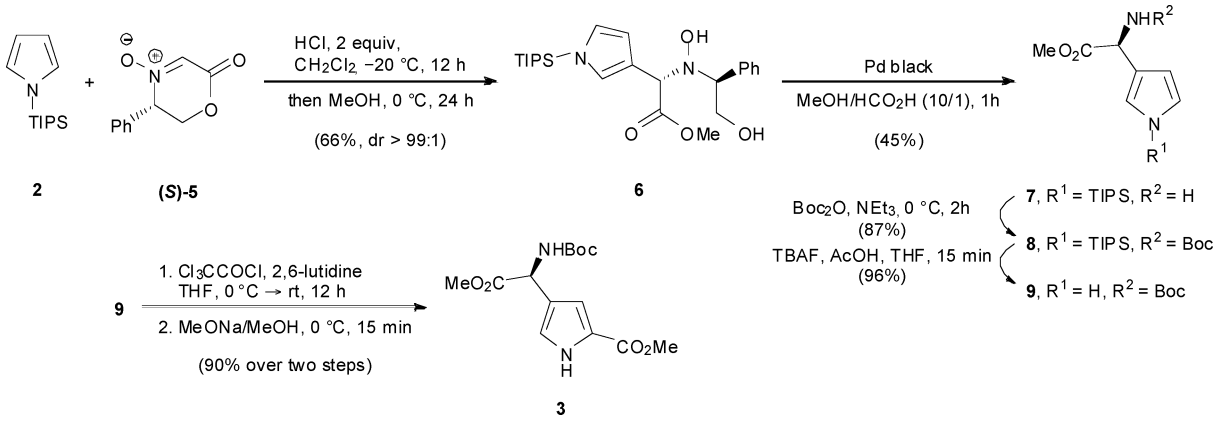
The introduction of the chiral glycinyl substituent was first performed according to our previous works,[19] by addition of *N*-triisopropylsilylpyrrole **2**[20] onto the known cyclic chiral nitrone **(*S*)-5**[21] under mild acidic conditions. The final methanolysis produced the C-3 pyrrolic hydroxylamine **6** as a unique regio- and diasteroisomer in 66% isolated yield (Scheme 2). Removal of the chiral auxiliary and N–O bond cleavage using palladium black as the catalyst in the presence of formic acid gave amino ester **7**.[22] In order to prevent any self condensation of compound **7**, protection of the amino group was performed under classical conditions to give the *tert*-butyl carbamate **8**. As selective functionalization at the α-position of the pyrrole was needed in the next steps, the bulky silyl group on the nitrogen atom was first removed using TBAF in the presence of acetic acid. Subsequent trichloroacetylation of compound **9** followed by treatment of the crude mixture with sodium methoxide gave the corresponding methyl ester **3** in 90% yield as a unique regioisomer that possesses the framework of the target molecule **1**. The structure of compound **3** has been confirmed through some 1D and 2D NMR experiments.

In order to explore the stereoselective hydrogenation of the pyrrole nucleus into the corresponding pyrrolidine, the protected derivatives **10a**, **10b** and **10c** were then prepared with good to excellent yields following typical procedures.[23] Indeed, all our preliminary attempts at reduction of the unprotected pyrrole **3**—using either Rh/Al_2O_3 or Pt/C as the catalyst under levels of hydrogen pressure ranging from 1 to 60 bars in methanol or acetic acid—only left the unreacted starting material. Although Frontier and Jiang found that the hydrogenation of *N*-methyl pyrroles was an efficient process,[18] in our case compound **10a** was not reactive at all, even under a 60 bar hydrogen pressure using a catalytic amount of Rh/Al_2O_3 in methanol. The use of the *N*-benzoyl derivative **10b** was unsuccessful as well. In this case, the non-quantitative cleavage of the benzoyl group was observed, as was previously described when using Raney nickel.[24]

Finally, hydrogenation of the *N*-Boc derivative **10c**[25] under the same conditions provided a (1:1) mixture of the pyrrolidines **4a,b** in very good yield (Scheme 3). At this stage, the two diastereoisomers were inseparable. The subsequent oxidation using ruthenium tetroxide in a ternary solvent system was then performed starting from this mixture.[26] The corresponding diastereomeric pyrrolidinones **11** and **12** were obtained in 89% yield and were separated by silica gel chromatography. Careful analysis of the NMR spectra allowed the assignment of the *cis-syn* configuration for compound **11**, and *cis-anti* for compound **12** (Scheme 3). The final deprotection sequence was performed in two steps on each compound with good overall yields.[27]



Scheme 3 Synthesis of title compound **1** and its stereoisomer **13**.



Scheme 2 Synthesis of compound **3**.

Conclusions

In conclusion, our synthetic sample of penmacric acid (**1**) was obtained by an 11-step sequence with a good overall yield (6.9%) and displayed the same physical properties as the natural compound ($[\alpha]_D^{20}$ +33.6 (*c* 0.070, 0.1 N HCl); lit.[10] $[\alpha]_D^{20}$ +35 (*c* 0.070, 0.1 N HCl); consistent with an ee value of 96%). Furthermore, this original strategy allowed access to another stereoisomer **13**, which is the antipode of the known epipenmacric acid,[17] in 11 steps with a very good overall yield (8.0%). Further studies in the field of the synthesis of C-4 substituted pyroglutamic acid derivatives are currently being undertaken by our team.

Experimental

General experimental

All reactions were carried out using oven-dried glassware under an argon atmosphere. Solvents were purified prior to use by conventional methods. All other reagent-grade chemicals were used as supplied (analytical or HPLC grade) without prior purification. Thin layer chromatography was performed on aluminium plates coated with 60 PF254 silica. Plates were visualised using UV light (254 nm), followed by heating after treatment with an appropriate revelatory ($KMnO_4$, TTC, phosphomolybdic acid, ninhydrin). Flash column chromatography was performed on Kieselgel 60 silica (40-60 mesh).

Elemental analyses were recorded by the microanalysis service of the Département de Chimie Moléculaire, Grenoble, France. Melting points were recorded on a Büchi B35 apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 341 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g per 100 mL. Circular dichroisms were recorded on a JASCO J-810 spectropolarimeter. IR spectra were recorded on a Nicolet Impact-400 Fourier transform infrared spectrometer (FTIR) as either thin films on NaCl plates (thin film) or as a KBr disc (KBr disc), as stated. Selected characteristic bands are reported in cm^{-1}. NMR spectra were recorded either on a Bruker Advance300 or on an Advance400 spectrometer in the deuterated solvent as stated. The field was locked by external referencing to the relevant deuteron resonance. Low Resolution Mass Spectra (LRMS) were recorded on a Bruker Esquire 3000 plus (ESI) or a ThermoFinnigan PolarisQ ion-trap spectrometer, using DCI (ammonia/isobutane 63/37). Accurate mass measurements were run in the "Structure et Fonction de Molécules Bioactives" laboratory, Paris, France.

(*S*)-[Hydroxy-((*S*)-2-hydroxy-1-phenylethyl)amino]-(1-triisopropylsilanyl-1*H*-pyrrol-3-yl)acetic acid methyl ester (6). To a stirred solution of nitrone **(*S*)-5** (0.96 g, 5.02 mmol) in anhydrous CH_2Cl_2 (25 mL) at −40 °C was added HCl (5.0 mL, 2.0 N in Et_2O, 10.0 mmol) and *N*-TIPS-pyrrole **2** (1.23 g, 5.51 mmol). The resulting mixture was slowly warmed to −20 °C and then stirred at this temperature for 12 hours whereupon anhydrous MeOH (25 mL) was added. It was then allowed to react at 0 °C for 24 hours. The mixture was then treated with a saturated aqueous $NaHCO_3$ solution until pH 8–9. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (eluent: pentane/EtOAc, 9/1 to 7/3) to afford pure *N*-hydroxylamine **6** (1.48 g, 66%) as a pale pink solid; mp 50–51 °C; $[\alpha]_D^{20}$ +119.3 (*c* 1.00 in $CHCl_3$); ν_{MAX}/cm^{-1} (KBr disc) 3550–3350 (broad, OH × 2), 1752 (CO); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.09–1.13 (18H, m, $((CH_3)_2CH)_3Si$), 1.38–1.50 (3H, m, $((CH_3)_2CH)_3Si$), 3.54–3.58 (1H, m, C(2′)H_2), 3.63 (3H, s, OCH_3), 4.00 (1H, dd, J = 9.7 and 3.8 Hz, C(1′)*H*), 4.23 (1H, br s, O*H*), 4.33–4.38 (1H, m, C(2′)H_2), 4.39 (1H, s, C(2)*H*), 6.42 (1H, dd, J = 2.4 and 1.2 Hz, pyrr*H*), 6.57 (1H, s, O*H*), 6.70 (1H, s, pyrr*H*), 6.76 (1H, t, J = 2.4 Hz, pyrr*H*), 7.30–7.32 (5H, m, Ar*H*); δ_C (75 MHz; $CDCl_3$; Me_4Si) 11.7 ($((CH_3)_2CH)_3Si$), 17.8 ($((CH_3)_2CH)_3Si$), 52.2 (OCH_3), 63.4 (*C*(2′)H_2), 66.6 (*C*(2)H), 67.6 (*C*(1′)H), 110.5 (pyrr*C*H), 117.8 (pyrr*C*), 124.5 (pyrr*C*H), 124.9 (pyrr*C*H), 127.8 (Ar*C*H), 127.9 (Ar*C*H), 130.2 (Ar*C*H), 140.2 (Ar*C*), 174.0 (*C*=O); *m/z* (DCI, NH_3-isobutane) 447 ($[M+H]^+$), 431, 399, 294 (100%); Elemental analysis, calcd (%) for $C_{24}H_{38}N_2O_4Si$: C, 64.54; H, 8.58; N, 6.28. Found: C, 64.36; H, 8.73; N, 6.38.

4-[(*S*)-*tert*-Butoxycarbonylamino-methoxycarbonyl-methyl]-1*H*-pyrrole-2-carboxylic acid methyl ester 3. To a stirred solution of compound **9** (1.03 g, 4.05 mmol) in anhydrous THF (32 mL) at 0 °C was added 2,6-lutidine (1.20 mL, 10.3 mmol). Freshly distilled trichloroacetyl chloride (1.20 mL, 10.3 mmol) was added dropwise and the mixture was allowed to warm to room temperature. After being stirred for 12 hours, the reaction mixture was quenched with water. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was dissolved in anhydrous MeOH (81 mL) and cooled to 0 °C. Sodium methoxide (1.00 g, 18.5 mmol) was added and the mixture was stirred at 0 °C for 15 minutes. It was then acidified with 3.0 N aqueous HCl to pH 3–4. After removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2. Water was added and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (eluent: pentane/EtOAc, 9/1 to 7/3) to afford **3** (1.14 g, 90% over two steps) as a white solid: mp 40–41 °C; $[\alpha]_D^{20}$ +86.8 (*c* 1.00 in $CHCl_3$); ν_{MAX}/cm^{-1} (KBr disc) 3400–3200 (broad, NH), 1735 (CO), 1693 (CO); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.44 (9H, s, $C(CH_3)_3$), 3.76 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 5.11–5.33 (2H, m, C(2)*H* and N*H*), 6.86–6.87 (1H, m, pyrr*H*), 6.96–6.97 (1H, m, pyrr*H*), 9.07 (1H, br s, N*H*); δ_C (75 MHz; $CDCl_3$; Me_4Si) 28.2 ($C(CH_3)_3$), 51.3 (*C*H), 51.5 (OCH_3), 52.5 (OCH_3), 80.1 ($C(CH_3)_3$), 113.4 (pyrr*C*H), 121.3 (pyrr*C*), 121.4 (pyrr*C*H), 123.0 (pyrr*C*), 155.0 (*C*=O), 161.4 (*C*=O), 171.2 (*C*=O); *m/z* (DCI, NH_3/isobutane) 313 ($[M+H]^+$), 274, 213, 196 (100%); Elemental analysis, calcd (%) for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.46; N, 8.97. Found: C, 53.95; H, 6.73; N, 8.98.

(2*S*,4*R*)-4-[(*S*)-*tert*-Butoxycarbonylamino-methoxycarbonyl-methyl]-5-oxo-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester 11 and (2*R*,4*S*)-4-[(*S*)-*tert*-Butoxycarbonylamino-methoxycarbonyl-methyl]-5-oxo-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester 12. To a stirred solution of pyrrolidines **4a,b** (500 mg, 1.20 mmol) in a mixture of CCl_4, CH_3CN and H_2O (3/3/4, 24 mL) at 0 °C were sequentially added

$NaIO_4$ (1.30 g, 6.06 mmol) and $RuCl_3 \cdot 3H_2O$ (50 mg, 0.24 mmol). The resulting mixture was slowly warmed to room temperature and then stirred at this temperature for 36 hours. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered through a celite pad and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: pentane/EtOAc, 9/1 to 1/1) to afford pyrrolidinone **11** (*cis-syn*) (230 mg, 44%) as a white solid and pyrrolidinone **12** (*cis-anti*) (233 mg, 45%) as a white solid. **Data for compound 11** (*cis-syn*): mp 69–70 °C; $[\alpha]_D^{20}$ +15.1 (*c* 1.00 in $CHCl_3$); ν_{MAX}/cm^{-1} (KBr disc) 3500–3300 (broad, NH), 1798 (CO), 1748 (CO), 1714 (CO); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.44 (9H, s, C(CH_3)$_3$), 1.46 (9H, s, C(CH_3)$_3$), 1.93 (1H, ddd, J = 13.3, 10.9 and 8.9 Hz, 1H of C(3)H_2), 2.55 (1H, ddd, J = 13.2, 9.7 and 8.2 Hz, 1H of C(3)H_2), 3.48 (1H, dt, J = 10.8, and 3.0 Hz, C(4)*H*), 3.76 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.50 (1H, dd, J = 10.7 and 8.5 Hz, C(2)*H*), 4.53 (1H, d, J = 8.9 Hz, C(1′)*H*), 5.29 (1H, d, J = 8.7 Hz, N*H*); δ_C (100 MHz; $CDCl_3$; Me_4Si) 24.3 (*C*(3)H_2), 27.7 (C(*C*H_3)$_3$), 28.1 (C(*C*H_3)$_3$), 45.7 (*C*(4)H), 52.4 (2 × O*C*H_3), 52.8 (*C*(1′)H), 57.1 (*C*(2)H), 80.3 (*C*(CH_3)$_3$), 84.0 (*C*(CH_3)$_3$), 148.7 (*C*=O), 156.1 (*C*=O), 170.3 (*C*=O), 171.1 (*C*=O), 171.8 (*C*=O); *m/z* (DCI, NH_3/isobutane) 448 ([M+NH_4]$^+$), 376, 331, 231 (100%); Elemental analysis, calcd (%) for $C_{19}H_{30}N_2O_9$: C, 53.02; H, 7.03; N, 6.51. Found: C, 52.67; H, 7.18; N, 6.34; **Data for compound 12** (*cis-anti*): mp 50–51 °C; $[\alpha]_D^{20}$ +14.1 (*c* 1.00 in $CHCl_3$); ν_{MAX}/cm^{-1} (KBr disc) 3500–3300 (broad, NH), 1790 (CO), 1752 (broad, CO), 1718 (CO); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.44 (9H, s, C(CH_3)$_3$), 1.49 (9H, s, C(CH_3)$_3$), 2.06–2.16 (1H, m, 1H of C(3)H_2), 2.49–2.60 (1H, m, 1H of C(3)H_2), 3.07 (1H, dt, J = 9.9 and 4.1 Hz, C(4)*H*), 3.76 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.52 (1H, dd, J = 8.8 and 7.7 Hz, C(2)*H*), 4.57 (1H, dd, J = 8.7 and 4.2 Hz, C(1′)*H*), 5.64 (1H, br s, N*H*); δ_C (100 MHz; $CDCl_3$; Me_4Si) 24.0 (*C*(3)H_2), 27.8 (C(*C*H_3)$_3$), 28.1 (C(*C*H_3)$_3$), 45.4 (*C*(4)H), 52.5 (O*C*H_3), 52.6 (O*C*H_3), 52.9 (*C*(1′)H), 57.0 (*C*(2)H), 80.3 (*C*(CH_3)$_3$), 84.0 (*C*(CH_3)$_3$), 148.9 (*C*=O), 155.2 (*C*=O), 170.5 (*C*=O), 171.3 (*C*=O), 172.1 (*C*=O); *m/z* (DCI, NH_3/isobutane) 448 ([M+NH_4]$^+$), 376, 331, 231 (100%); Elemental analysis, calcd (%) for $C_{19}H_{30}N_2O_9$: C, 53.02; H, 7.03; N, 6.51. Found: C, 52.73; H, 7.09; N, 6.23.

Penmacric acid 1. To a stirred solution of pyrrolidinone **11** (186 mg, 0.43 mmol) in anhydrous CH_2Cl_2 (4.3 mL) at 0 °C was added anhydrous trifluoroacetic acid (640 µL, 8.64 mmol). After being stirred for 2 hours at this temperature, solvents were evaporated under reduced pressure. The resulting crude product was dissolved in a THF/H_2O mixture (3/1, 21 mL) at 0 °C. Lithium hydroxide monohydrate (72 mg, 1.72 mmol) was added and the resulting mixture was stirred for 2 hours at this temperature. It was then acidified with 0.2 N aqueous HCl to pH 3. After removal of the solvent *in vacuo*, the residue was passed through a column of Dowex 50W-X8 ion exchange resin (H^+ form), eluted with water and then 0.5 N aqueous ammonia. Lyophilization afforded penmacric acid **1** (67 mg, 77% over two steps) as a white hygroscopic solid: mp 194–195 °C; $[\alpha]_D^{20}$ +33.6 (*c* 0.070 in 0.1 N HCl), lit.[10] $[\alpha]_D^{20}$ +35 (*c* 0.070 in 0.1 N HCl); ν_{MAX}/cm^{-1} (KBr disc) 3600–2800 (broad, NH, NH_2 and OH), 1689 (broad, CO); δ_H (300 MHz; D_2O) 1.96 (1H, dd, J = 22.2 and 10.8 Hz, 1H of C(3)H_2), 2.75 (1H, ddd, J = 13.1, 8.5 and 8.4 Hz, 1H of C(3)H_2), 3.10 (1H, dd, J = 18.1 and 8.4 Hz, C(4)*H*), 3.94 (1H, d, J = 7.3 Hz, C(1′)*H*), 4.21 (1H, t, J = 8.3 Hz, C(2)*H*); δ_C (100 MHz; D_2O) 29.3 (*C*(3)H_2), 41.7 (*C*(4)H), 55.0 (*C*(1′)H), 56.1 (*C*(2)H), 172.0 (*C*=O), 177.7 (*C*=O), 178.9 (*C*=O); *m/z* (ESI$^+$) 225 ([M+Na]$^+$), 203 ([M+H]$^+$); HRMS (ESI$^+$) $C_7H_{11}N_2O_5$ ([M+H]$^+$) requires 203.06625 found 203.06563.

(2*R*,4*S*)-4-[(*S*)-Amino-carboxy-methyl]-5-oxo-pyrrolidine-2-carboxylic acid (13). The same procedure applied to pyrrolidinone **12** (220 mg, 0.51 mmol) afforded penmacric acid's stereoisomer **13** (91 mg, 89% over two steps) as a white hygroscopic solid: mp 137–138 °C (decomp.); $[\alpha]_D^{20}$ +32.4 (*c* 0.50 in 0.1 N HCl); ν_{MAX}/cm^{-1} (KBr disc) 3600–2800 (broad, NH, NH_2 and OH), 1680 (broad, CO); δ_H (300 MHz; D_2O) 1.93 (1H, ddd, J = 13.5, 10.0 and 8.4 Hz, 1H of C(3)H_2), 2.65 (1H, ddd, J = 14.1, 11.4 and 8.8 Hz, 1H of C(3)H_2), 3.47 (1H, dt, J = 10.0 and 3.3 Hz, C(4)*H*), 4.19 (1H, d, J = 3.0 Hz, C(1′)*H*), 4.24 (1H, t, J = 8.1 Hz, C(2)*H*); δ_C (100 MHz; D_2O) 25.9 (*C*(3)H_2), 42.7 (*C*(4)H), 52.8 (*C*(1′)H), 56.0 (*C*(2)H), 172.6 (*C*=O), 177.2 (*C*=O), 179.2 (*C*=O); *m/z* (ESI$^+$) 225 ([M+Na]$^+$), 203 ([M+H]$^+$); HRMS (ESI$^+$) $C_7H_{11}N_2O_5$ ([M+H]$^+$) requires 203.06625 found 203.06561.

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