Tetrahedron xxx (2013) 1–9

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total synthesis of penmacric acids via an intermolecular radical addition reaction

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ARTICLE INFO

Article history:
Received 11 May 2013
Received in revised form 30 May 2013
Accepted 1 June 2013
Available online xxx

Keywords:
Penmacric acid
Total synthesis
Radical reaction
Amino acid

ABSTRACT

The total syntheses of penmacric acid and its three stereoisomers were accomplished through the intermolecular radical addition reaction of the 4-pyrrolidyl radical derived from *trans*-4-hydroxy-L-proline. Furthermore, 1′,3-di*epi*-penmacric acid was synthesized stereoselectively via double stereoinduction in the radical reaction.

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1. Introduction

Various non-proteinogenic amino acids have been found in nature in the free zwitterionic form or as constituents of peptidic compounds. Because of their important biological activities, scientists have devoted much attention to these amino acids, such as antibiotics, neurotoxins, or enzyme inhibitors,[1] and thus many of them are interesting synthetic targets.[2,3] Pyroglutamic acids, in particular, are found to play an important role in organic chemistry. They are widely used as building blocks in synthetic chemistry[4] and are found as core units in biologically active molecules such as oxazolomycin A,[5] salinosporamide A,[6] boneratamides,[7] and amphiasterins C.[8] Among the naturally occurring pyroglutamic acid derivatives, penmacric acid **1** has an interesting and unique structure, consisting of glycine and pyroglutamic acid, which are connected via a carbon–carbon bond linkage. It was isolated in 1975 independently by both Welter[9] and Mbadiwe[10] from the seeds of the leguminous tree *Pentaclethra macrophylla*, which is traditionally used for food, dye, and medicine for anti-inflammatory use in West Africa. The structure was elucidated by ^{1}H NMR, ^{13}C NMR, CD, and X-ray studies.[11] Despite its unique structural features, biological studies have not been reported. The first synthetic study was reported by Moloney in 2003, but the total synthesis was not completed yet.[12] In 2007, we achieved the first total synthesis of penmacric acid and its 1′-epimer by using a diastereoselective intermolecular radical addition reaction.[13] Subsequently, in 2009, Minassian reported the total synthesis of **1** and its 3,5-epimer via hydrogen chloride-mediated alkylation of pyrrole.[14] This was followed by short synthesis of three protected epimers based on the reaction of the enolate of pyroglutamate with imine reported by Dikshit.[15] Our interest is in the development of flexible synthetic methodologies that will allow the synthesis of various stereoisomers. To evaluate the biological activity of penmacric acids, the synthesis of various stereoisomers and related compounds is important. We anticipated that the addition reaction of 4-pyrrolidinyl radical **B** to the oxime ether derivative of glyoxylate **A** would lead to the stereodivergent synthesis of penmacric acids (Scheme 1). Herein, we provide a full account of the total synthesis of penmacric acid and three stereoisomers. Furthermore, the stereoselective synthesis of 1′,3-di*epi*-penmacric acid by double stereoinduction via a radical reaction is reported in this article.

2. Results and discussion

2.1. Total synthesis of penmacric acid and 1′-*epi*-penmacric acid

Our initial target was penmacric acid **1** and 1′-*epi*-penmacric acid **2**. The retrosynthetic strategy is depicted in Scheme 2, which

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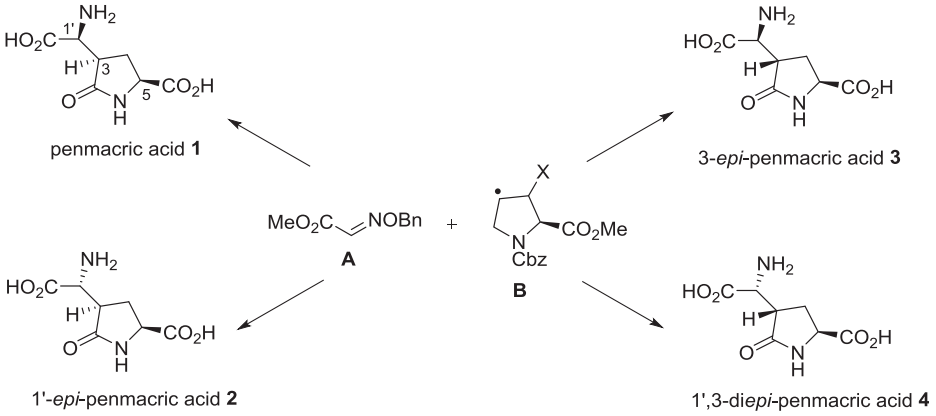
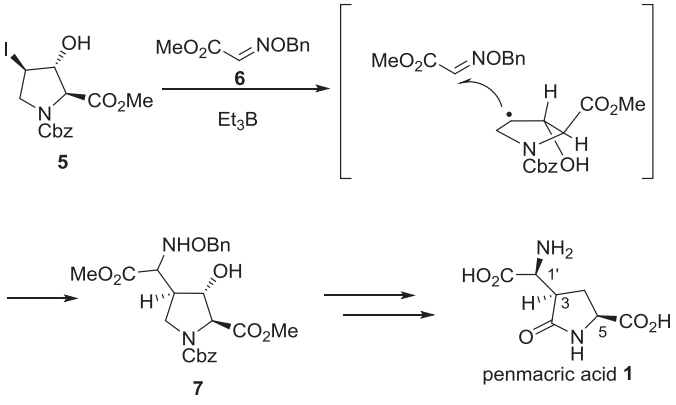
0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.06.006



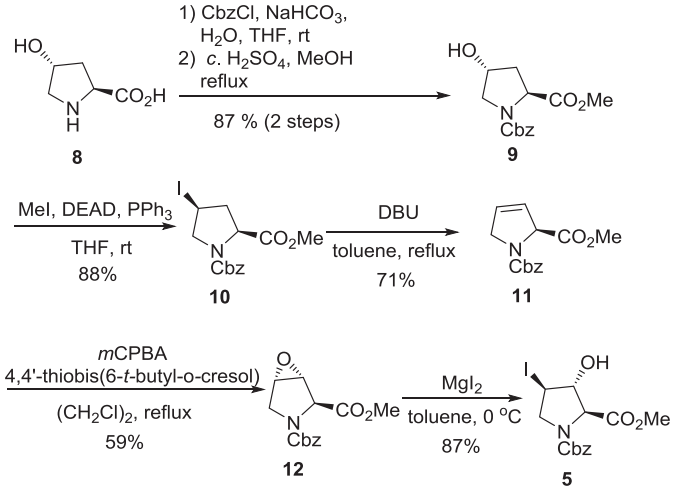
Scheme 1. Synthetic strategy.



Scheme 2. Synthetic strategy toward penmacric acid **1**.

was based on the Et_3B-induced radical reaction of iodoproline **5** bearing the hydroxyl group as a stereochemical auxiliary with oxime ether **6**. We expected the stereoselective construction of the C3–C1′ bond in the radical addition of the pyrrolidine ring onto the glycine equivalent.

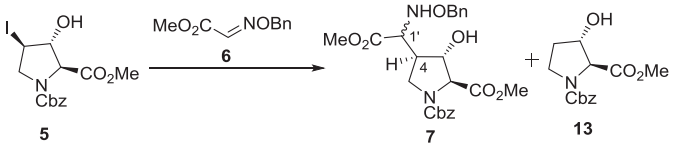
The synthesis started with the preparation of the hydroxylated iodoproline **5** from commercially available *trans*-4-hydroxy-L-proline **8** (Scheme 3). After protection of the amino group with CbzCl in THF and the carboxyl group with a catalytic amount of H_2SO_4 in MeOH, the hydroxyl group was converted into the iodo group under the Mitsunobu reaction condition. Thus, treatment of **9** with MeI, DEAD, PPh_3 gave 4-iodoproline **10** in 88% yield.[16] Elimination of the iodo group with DBU afforded 3,4-dehydroproline **11** in 71% yield. The 3,4-dehydroproline **11** was then oxidized with *m*-CPBA in the presence of 4,4′-thiobis(6-*tert*-butyl-*o*-cresol) as a radical scavenger to give the epoxide **12** in 59% yield as a single stereoisomer.[17] Regioselective ring opening of the epoxide **12** with magnesium iodide afforded the expected 3-hydroxy-4-iodoproline **5** in 87% yield.[18]



Scheme 3. Synthesis of 3-hydroxy-4-iodoproline **5**.

With the radical precursor **5** in hand, we next investigated a radical reaction of **5** with glyoxylic oxime ether **6**, which was found to be an excellent radical acceptor as we previously reported.[19] Several conditions for the radical reaction were screened to optimize the yield and these are summarized in Table 1. When the reaction of 3-hydroxyl-4-iodoproline **5** with 1 equiv of oxime ether **6** was carried out in CH_2Cl_2 at room temperature using 5 equiv of Et_3B as the radical initiator, no desired product was isolated and 3-hydroxyproline **13**[20] was obtained in 46% yield (entry 1). This result indicated the generation of 4-pyrrolidinyl radical, which however was reduced prior to addition to oxime ether. Even the addition of $BF_3{\cdot}OEt_2$ to the reaction mixture for the enhancement of the reactivity of oxime ether did not produce any of the desired adduct (entry 2). We were pleased to find that the expected radical addition reaction proceeded to afford the adduct **7** upon increasing the amount of oxime ether and Et_3B. The reaction with 20 equiv of oxime ether **6** and 12.5 equiv of Et_3B in CH_2Cl_2 at room temperature gave **7** in 30% yield as an inseparable 1:1 mixture of two diastereomers at the C1′ position (entry 3). This result showed that facial selectivity of the pyrrolidine ring is completely

Table 1
Radical addition to oxime ether **6**

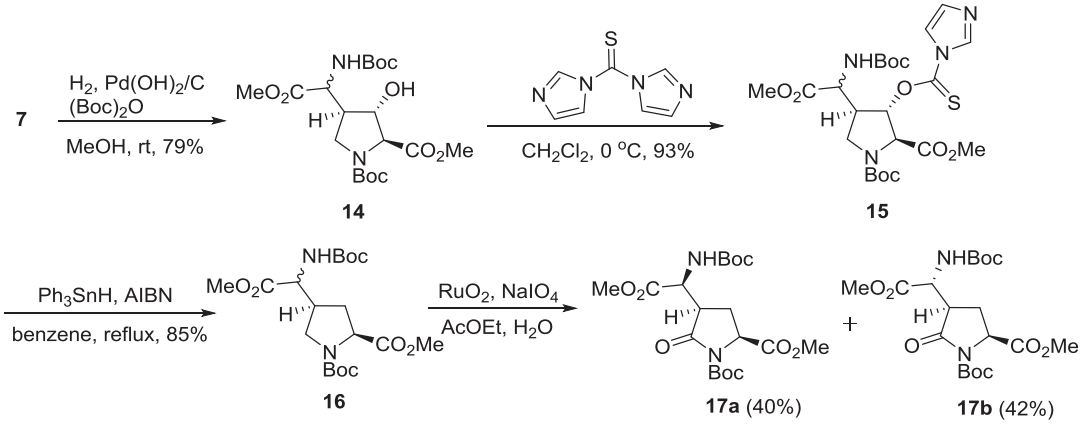


Entry	Radical initiator (equiv)	**6** (equiv)	Solvent	*T* (°C)	Yield (%)
1	Et_3B (5)	1	CH_2Cl_2	rt	**13**: 46
2[a]	Et_3B (5)	1	CH_2Cl_2	rt	**13**: 57
3	Et_3B (12.5)	20	CH_2Cl_2	rt	**7**[b]: 30
4	Et_3B (15)	20	CH_2Cl_2	Reflux	**7**[b]: 81
5	Et_3B (15)	20	Benzene	Reflux	**7**[b]: 68
6	Et_3B (15)	20	$(CH_2Cl)_2$	Reflux	**7**[c]: 44
7[d]	AIBN (0.5)	15	Benzene	Reflux	**13**: 81

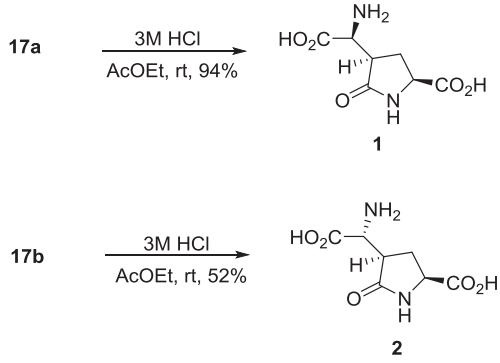
[a] Reaction was run in the presence of $BF_3{\cdot}OEt_2$ (1.2 equiv).
[b] 1:1 mixture of diastereomers.
[c] C4 isomers were obtained in 22% yield.
[d] Reaction was run in the presence of Bu_3SnH (1.2 equiv).

controlled by the hydroxyl group that was introduced as a stereochemical auxiliary. Reaction temperature and choice of solvent were a key factor in improving the yield, and the best result was obtained in refluxing CH_2Cl_2 solution (entries 4–6). Et_3B was found to be a superior radical initiator than the other initiators, such as AIBN (entry 7).

The remaining steps began with reductive cleavage of the N–O bond, deprotection of the Cbz group and Boc-protection of the resulting amino groups by hydrogenolysis in the presence of $(Boc)_2O$ (Scheme 4).[21] Removal of the hydroxyl group was accomplished by the Barton–McCombie radical deoxygenation.[22] The corresponding imidazolethiocarbamate **15** was prepared with *N*,*N*-thiocarbonyldiimidazole in 93% yield, and then reduced with Ph_3SnH and AIBN to yield the deoxygenated compound **16** in 85% yield, whereas the reduction with Bu_3SnH led to decomposition. The oxidation of proline derivative **16** with ruthenium tetraoxide under EtOAc/H_2O biphasic conditions furnished the desired lactams **17a** and **17b**, which were separated at this stage by column chromatography on silica gel.[23] Finally, two Boc groups and two methyl esters were deprotected with 3 M HCl to give penmacric acid **1** and the 1′-*epi*-penmacric acid **2** in 94% and 52% yields, respectively (Scheme 5). The spectral data for our synthetic sample **1** were identical in all respects with those of the published data.[10] The stereostructure of **2** was confirmed by comparison with the reported spectroscopic data.[14]



Scheme 4. Synthesis of **17a** and **17b**.



Scheme 5. Completion of the total synthesis of penmacric acid **1** and 1′-*epi*-penmacric acid **2**.

2.2. Total synthesis of 3-*epi*-penmacric acid and 1′,3-di*epi*-penmacric acid

We next investigated the synthesis of the two C3-epimers of penmacric acid, which have an *anti* relationship between the glycine moiety and the carboxyl group at C5 position in the pyrrolidine ring (Scheme 6). For the *anti*-selective radical addition reaction, 4-iodoproline **10** was used as a radical precursor. We anticipated the 4-pyrrolidinyl radical would add to oxime ether, avoiding steric repulsion by the ester moiety of proline. In contrast to the previously mentioned reaction with hydroxyl proline **5**, the radical addition reaction of **10** induced by Et_3B proceeded efficiently, even at room temperature, to provide a diastereomeric mixture (1:1) of alkylated proline **18**, both of which had the desired stereogenic center at the C3 position. Hydrogenolysis, Boc-protection, and oxidation by the same operations as those of **17** gave the desired lactams **20a** in 47% yield and **20b** in 40% yield. The stereostructures of the lactams were identified by comparison with the reported spectroscopic data.[15] Completion of syntheses of 3-*epi*-penmacric acid **3** and 1′,3-di*epi*-penmacric acid **4** was accomplished by deprotection under acidic conditions.[24]

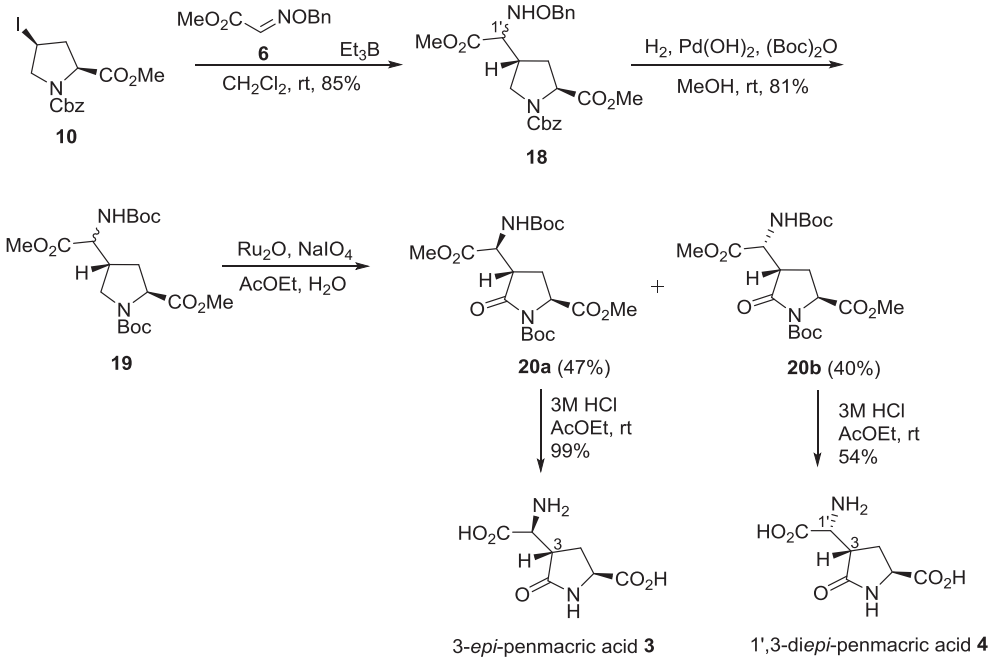
2.3. Asymmetric total synthesis of 1′,3-di*epi*-penmacric acid

In the previously mentioned synthetic routes for penmacric acid, at least one of three chiral centers was unable to be constructed stereoselectively, and therefore a separation step was required. We finally investigated the stereoselective synthesis of 1′,3-di*epi*-penmacric acid **4** by the diastereoselective radical addition reaction to chiral oxime ether as a key step. For the stereoselective construction of the C1′ position, the auxiliary of choice was Oppolzer's camphorsultam, because it had shown a good result in our previous work on radical reactions of oxime ether, hydrazone, and nitrone.[19c,25,26] The chiral oxime ether **21** was subjected to the radical addition reaction with 4-iodoproline **10**. As expected, the reaction proceeded stereoselectively to give the adduct **22a** in 55% yield, in which the absolute configurations at C-1′ and C-4 are both *R*, along with a small amount of diastereomer **22b** (Scheme 7).

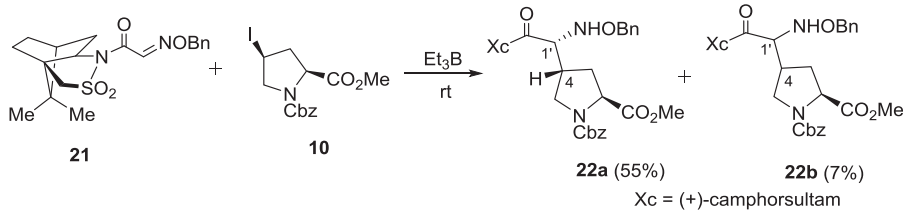
With stereochemically pure adduct **22a** in hand, the transformation to the synthetic intermediate for 1′,3-di*epi*-penmacric acid **4** was investigated (Scheme 8). Hydrolysis of imide and ester groups with LiOH, followed by methylation with $TMSCHN_2$ gave diester **23**. Hydrogenolysis, Boc-protection, and oxidation furnished the lactam **20b** in good yields, which indicated the accomplishment of the stereoselective total synthesis of 1′,3-di*epi*-penmacric acid because **20b** has been converted into **4**, as in Scheme 6.

3. Conclusion

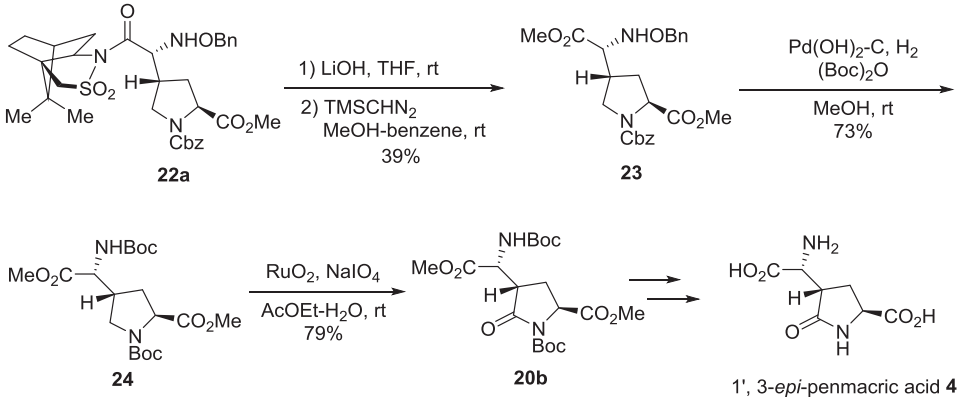
We achieved the concise total syntheses of penmacric acid and three epimers by a radical reaction of an iodoproline derivative



Scheme 6. Total synthesis of 3-*epi*-penmacric acid **3** and 1′,3-di*epi*-penmacric acid **4**.



Scheme 7. Diastereoselective radical addition reaction of **10** with **21**.



Scheme 8. Synthesis of **20b**.

with an oxime ether. The hydroxyl group-induced stereoselective construction of the C3 stereogenic center was applied to the synthesis of penmacric acid and 1′-*epi*-penmacric acid, whereas the C3-epimers were synthesized by a stereoselective radical reaction controlled by the inherent ester moiety. Furthermore, stereoselective synthesis of 1′,3-di*epi*-penmacric acid by double diastereoselective radical addition reaction of chiral iodoproline to chiral oxime ether has been accomplished. The advantage of our strategy centers on the stereoselective synthesis of various types of α-substituted α-amino acids, including natural and unnatural compounds. Therefore, our route can be applied to produce various analogs.

4. Experimental section

4.1. General

NMR spectra were recorded at 300 MHz/75 MHz (^{1}H NMR/^{13}C NMR) or 500 MHz/125 MHz (^{1}H NMR/^{13}C NMR) using a Varian Gemini-300 (300 MHz), Varian MERCURY plus 300 (300 MHz), or

Please cite this article in press as: Ueda, M.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.06.006

Varian NMR system AS 500 (500 MHz) spectrometers. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), coupling constants, and integration. IR spectra were obtained on a Perkin–Elmer SpectrumOne A spectrometer. Mass spectra were obtained by electrospray ionization on a Hitachi M-4100 mass spectrometer. Flash column chromatography was performed with a 40–63 μm silica gel (Silicycle). Tetrahydrofuran (THF) was freshly distilled from the benzophenone ketyl radical anion prior to use.

4.2. (2*S*,4*R*)-4-Hydroxy-1,2-pyrrolidinedicarboxylic acid 2-methyl 1-(phenylmethyl) ester (9)

To a stirred solution of (2*S*,4*R*)-*trans*-4-hydroxy-L-proline **8** (10 g, 76 mmol) and $NaHCO_3$ (8.3 g, 99 mmol) in H_2O (20 mL) and THF (65 mL) was added, dropwise, benzyl chloroformate (14 mL, 99 mmol) under an N_2 atmosphere at 0 °C. The reaction mixture was allowed to reach room temperature and stirred overnight. The reaction mixture was diluted with 20% aqueous NaOH and washed with Et_2O. The aqueous phase was acidified to pH 3 with concentrated HCl and extracted with AcOEt. The combined organic phase was washed with water, dried over $MgSO_4$, and concentrated at reduced pressure to give *N*-Cbz-proline. To a solution of the Cbz-proline (19 g, 73 mmol) in MeOH (100 mL) was added, dropwise, concentrated H_2SO_4 (2 mL) at room temperature. After stirring under reflux for 10 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. The residue was purified by flash column chromatography on silica gel (AcOEt) to give **9** (18 g, 87%) as a colorless oil. Analytical data were consistent with those reported in the literature.[27]

4.3. (2*S*,4*S*)-4-Iodo-1,2-pyrrolidinedicarboxylic acid 2-methyl 1-(phenylmethyl) ester (10)

To a stirred solution of **9** (15 g, 55 mmol) in THF (400 mL) was added triphenylphosphine (17 g, 66 mmol) under N_2 atmosphere at room temperature. After the reaction mixture was cooled to 0 °C, diethyl azodicarboxylate (40% solution in toluene, 28.6 mL, 66 mmol) and methyl iodide (4.1 mL, 66 mmol) were added dropwise. The reaction mixture was stirred for 17 h. The solvent was evaporated at reduced pressure and the resulting residue was purified by flash column chromatography on silica gel (hexane/AcOEt (3:1)) to afford **10** (19 g, 88%) as a yellow oil. IR (neat): 1750, 1702 cm^{-1}. ^1H NMR (1:1 mixture of rotamers, 200 MHz, $CDCl_3$) δ: 7.35–7.32 (5H, br m), 5.25–5.00 (2H, br m), 4.56–4.47 (1/2H, br m), 4.38–4.30 (1H, br m), 4.15–3.99 (1H+1/2H, br m), 3.84–3.76 (1H+3/2H, br m), 3.60–3.56 (3/2H, br m), 2.95–2.85 (1/2H, br m), 2.62–2.56 (1/2H, br m), 2.50–2.40 (1H, br m). ^{13}C NMR (1:1 mixture of rotamers, 50 MHz, $CDCl_3$) δ: 172.2, 172.1, 171.6, 171.4, 154.2, 153.8, 153.2, 136.1, 128.44, 128.36, 128.0, 127.8, 67.4, 58.9, 58.7, 58.5, 57.9, 57.4, 57.2, 56.8, 52.5, 52.3, 43.0, 42.7, 42.0, 41.7. HRMS (EI): calcd for $C_{14}H_{16}INO_4$ (M^+) 389.0123, found 389.0121. $[\alpha]_D^{29}$ −19.7 (*c* 1.87, $CHCl_3$).

4.4. (2*S*)-2,5-Dihydro-1*H*-pyrrole-1,2-dicarboxylic acid 2-methyl 1-(phenylmethyl) ester (11)

To a solution of **10** (18 g, 46 mmol) in toluene (450 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 7.6 mL, 51 mmol) at room temperature. After being stirred under an N_2 atmosphere under reflux for 6.5 h, the reaction mixture was filtered to remove DBU·HI and the filtrate was concentrated at reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/AcOEt (4:1)) afforded 3,4-dehydroproline **11** (8.5 g, 71%) as a colorless oil. The spectral data were identical with those reported in the literature.[28]

4.5. (1*R*,2*S*,5*S*)-6-Oxa-3-azabicyclo[3.1.0]hexane-2,3-dicarboxylic acid 2-methyl 3-(phenylmethyl) ester (12)

To a solution of **11** (6.6 g, 25 mmol) in 1,2-dichloroethane (500 mL) was added *m*-CPBA (77%, 6.8 g, 30 mmol) and 4,4′-thiobis(6-*tert*-butyl-*o*-cresol) (541 mg, 1.5 mmol) at room temperature under an N_2 atmosphere. After stirring under reflux for 10 h, the reaction mixture was washed with 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification of the residue by flash column chromatography on silica gel (hexane/AcOEt (4:1)) afforded **12** (4.1 g, 59%) as a colorless oil. IR (neat): 1752, 1713 cm^{-1}. ^1H NMR (1:1 mixture of rotamers, 200 MHz, $CDCl_3$) δ: 7.35–7.30 (5H, m), 5.13 (2/2H, s), 5.18, 5.04 (2/2H, ABq, *J*=12.5 Hz), 4.73 (1/2H, s), 4.65 (1/2H, s), 3.97 (1/2H, d, *J*=12.5 Hz), 3.92 (1/2H, d, *J*=12.5 Hz), 3.79 (3/2H, s), 3.68 (3/2H, s), 3.80–3.67 (1H+1H, m), 3.55 (1/2H, d, *J*=12.5 Hz), 3.49 (1/2H, d, *J*=12.5 Hz). ^{13}C NMR (1:1 mixture of rotamers, 50 MHz, $CDCl_3$) δ: 168.9, 154.8, 154.3, 135.90, 135.86, 128.11, 128.06, 127.74, 127.66, 127.5, 127.3, 66.9, 66.8, 60.3, 60.1, 56.7, 56.0, 54.3, 53.8, 52.3, 52.2, 47.0, 46.7. HRMS (EI): calcd for $C_{14}H_{15}NO_5$ (M^+) 277.0949, found: 277.0934. $[\alpha]_D^{27}$ −8.70 (*c* 1.28, $CHCl_3$).

4.6. (2*S*,3*R*,4*R*)-3-Hydroxy-4-iodo-1,2-pyrrolidinedicarboxylic acid 2-methyl 1-(phenyl methyl) ester (5)

To a solution of **12** (4.5 g, 16 mmol) in toluene (300 mL) was added a solution of MgI_2 (4.9 g, 18 mmol) in Et_2O (10 mL) at 0 °C under an Ar atmosphere. After vigorous stirring at the same temperature for 2 h, the mixture was washed with 10% aqueous $Na_2S_2O_3$ and brine. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt (3:1)) and then recrystallized to give **5** (5.6 g, 87%) as colorless crystals. Mp: 93.8–94.5 °C (hexane/AcOEt). IR (KBr): 3287, 1752, 1679 cm^{-1}. ^1H NMR (1:1 mixture of rotamers, 500 MHz, $CDCl_3$) δ: 7.36–7.29 (5H, m), 5.19, 5.11 (2/2H, ABq, *J*=12.5 Hz), 5.19, 5.04 (2/2H, ABq, *J*=12.5 Hz), 4.57–4.53 (1H, m), 4.29–4.19 (1H+1H, m), 4.07–4.00 (1H, m), 3.82 (3/2H, s, CO_2Me), 3.81–3.74 (1H, m), 3.62 (3/2H, s, CO_2Me), 2.68 (1H, br s, OH). ^{13}C NMR (1:1 mixture of rotamers, 125 MHz, $CDCl_3$) δ: 170.5, 170.3, 154.0, 153.6, 136.0, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 83.3, 82.4, 67.7, 67.6, 64.6, 64.5, 54.34, 54.25, 52.8, 52.6, 21.5, 21.0. HRMS (EI): calcd for $C_{14}H_{16}INO_5$ (M^+) 405.0072, found: 405.0079. Anal. Calcd for $C_{14}H_{16}INO_5$: C, 41.50; H, 3.98; N, 3.46, found: C, 41.45; H, 3.88; N, 3.41. $[\alpha]_D^{27}$ +3.89 (*c* 0.90, $CHCl_3$).

4.7. (3*S*,4*S*,5*S*)-3-Hydroxy-4-[2-methoxy-2-oxo-1-[(phenylmethoxy)amino]ethyl]-1,2-pyrrolidinedicarboxylic acid 2-methyl 1-(phenylmethyl) ester (7)

To a solution of oxime ether **6** (7.8 g, 40 mmol) and iodide **5** (1.1 g, 2.7 mmol) in CH_2Cl_2 (5 mL) was added Et_3B (1.0 M in hexane, 6.7 mL, 6.7 mmol) three times every 1.5 h under an N_2 atmosphere under reflux. After stirring the reaction mixture at the same temperature for 1.5 h, a solution of oxime ether **6** (2.6 g, 13 mmol) in CH_2Cl_2 (2 mL) was added. Additionally, Et_3B (1.0 M in hexane, 6.7 mL, 6.7 mmol) was added three times, at 1.5 h intervals. After stirring at the same temperature for 10 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt (1:1)) to afford **7**

Please cite this article in press as: Ueda, M.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.06.006

(1.02 g, 81%) as a colorless oil and a 1:1 mixture of diastereomers at the C1′. IR (neat): 3440, 1745, 1704 cm^{-1}. ^1H NMR (1:1:1:1 mixture of diastereomers and rotamers, 500 MHz, $CDCl_3$) δ: 7.37–7.28 (10H, m), 5.19–4.99 (2H, m), 4.71–4.63 (2H, m), 4.35–4.33 (1/4H, m), 4.17–4.09 (1/4H+1/4H), 4.05–3.96 (1/4H+1/2H, m), 3.89–3.83 (1/4H, m), 3.81 (3/4H, s), 3.73 (3/4H, s), 3.78 (3/4H, s), 3.77 (12/4H, s), 3.81–3.72 (1/4H+1/2H, m), 3.71–3.60 (1/2H, m), 3.58 (3/4H, s), 3.59–3.52 (1/2H+1/2H, m), 3.41–3.19 (1H, m), 2.50–2.30 (1/2H, br m), 2.18–2.00 (1/2H, br m). ^{13}C NMR (1:1:1:1 mixture of diastereomers and rotamers, 125 MHz, $CDCl_3$) δ: 173.1, 172.4, 172.1, 172.0, 171.8, 171.7, 171.5, 170.6, 154.4, 154.2, 154.0, 153.9, 137.3, 136.8, 136.76, 136.4, 136.3, 136.0, 128.8, 128.75, 128.7, 128.6, 128.57, 128.5, 128.44, 128.40, 128.37, 128.28, 128.25, 128.2, 128.1, 127.98, 127.93, 127.7, 79.6, 78.5, 76.5, 76.4, 76.3, 76.2, 75.6, 74.5, 67.9, 67.6, 67.5, 67.4, 67.37, 67.1, 66.1, 66.0, 65.7, 65.6, 65.0, 64.7, 63.9, 63.8, 62.3, 52.7, 52.67, 52.42, 52.38, 52.3, 48.1, 47.7, 47.5, 47.2, 46.9, 46.6, 46.4, 45.7, 45.3, 45.1, 44.8, 42.2, 41.4. HRMS (EI): calcd for $C_{24}H_{28}N_2O_8$ (M^+) 472.1843, found: 472.1838. $[\alpha]_D^{27}$ +2.25 (*c* 1.22, $CHCl_3$).

4.8. (2*S*,3*S*,4*S*)-3-Hydroxy-4-[1-[[(1,1-dimethylethoxy)carbonyl]amino]-2-methoxy-2-oxoethyl]-1,2-pyrrolidinedicarboxylic acid 1-(1,1-dimethylethyl) 2-methyl ester (14)

After a suspension of palladium hydroxide (93 mg, 20 wt %) in MeOH (5 mL) was stirred under an H_2 atmosphere at room temperature for 30 min, a solution of **7** (78 mg, 0.17 mmol) in MeOH (3 mL) and $(Boc)_2O$ (0.08 mL, 0.36 mmol) were added to the suspension. After stirring at room temperature under an H_2 atmosphere for 23 h, the reaction mixture was filtered through Celite and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/AcOEt (1:1)) to afford **14** (56 mg, 79%) as a colorless oil. IR (neat): 3392, 1748, 1694 cm^{-1}. ^1H NMR (mixture of diastereomers and rotamers, 200 MHz, $CDCl_3$) δ: 5.46 (1H, br), 4.62–3.92 (1H+1H+1H, m), 3.78 (3H+3/2H, br s), 3.76 (3/2H, br s), 3.30–3.03 (1H+1/2H, br m), 2.89–2.83 (1/2H, br m), 2.56–2.48 (1H, br m), 1.80 (1H, br s), 1.45 (9H, br s), 1.36 (9H, br s). ^{13}C NMR (mixture of diastereomers and rotamers, 50 MHz, $CDCl_3$) δ: 172.3, 172.2, 171.9, 171.7, 171.3, 156.5, 155.6 (br), 154.6, 153.8, 153.2, 80.7, 80.5, 80.4, 79.9, 79.1, 77.2, 75.4 (br), 74.8, 73.8, 69.6, 67.7, 67.5, 66.0, 65.7, 64.4, 52.7, 52.3, 52.2, 52.0, 51.2, 47.7, 47.1, 46.8, 46.3 (br), 44.5, 44.0, 42.5, 41.9, 32.3, 32.0, 28.04, 27.96. HRMS (EI): calcd for $C_{19}H_{33}N_2O_9$ ($M+H^+$) 433.2184, found: 433.2193. $[\alpha]_D^{27}$ +3.62 (*c* 1.87, $CHCl_3$).

4.9. (2*S*,3*S*,4*S*)-4-[1-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-methoxy-2-oxoethyl]-3-(1*H*-imidazol-1-ylthioxomethoxy)-1,2-pyrrolidinedicarboxylic acid 1-(1,1-dimethylethyl) 2-methyl ester (15)

To a solution of **14** (113 mg, 0.26 mmol) in CH_2Cl_2 (3 mL) was added *N*,*N*-thiocarbonyldiimidazole (93 mg, 0.52 mmol) at 0 °C under an N_2 atmosphere. After the reaction mixture was vigorously stirred at the same temperature for 30 min, the solvent was evaporated at reduced pressure and the resulting residue was purified by flash column chromatography on silica gel (hexane/AcOEt (1:1)) to afford **15** (131 mg, 93%) as a yellow oil. IR (neat): 1748, 1705, 1168 cm^{-1}. ^1H NMR (mixture of diastereomers and rotamers, 200 MHz, $CDCl_3$) δ: 8.32 (1H, br s), 7.60 (1H, br s), 7.07 (1H, br s), 6.13 (1H, br s), 5.35–5.31 (1H, m), 4.55–4.36 (1H+1H, br m), 3.96–3.86 (1H, br m), 3.80 (3H, s, CO_2Me), 3.70 (3H, s, CO_2Me), 3.58–3.45 (1H, br m), 3.18–3.02 (1H, br m), 1.47 (9H, s), 1.42 (9H, s). ^{13}C NMR (mixture of diastereomers and rotamers, 50 MHz, $CDCl_3$) δ: 182.4, 170.9, 170.3, 155.2, 153.0, 137.0, 131.2, 118.0, 84.3, 83.6, 81.2, 80.7, 77.2, 64.1, 60.3, 52.8, 46.7, 45.8, 31.5, 28.1, 22.6, 14.0. HRMS (EI): calcd for $C_{23}H_{35}N_4O_9S$ ($M+H)^+$ 543.2122, found: 543.2121. $[\alpha]_D^{23}$ +0.38 (*c* 3.96, $CHCl_3$).

4.10. (2*S*,4*S*)-4-[1-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-methoxy-2-oxoethyl]-1,2-pyrrolidinedicarboxylic acid 1-(1,1-dimethylethyl) 2-methyl ester (16)

To a solution of **15** (219 mg, 0.40 mmol) and AIBN (13 mg, 0.08 mmol) in benzene (5 mL) was added Ph_3SnH (213 mg, 0.6 mmol) at room temperature. After stirring under reflux for 2 h in an N_2 atmosphere, the reaction mixture was concentrated at reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/AcOEt (1:1)) to afford **16** (142 mg, 85%) as a colorless oil. IR (neat) 3363, 1750, 1698 cm^{-1}. ^1H NMR (mixture of diastereomers and rotamers, 200 MHz, $CDCl_3$) δ: 5.18–5.02 (1H, m), 4.44–4.14 (1H+1H, m), 3.74–3.72 (1H, m) 3.75 (3H, s), 3.74 (3H, s), 3.32–3.17 (1H, m), 2.70–2.23 (2H, m), 1.91–1.74 (1H, m), 1.44 (9H, br s), 1.40 (9H, br s). ^{13}C NMR (mixture of diastereomers and rotamers, 50 MHz, $CDCl_3$) δ: 173.0, 171.7, 155.3, 153.3, 80.2, 58.6, 54.3, 52.4, 51.9, 48.7, 40.5, 33.3, 31.7, 28.1. HRMS (EI): calcd for $C_{19}H_{32}N_2O_8$ (M^+) 416.2156, found: 416.2162. $[\alpha]_D^{24}$ −4.21 (*c* 0.95, $CHCl_3$).

4.11. Oxidation of proline derivative 16

To a solution of **16** (144 mg, 0.35 mmol) in AcOEt (2 mL) was added a solution of RuO_2 hydrate (6.5 mg, 0.05 mmol) and $NaIO_4$ (84 mg, 0.39 mmol) in H_2O (1 mL). After vigorous stirring overnight at room temperature under an N_2 atmosphere, the reaction mixture was diluted with H_2O and extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. The resulting residue was dissolved in 2-propanol (3 mL) and stirred at room temperature for 2 h to remove insoluble material in the organic solvent. The solution was washed with H_2O and dried over $MgSO_4$. Evaporation of the solvent at reduced pressure then gave a residue, which was purified by preparative thin layer chromatography (TLC) (hexane/AcOEt (1:1)) to afford **17a** (60 mg, 40%) and **17b** (63 mg, 42%).

*4.11.1. (αS,3R,5S)-5-(Methoxycarbonyl)-1-(1,1-dimethylethoxy)carbonyl-α-[(1,1-dimethylethoxy)carbonyl]amino]-2-oxo-3-pyrrolidineacetic acid methyl ester (**17a**).* IR (neat): 3379, 1748, 1715 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 5.31 (1H, d, *J*=9 Hz), 4.54 (1H, dd, *J*=9, 3 Hz), 4.49 (1H, t, *J*=8.5 Hz), 3.80 (3H, s), 3.76 (3H, s), 3.49 (1H, br m, 3-H), 2.56 (1H, ddd, *J*=13, 9, 8.5 Hz), 1.96–1.90 (1H, m), 1.48 (9H, s), 1.44 (9H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.9, 171.2, 170.5, 156.3, 148.9, 84.2, 80.4, 57.2, 53.0, 52.5, 45.9, 28.2, 27.8, 24.5. HRMS (EI): calcd for $C_{19}H_{30}N_2O_9$ (M^+) 430.1949, found: 430.1962. $[\alpha]_D^{22}$ +5.07 (*c* 1.38, $CHCl_3$).

*4.11.2. (αR,3R,5S)-5-(Methoxycarbonyl)-1-(1,1-dimethylethoxy)carbonyl-α-[(1,1-dimethylethoxy)carbonyl]amino]-2-oxo-3-pyrrolidineacetic acid methyl ester (**17b**).* IR (neat): 3401, 1750, 1717, 1698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 5.67 (1H, br s, NH), 4.61–4.56 (1H, br m), 4.55–4.47 (1H, m), 3.80 (3H, s), 3.76 (3H, s), 3.08 (1H, td, *J*=10, 4 Hz), 2.59–2.53 (1H, m), 2.16–2.06 (1H, m), 1.49 (9H, s), 1.44 (9H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.6, 171.4, 170.6, 155.3, 149.0, 84.2, 80.4, 57.1, 53.0, 52.8, 52.7, 45.6, 28.2, 27.9, 24.2. HRMS (EI): calcd for $C_{19}H_{30}N_2O_9$ (M^+) 430.1949, found: 430.1974. $[\alpha]_D^{22}$ −1.49 (*c* 0.84, $CHCl_3$).

4.12. (α*S*,3*R*,5*S*)-α-Amino-5-carboxy-2-oxo-3-pyrrolidineacetic acid (penmacric acid (1))

To a solution of **17a** (18 mg, 0.042 mmol) in AcOEt (1 mL) was added 3 M aqueous HCl (1 mL) at room temperature. After stirring

vigorously for 5 h, the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by ion exchange chromatography (Dowex 50W, 10% NH_3). The eluate from 10% NH_3 was concentrated under reduced pressure. The resulting residue was then washed with MeCN/water (5:1) to afford **1** (8.0 mg, 94%) as a hygroscopic white solid. IR (KBr): 3422, 1683 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ: 4.34 (1H, t, J=8.5 Hz), 4.08 (1H, d, J=7.0 Hz), 3.11 (1H, dt, J=10.0, 6.5 Hz), 2.77 (1H, ddd, J=13.0, 9.0, 8.5 Hz), 2.00 (1H, ddd, J=13.0, 11.0, 8.5 Hz). ^{13}C NMR (125 MHz, D_2O) δ: 179.0, 177.8, 172.0, 56.3, 55.1, 41.8, 29.5. HRMS (EI): calcd for $C_7H_{10}N_2O_5$ (M^+) 202.0589, found: 202.0562. $[\alpha]_D^{26}$ +10.1 (*c* 0.32, H_2O).

4.13. (α*R*,3*R*,5*S*)-α-Amino-5-carboxy-2-oxo-3-pyrrolidineacetic acid (1′-*epi*-penmacric acid (2))

According to the procedure for penmacric acid (**1**), the treatment of **17b** (63 mg, 0.15 mmol) with 3 M HCl (1.5 mL) in AcOEt (1.5 mL) at room temperature gave **2** (15.5 mg, 52%) as a hygroscopic white solid. IR (KBr): 3423, 1696 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ: 4.19 (1H, t, J=8.0 Hz), 4.14 (1H, d, J=3.0 Hz), 3.41 (1H, td, J=10.0, 3.5 Hz), 2.60 (1H, ddd, J=13.5, 10.0, 8.0 Hz), 1.88 (1H, ddd, J=13.5, 10.0, 8.0 Hz). ^{13}C NMR (125 MHz, D_2O) δ: 182.1, 180.0, 175.2, 58.9, 55.6, 45.6, 28.8. HRMS (EI): calcd for $C_7H_{10}N_2O_5$ (M^+) 202.0589, found: 202.0565. $[\alpha]_D^{26}$ −3.74 (*c* 0.09, H_2O).

4.14. (2*S*,4*R*)-4-[2-Methoxy-2-oxo-1-[(phenylmethoxy)amino] ethyl]-1,2-pyrrolidinedicarboxylic acid 2-methyl 1-(phenylmethyl) ester (18)

To a solution of 4-iodoproline **10** (8.3 g, 21.4 mmol) and oxime ether **6** (250 mg, 1.3 mmol) in CH_2Cl_2 (100 mL) was added Et_3B (1.0 M in hexane, 3.9 mL, 3.9 mmol) under an N_2 atmosphere at room temperature. After stirring at the same temperature for 1.5 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt (2:1)) to afford **18** (502 mg, 85%) as a colorless oil and a 1:1 mixture of diastereomers at the C1′. IR (neat): 3260, 1744, 1709 cm^{-1}. ^1H NMR (mixture of diastereomers and rotamers, 500 MHz, $CDCl_3$) δ: 7.39–7.28 (10H, m), 6.00–5.94 (1H, m), 5.19–5.02 (2H, m), 4.642 (2/4H, s), 4.638 (2/4H, s), 4.621 (2/4H, s), 4.618 (2/4H, s), 4.42–4.15 (1/2H+1H, m), 3.79–3.55 (1/2H+1/2H), 3.77 (3/4H, s), 3.75(6/4H, s), 3.74 (3/4H, s), 3.722 (3/4H, s), 3.716 (3/4H, s), 3.57 (3/4H, s), 3.56 (3/4H, s), 3.47–3.11 (1H+1/2H, m), 2.50–2.20 (1H, m), 2.18–1.91 (2H, m). ^{13}C NMR (mixture of diastereomers and rotamers, 125 MHz, $CDCl_3$) δ: 173.1, 173.0, 172.7, 172.6, 172.5, 154.6, 154.0, 137.4, 136.5, 136.4, 128.71, 128.66, 128.60, 128.48, 128.46, 128.4, 128.32, 128.29, 128.1, 128.04, 127.99, 127.96, 127.9, 127.8, 127.3, 76.3, 67.18, 67.16, 67.1, 66.1, 65.8, 65.54, 65.45, 58.8, 58.7, 58.5, 52.37, 52.35, 52.31, 52.27, 52.24, 52.21, 52.18, 52.1, 50.1, 49.7, 49.6, 49.2, 48.6, 37.5, 37.4, 37.3, 36.5, 36.4, 34.3, 33.5, 33.3, 33.1, 32.5. HRMS (EI): calcd for $C_{24}H_{28}N_2O_7$ (M^+) 456.1895, found: 456.1879. $[\alpha]_D^{25}$ −25.98 (*c* 1.67, $CHCl_3$).

4.15. (2*S*,4*R*)-4-[1-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-methoxy-2-oxoethyl]-1,2-pyrrolidinedicarboxylic acid 1-(1,1-dimethylethyl) 2-methyl ester (19)

After a suspension of palladium hydroxide (1.2 g, 20 wt %) in MeOH (50 mL) was stirred under an H_2 atmosphere at room temperature for 30 min, a solution of **18** (1.06 g, 2.32 mmol) in MeOH (10 mL) and di-*tert*-butyl dicarbonate (1.17 mL, 5.11 mmol) were added to the suspension. After stirring at room temperature under an H_2 atmosphere for 18 h, the reaction mixture was filtered through Celite and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/AcOEt (2:1)) to afford **19** (782 mg, 81%) as a colorless oil. IR (neat): 3020, 1744, 1708 cm^{-1}. ^1H NMR (mixture of diastereomers and rotamers, 200 MHz) δ: 5.12 (1H, br s), 4.40–4.26 (2H, m), 4.18 (1/2H, m), 3.75 (3H, s), 3.72 (3H, s), 3.33–3.10 (1H+1/2H, m), 2.81–2.59 (1H, m), 2.29–2.05 (2H, m), 1.44 (9H, s), 1.40 (9H, s). ^{13}C NMR (50 MHz) δ: 173.2, 173.0, 171.7, 155.4, 154.0, 153.3, 80.2, 80.1, 58.7, 58.4, 58.0, 54.1, 52.4, 52.1, 52.0, 48.3, 47.4, 40.3, 40.1, 39.7, 39.1, 33.1, 32.1, 31.6, 28.2, 28.1. HRMS (EI): calcd for $C_{19}H_{32}N_2O_8$ (M^+) 416.2157, found: 416.2159. $[\alpha]_D^{27}$ −22.7 (*c* 1.10, $CHCl_3$).

4.16. Oxidation of proline derivative 19

To a solution of **19** (409 mg, 0.98 mmol) in AcOEt (4 mL) was added a solution of RuO_2 hydrate (24 mg, 0.18 mmol) and $NaIO_4$ (385 mg, 1.8 mmol) in H_2O (12 mL). After vigorous stirring overnight at room temperature under an N_2 atmosphere, the mixture was diluted with H_2O and extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. The resulting residue was dissolved in 2-propanol (3 mL) and stirred at room temperature for 12 h to remove insoluble material in the organic solvent. The reaction mixture was washed with H_2O, dried over $MgSO_4$, and concentrated at reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (hexane/AcOEt (1:1)) to afford **20a** (198 mg, 47%) and **20b** (170 mg, 40%) as a colorless oil.

*4.16.1. (αS,3S,5S)-5-(Methoxycarbonyl)-1-(1,1-dimethylethoxy)carbonyl-α-[(1,1-dimethylethoxy)carbonyl]amino]-2-oxo-3-pyrrolidineacetic acid methyl ester (**20a**).* IR ($CHCl_3$): 3432, 1749, 1717 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 5.74 (1H, br s), 4.63 (1H, dd, J=10, 1.5 Hz), 4.59 (1H, dd, J=9, 3.5 Hz), 3.78 (3H, s), 3.75 (3H, s), 3.13–3.08 (1H, m), 2.51–2.49 (1H, m), 2.23–2.19 (1H, m), 1.50 (9H, s), 1.44 (9H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.5, 170.8, 155.2, 149.1, 83.9, 57.0, 52.72, 52.66, 45.1, 28.23, 28.17, 27.9, 27.8. HRMS (EI): calcd for $C_{19}H_{31}N_2O_9$ ($M+H^+$) 431.2027, found: 431.2023. $[\alpha]_D^{29}$ +6.20 (*c* 0.90, $CHCl_3$).

*4.16.2. (αR,3S,5S)-5-(Methoxycarbonyl)-1-(1,1-dimethylethoxy)carbonyl-α-[(1,1-dimethylethoxy)carbonyl]amino]-2-oxo-3-pyrrolidineacetic acid methyl ester (**20b**).* IR ($CHCl_3$): 3423, 1748, 1731 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 5.25 (1H, br d, J=9 Hz), 4.59 (1H, dd, J=9, 2 Hz), 4.49 (1H, br dd, J=9, 2.5 Hz), 3.801 (3H, s), 3.798 (3H, s), 3.59–3.52 (1H, m), 2.31–2.21 (2H, m), 1.49 (9H, s), 1.45 (9H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.2, 171.4, 170.6, 156.4, 149.1, 84.1, 80.5, 56.9, 52.9, 52.7, 52.0, 45.2. HRMS (EI): calcd for $C_{19}H_{31}N_2O_9$ ($M+H^+$) 431.2028, found: 431.2034. $[\alpha]_D^{27}$ −42.99 (*c* 1.64, $CHCl_3$).

4.17. (α*S*,3*S*,5*S*)-α-Amino-5-carboxy-2-oxo-3-pyrrolidineacetic acid (3-*epi*-penmacric acid (3))

To a solution of **20a** (24 mg, 0.056 mmol) in AcOEt (0.5 mL) was added 3 M aqueous HCl (0.5 mL). After vigorous stirring for 26 h at room temperature, the reaction mixture was evaporated under reduced pressure. The resulting residue was purified by ion exchange chromatography (Dowex 50W, 10% NH_3) to afford **3** (11 mg, 99%) as a hygroscopic white solid. IR (KBr): 3211, 1688 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ: 4.13 (1H, dd, J=9.5, 3 Hz), 4.07(1H, d, J=3.5 Hz), 3.26 (1H, td, J=9.5, 3 Hz), 2.53 (1H, dt, J=14, 9.5 Hz), 2.28 (1H, ddd, J=14, 9.5, 3 Hz). ^{13}C NMR (125 MHz, D_2O) δ: 182.5, 180.6, 174.9, 58.8, 56.3, 44.1, 29.9. HRMS (EI): calcd for $C_7H_{10}N_2O_5$ (M^+) 202.0589, found: 202.0574. $[\alpha]_D^{22}$ +33.3 (*c*1.78, H_2O).

Please cite this article in press as: Ueda, M.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.06.006

4.18. (αR,3S,5S)-α-Amino-5-carboxy-2-oxo-3-pyrrolidineacetic acid (1′,3-di*epi*-penmacric acid (4))

To a solution of **20b** (223 mg, 0.52 mmol) in AcOEt (1 mL) was added 3 M aqueous HCl (1 mL). After vigorous stirring for 26 h at room temperature, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by ion exchange chromatography (Dowex 50W, 10% NH_3) to afford **4** (62 mg, 59%) as a hygroscopic white solid. IR (KBr): 3242, 1686 cm^{-1}. ^1H NMR (500 MHz, D_2O) δ: 3.98 (1H, dd, J=9.5, 3.5 Hz), 3.92 (1H, d, J=5 Hz), 2.88 (1H, td, J=9.5, 5.5 Hz), 2.25–2.16 (2H, m). ^{13}C NMR (125 MHz, D_2O) δ: 180.0, 178.3, 171.7, 56.1, 55.1, 41.3, 28.4. HRMS (EI): calcd for $C_7H_{11}N_2O_5$ ($M+H^+$) 203.0667, found: 203.0687. $[\alpha]_D^{23}$ +3.07 (*c* 1.75, H_2O).

4.19. Diastereoselective radical reaction of chiral oxime ether 21 with 4-iodoproline 10

To a solution of oxime ether **21** (37.7 mg, 0.1 mmol) and iodide **10** (194.5 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) was added Et_3B (1.0 M in hexane, 0.25 mL, 0.25 mmol) under an N_2 atmosphere at room temperature. After stirring at the same temperature for 1 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt (2:1)) to afford **22a** (34.9 mg, 55%) and **22b** (8.2 mg, 7%) as a colorless oil.

*4.19.1. (2S,4R)-4-[(1R)-2-[(3aR,6S,7aS)-Tetrahydro-8,8-dimethyl-2,2-dioxido-3H-3a,6-methano-2,1-benzisothiazol-1(4H)-yl]-2-oxo-1-(phenylmethoxy)amino]ethyl-1-(phenylmethoxy)carbonyl-2-pyrrolidinecarboxylic acid methyl ester (**22a**).* IR (neat): 3030, 1744, 1698 cm^{-1}. ^1H NMR (1:1 mixture of rotamers, 500 MHz, $CDCl_3$) δ: 7.38–7.26 (10H, m), 6.17 (1/2H, br d, J=11.0 Hz), 6.14 (1/2H, br d, J=11.0 Hz), 5.16 (1H, d, J=12.0 Hz), 5.09 (1/2H, d, J=12.0 Hz), 5.02 (1/2H, d, J=12.0 Hz), 4.66 (1/2H, br d, J=11.5 Hz), 4.65 (1/2H, br d, J=11.5 Hz), 4.61 (1/2H, br d, J=11.5 Hz), 4.60 (1/2H, br d, J=11.5 Hz), 4.43 (1/2H, br dd, J=9.0, 2.0 Hz), 4.39 (1/2H, br dd, J=9.0, 2.0 Hz), 4.24–4.16 (1H, br m), 3.97 (1H, br t, J=6.0 Hz), 3.69 (3/2H, s), 3.67 (1/2H, dd, J=11.0, 8.0 Hz), 3.64 (1/2H, dd, J=11.0, 8.0 Hz), 3.54 (3/2H, s), 3.51 (1H, s), 3.49 (1H, s), 3.26 (1/2H, dd, J=11.0, 9.0 Hz), 3.16 (1/2H, dd, J=11.0, 9.0 Hz), 2.47–2.40 (1H, m), 2.32–2.19 (1H, m), 2.13–2.03 (2H, m), 1.96–1.81 (4H, m), 1.44–1.34 (2H, m), 1.11, 0.97 (each 3H, s). ^{13}C NMR (1:1 mixture of rotamers, 125 MHz, $CDCl_3$) δ: 173.0, 172.7, 172.5, 154.6, 153.9, 137.6, 137.5, 136.6, 136.5, 128.89, 128.87, 128.83, 128.79, 128.5, 128.4, 128.19, 128.15, 128.04, 127.98, 127.87, 127.84, 127.77, 76.1, 76.0, 67.1, 67.0, 65.2, 64.9, 64.8, 58.9, 58.6, 53.1, 52.4, 52.2, 49.4, 49.2, 48.6, 48.5, 47.8, 44.5, 38.4, 37.6, 32.9, 32.8, 31.9, 26.4, 20.7, 19.9. HRMS (EI): calcd for $C_{33}H_{41}N_3O_8S$ (M^+) 639.2611, found: 639.2633. $[\alpha]_D^{26}$ +41.6 (*c* 0.565, $CHCl_3$).

*4.19.2. (2S,4R)-4-[(1S)-2-[(3aR,6S,7aS)-Tetrahydro-8,8-dimethyl-2,2-dioxido-3H-3a,6-methano-2,1-benzisothiazol-1(4H)-yl]-2-oxo-1-(phenylmethoxy)amino]ethyl-1-(phenylmethoxy)carbonyl-2-pyrrolidinecarboxylic acid methyl ester (**22b**).* IR (neat): 1745, 1701 cm^{-1}. ^1H NMR (1:1 mixture of rotamers, 500 MHz, $CDCl_3$) δ: 7.34–7.26 (10H, m), 6.29 (1/2H, br d, J=8.0 Hz), 6.26 (1/2H, br d, J=8.0 Hz), 5.16 (1/2H, d, J=12.5 Hz), 5.12 (1H, s), 5.03 (1/2H, d, J=12.5 Hz), 4.61 (2H, s), 4.41 (1/2H, dd, J=8.5, 3.0 Hz), 4.36 (1/2H, dd, J=8.5, 3.0 Hz), 4.00 (1/2H, br t, J=8.0 Hz), 3.97 (1/2H, br t, J=8.0 Hz), 3.92–3.88 (1H, m), 3.81–3.75 (1H, m), 3.73, 3.57 (each 3/2H, s), 3.49 (1H, d, J=13.0 Hz), 3.45 (1/2H, d, J=13.0 Hz), 3.41 (1/2H, d, J=13.0 Hz), 3.31 (1/2H, dd, J=11.0, 8.0 Hz), 3.22 (1/2H, dd, J=11.0, 8.0 Hz), 2.88–2.74 (1H, m), 2.14–1.81 (7H, m), 1.43–1.29 (2H, m), 1.07, 0.95 (each 3H, s). ^{13}C NMR (1:1 mixture of rotamers, 125 MHz, $CDCl_3$) δ: 172.9, 172.7, 171.6, 154.8, 154.0, 137.32, 137.27, 136.7, 136.4, 128.6, 128.43, 128.38, 128.2, 127.92, 127.89, 127.83, 127.81, 127.76, 76.44, 76.38, 67.1, 66.9, 65.3, 65.2, 64.9, 58.9, 58.6, 53.0, 52.3, 52.1, 49.3, 48.9, 48.8, 47.8, 44.62, 44.57, 37.9, 36.5, 35.7, 33.7, 32.7, 32.6, 29.7, 26.4, 20.6, 20.5, 19.9. HRMS (EI): calcd for $C_{33}H_{41}N_3O_8S$ (M^+) 639.2611, found: 639.2595. $[\alpha]_D^{26}$ −11.1 (*c* 0.15, $CHCl_3$).

4.20. (2S,4R)-4-[(1R)-2-Methoxy-2-oxo-1-[(phenylmethoxy)amino]ethyl]-1,2-pyrrolidinedicarboxylic acid 2-methyl 1-(phenylmethyl) ester (23)

To a solution of **22a** (26.2 mg, 0.04 mmol) in THF (8 mL) was added a solution of LiOH (83.9 mg, 2 mmol) in H_2O (2 mL) under an N_2 atmosphere at room temperature. After stirring at the same temperature for 3 h, the reaction mixture was concentrated under reduced pressure. The residue was diluted with $CHCl_3$ and then extracted with H_2O. The aqueous phase was acidified to pH 4 with 3 M HCl and then extracted with $CHCl_3$. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give crude carboxylic acid. To a solution of the crude carboxylic acid (91.3 mg, 0.21 mmol) in MeOH (2 mL) and benzene (7 mL) was added dropwise $TMSCHN_2$ (0.63 mL, 0.55 mmol) at room temperature. After stirring at the same temperature for 30 min, the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/AcOEt (2:1)) to give **23** (7.3 mg, 39%) as a colorless oil. IR (neat): 3252, 1742, 1707 cm^{-1}. ^1H NMR (1:1 mixture of rotamers, 500 MHz, $CDCl_3$) δ: 7.39–7.27 (10H, m), 5.96 (1/2H, br d, J=10.0 Hz), 5.95 (1/2H, br d, J=10.0 Hz), 5.18 (1/2H, d, J=12.0 Hz), 5.17 (1/2H, d, J=12.0 Hz), 5.11 (1/2H, d, J=12.0 Hz), 5.03 (1/2H, d, J=12.0 Hz), 4.64 (1H, s), 4.62, 4.61 (1H, ABq, J=12.0 Hz), 4.41 (1/2H, br dd, J=8.0, 2.5 Hz), 4.36 (1/2H, br dd, J=8.0, 2.5 Hz), 3.77 (1/2H, dd, J=11.0, 8.0 Hz), 3.75 (3/2H, s), 3.71 (3/2H, s), 3.69 (1/2H, dd, J=11.0, 8.0 Hz), 3.56 (3H, s), 3.37 (1/2H, t, J=10.0 Hz), 3.33 (1/2H, t, J=10.0 Hz), 3.24 (1/2H, dd, J=11.0, 9.0 Hz), 3.13 (1/2H, dd, J=11.0, 9.0 Hz), 2.43–2.33 (1H, m), 2.09–1.89 (2H, m). ^{13}C NMR (1:1 mixture of rotamers, 125 MHz, $CDCl_3$) δ: 173.2, 173.1, 172.7, 172.6, 154.6, 153.9, 137.40, 137.36, 136.5, 136.4, 128.7, 128.5, 128.4, 128.36, 128.32, 128.1, 128.0, 127.9, 127.8, 76.3, 76.2, 67.2, 67.1, 66.1, 58.7, 58.5, 52.4, 52.29, 52.27, 52.2, 50.24, 50.2, 49.7, 37.3, 36.4, 33.5, 32.5. HRMS (EI): calcd for $C_{24}H_{28}N_2O_7$ (M^+) 456.1894, found: 456.1879. $[\alpha]_D^{27}$ −8.1 (*c* 0.72, $CHCl_3$).

4.21. (2S,4R)-4-[(1R)-1-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-methoxy-2-oxoethyl]-1,2-pyrrolidinedicarboxylic acid 1-(1,1-dimethylethyl) 2-methyl ester (24)

After a suspension of palladium hydroxide (15 mg, 20 wt %) in MeOH (5 mL) was stirred under an H_2 atmosphere at room temperature for 1 h, a solution of **23** (13.1 mg, 0.03 mmol) in MeOH (5 mL) and di-*tert*-butyl dicarbonate (0.02 mL, 0.064 mmol) were added to the suspension. After stirring at room temperature under an H_2 atmosphere for 3.5 h, the reaction mixture was filtered through Celite and the solvent was evaporated under reduced pressure. The resulting residue was purified by preparative TLC (hexane/AcOEt (2:1)) to afford **24** (8.8 mg, 73%) as a colorless oil and a 1:1 mixture of rotamers. IR (neat): 3357, 1747, 1702 cm^{-1}. ^1H NMR (1:1 mixture of rotamers, 500 MHz, $CDCl_3$) δ: 5.09 (1H, br s), 4.41–4.34 (3/2H, m), 4.28 (1/2H, br dd, J=9.0, 2.0 Hz), 3.77 (3/2H, s), 3.75 (3/2H, s), 3.73 (3/2H, s), 3.72 (3/2H, s), 3.64 (1/2H, br dd, J=10.0, 8.0 Hz), 3.55 (1/2H, br t, J=10.0 Hz), 3.19 (1/2H, br t, J=10.0 Hz), 3.15 (1/2H, br t, J=10.0 Hz), 2.78–2.75 (1H, br m), 2.19–2.00 (2H, m), 1.46 (9/2H, s), 1.45 (9/2H, s), 1.44 (9/2H, s), 1.40 (9/2H, s). ^{13}C NMR (1:1 mixture of rotamers, 125 MHz, $CDCl_3$) δ: 173.3, 173.1, 171.8, 155.5, 154.1, 153.5, 80.4, 80.3, 80.2, 58.9, 58.5, 54.1, 52.6, 52.3, 52.1, 47.7, 47.5, 40.3, 39.3, 33.1, 32.3, 29.7, 28.4, 28.3. HRMS *m*/*z*: calcd for $C_{19}H_{33}N_2O_8$ (M^+) 417.2234. Found: 417.2223. $[\alpha]_D^{29}$ −33.6 (*c* 0.475, $CHCl_3$).

Please cite this article in press as: Ueda, M.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.06.006

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4.22. Oxidation of proline derivative 24

To a solution of **24** (7.3 mg, 0.018 mmol) in AcOEt (2 mL) was added a solution of RuO_2 hydrate (0.3 mg, 0.0024 mmol) and $NaIO_4$ (4.1 mg, 0.019 mmol) in H_2O (1 mL) at room temperature. After vigorous stirring overnight at room temperature under an N_2 atmosphere, the reaction mixture was diluted with H_2O and extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was dissolved in 2-propanol (1 mL) and stirred at room temperature for 1 h. The reaction mixture was washed with H_2O, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (hexane/AcOEt (1:1)) to afford **20b** (5.9 mg, 79%) as a colorless oil.

Acknowledgements

This work was supported in part by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT), the MEXT-Supported Program for the Strategic Research Foundation at Private Universities. M.U. is grateful for a Mitsubishi Chemical Award in Synthetic Organic Chemistry of Japan.

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