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First total synthesis of penmacric acid and its stereoisomer

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Abstract—The total synthesis of penmacric acid and its stereoisomer, epipenmacric acid, is reported for the first time starting from *trans*-4-hydroxy-L-proline. Et_3B-induced diastereoselective radical addition reaction was used to control stereoselectivity at the C3 stereogenic center as a key step.

Various unusual amino acids have been found in nature in free zwitterionic form or as constituents of peptides. Because these amino acids have attracted much attention from scientists due to their important biological activities such as antibiotics, neurotoxins, or enzyme inhibitors,[1] many of them are interesting synthetic targets.[2,3] Among them, penmacric acid (**1**) was isolated in 1975 independently by Welter et al.[4] and Mbadiwe[5] from the seeds of the leguminous tree *Pentaclethra macrophylla*, which is commonly used for food, dye, and medicine in West Africa. It has an interesting structure consisting of glycine and pyroglutamic acid which are connected via carbon–carbon bond linkage. The structure was elucidated by ^{1}H NMR, ^{13}C NMR, CD, and X-ray studies.[6] Despite the unique structural features, synthetic and biological studies have not been reported except for only one study reported by Moloney and co-workers in 2003.[7] His group reported an interesting synthetic strategy for penmacric acid using a diastereoselective nucleophilic addition of lactam enolate to various imines as the key reaction. However, the total synthesis was not completed yet and suffered from some inefficient steps including an inversion of the undesired stereocenter.

To the best of our knowledge, no example of the total synthesis of penmacric acid has been described in the literature probably because of the chemical instability of penmacric acid particularly under strong acidic conditions.[6c] Herein, we report the first total synthesis of penmacric acid (**1**) and its stereoisomer that we have named epipenmacric acid, using a stereoselective intermolecular radical addition to oxime ether as a key step. Although radical cyclization reactions have been well developed for the synthesis of biologically important natural and unnatural compounds,[8] the use of the intermolecular version has not been widely studied so far.[9]

Our retrosynthetic strategy is based on a Et_3B-induced radical reaction of oxime ether **4** and iodoproline **3** via an iodine atom-transfer process. We have recently developed intermolecular alkyl radical additions to various types of oxime ethers providing a new synthetic approach to amino acid derivatives.[10] We planned to use iodoproline **3** as a radical precursor bearing a hydroxyl group as a stereochemical auxiliary that would be expected to confer a high level of stereoinduction in the radical addition of the pyrrolidine ring onto the glycine equivalent (Fig. 1).

We initiated our synthesis with the preparation of the hydroxylated iodoproline **3** from commercially available *trans*-4-hydroxy-L-proline (**5**) (Scheme 1). After protection of the amino and carboxyl groups, a Mitsunobu reaction led to the conversion of the hydroxyl group to iodide to give **6**.[11] Elimination of HI using DBU afforded 3,4-dehydroproline **7** in 71% yield along with a small amount of the 4,5-dehydro regioisomer.[11b] 3,4-Dehydroproline **7** was then epoxidized with *m*CPBA in the presence of 4,4′-thiobis(6-*t*-butyl-*o*-cresol) as a radical scavenger to give epoxide **8** in a good yield and as a single stereoisomer.[12] Regioselective ring opening of epoxide **8** with magnesium iodide afforded the expected 3-hydroxy-4-iodoproline **3** in an 87% yield via nucleophilic attack of the iodide ion on less hindered carbon of the epoxy ring.[13]

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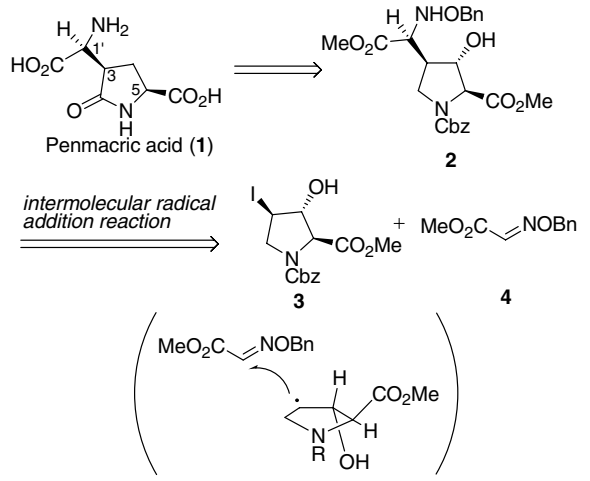
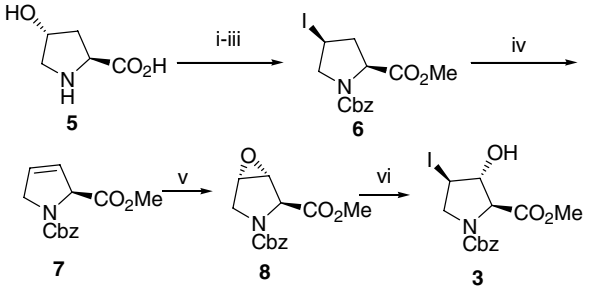


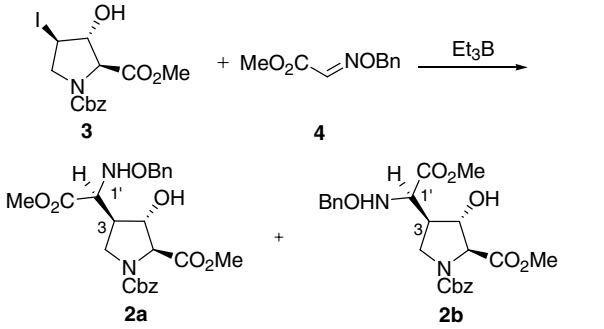
Figure 1. Retrosynthetic strategy toward penmacric acid (**1**).



Scheme 1. Reagents and conditions: (i) CbzCl, $NaHCO_3$, H_2O, THF, rt; (ii) concd H_2SO_4, MeOH, reflux, 87% (two steps); (iii) MeI, DEAD, PPh_3, THF, rt, 88%; (iv) DBU, toluene, reflux, 71%; (v) *m*CPBA, 4,4′-thiobis(6-*t*-butyl-*o*-cresol), 1,2-dichloroethane, reflux, 59% and (vi) MgI_2, toluene, 0 °C, 87%.

With the radical precursor **3** in hand, we next investigated a radical reaction of **3** with glyoxylic oxime ether **4**, which is known to be an excellent radical acceptor as we previously reported.[10] Several conditions for the radical reaction were screened to optimize the yield and are summarized in Table 1. When the radical addition reaction of hydroxyl proline **3** to oxime ether **4** was carried out in CH_2Cl_2 at room temperature using Et_3B as the radical initiator, two adducts **2a** and **2b** were obtained in 30% yield as an inseparable 1:1 mixture of two diastereomers at the C1′ position (entry 1). This result showed that facial selectivity of the pyrrolidine ring is completely controlled by the hydroxyl group which was introduced as a stereochemical auxiliary. Another epimer **2b** was expected to be used for the synthesis of epipenmacric acid in order to establish a divergent synthesis of penmacric acid and the related compounds. Although the configuration of **2a** and **2b** could not be determined at this stage, it was unambiguously confirmed later by the conversion of **2a** to the target compound **1**. The radical reaction temperature was a key factor in improving the yield and stereoselectivity, and the best result was obtained in refluxing CH_2Cl_2 solution (entry 2). However, higher temperatures such as in refluxing benzene or 1,2-dichloroethane did not increase the yield and decreased the stereoselectivity (entries 3 and 4).[14]

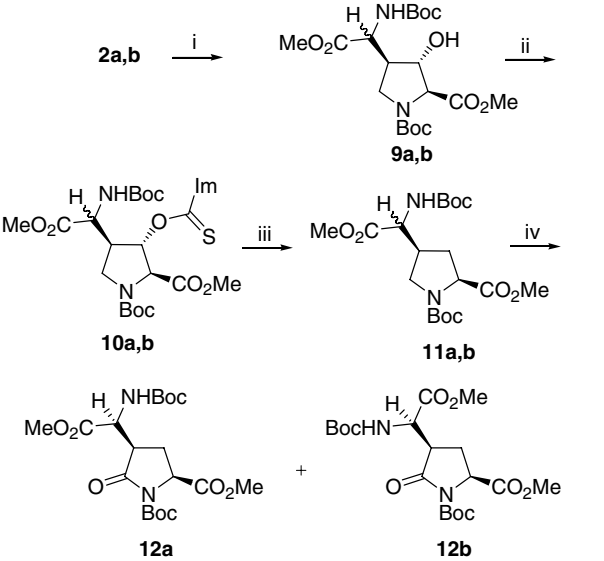
Table 1. Radical addition to oxime ether **4**



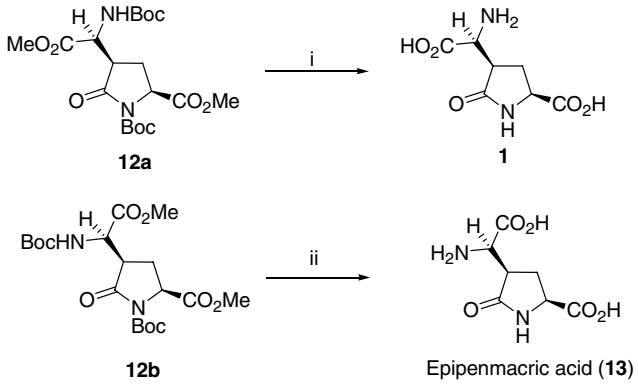
Entry	Solvent	*T* (°C)	Yield[a](%)
1	CH_2Cl_2	25	30
2	CH_2Cl_2	Reflux	81
3	Benzene	Reflux	68
4[b]	$(CH_2Cl)_2$	Reflux	44

[a] Combined yield of 1:1 mixture of **2a** and **2b**.
[b] C3 isomers were also obtained in 22% yield.

Reductive cleavage of the N–O bond in the benzyloxyamino group and removal of the Cbz group from the mixture of **2a** and **2b** gave the free amino groups which without separation were subsequently protected by the Boc groups to give **9** (Scheme 2).[15,16] Removal of the hydroxyl group was effectively accomplished by the Barton–McCombie radical deoxygenation. The corresponding imidazolethiocarbamate **10** was prepared in a 93% yield according to the conventional method and then reduced with triphenyltin hydride and AIBN to yield the deoxygenated compound **11** in an 85% yield.



Scheme 2. Reagents and conditions: (i) H_2, $Pd(OH)_2/C$, $(Boc)_2O$, MeOH, rt, 79%; (ii) TCDI, CH_2Cl_2, 0 °C, 93%; (iii) Ph_3SnH, AIBN, benzene, reflux, 85% and (iv) RuO_2, $NaIO_4$, AcOEt, H_2O, 82%.



Scheme 3. Reagents and conditions: (i) 3 M HCl, AcOEt, rt, 94% and (ii) 3 M HCl, AcOEt, rt, 52%.

The substituted proline **11** was then oxidized with ruthenium tetraoxide under EtOAc/H_2O biphasic conditions to give the desired lactams **12a** and **12b** which were separated at this stage by column chromatography on silica gel. Finally, deprotection of the two Boc groups and hydrolysis of two methyl esters with 3 M HCl gave penmacric acid (**1**)[17] and epipenmacric acid (**13**)[18] in 94% and 52% yields, respectively. The spectral data of our synthetic sample **1** was identical in all respects with those of the published data[5] (Scheme 3).

In conclusion, the first total and divergent syntheses of penmacric acid and epipenmacric acid featuring a highly diastereoselective radical reaction of an iodoproline derivative with an oxime ether has been accomplished starting from *trans*-4-hydroxy-L-proline (**5**). The advantage of our strategy is centered on the stereoselective synthesis of unusual and various types of α-substituted α-amino acids. Therefore, our route can be easily applied to produce various analogues.

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14. *Procedure for the radical addition reaction (Table 1, entry 3)*: To a solution of oxime ether **4** (7.8 g, 40 mmol) and iodide **3** (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 N_2 atmosphere at reflux. After the reaction mixture was stirred at the same temperature for 1.5 h, a solution of oxime ether **4** (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 every 1.5 h. After being stirred at the same temperature for 10 h, the reaction mixture was diluted with satd $NaHCO_3$ and then extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. The residue was purified by FCC (hexane:AcOEt (1:1)) to afford the 1:1 diastereomeric mixture of **2** (1.02 g, 81%) as a colorless oil.
15. The radical addition reaction with iodoproline protected by the Boc group instead of the Cbz group was not effective due to steric hindrance of the bulky *t*-Bu group.
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17. *Spectral data of* **1**: hygroscopic white solid. ^{1}H NMR ($CDCl_3$): δ 2.00 (1H, ddd, $J = 8.5$, 10.0, 13.0 Hz), 2.77 (1H, ddd, $J = 8.5$, 9.0, 13.0 Hz), 3.11 (1H, dt, $J = 6.5$, 10.0 Hz), 4.08 (1H, d, $J = 7.0$ Hz), 4.34 (1H, t, $J = 8.5$ Hz); ^{13}C NMR (D_2O): δ 180.3, 179.3, 174.1, 57.54, 57.46, 44.5, 30.9; HRMS: Calcd for $C_7H_{10}N_2O_5$ (M^+) 202.0589. Found 202.0586; $[\alpha]_D^{26}$ +10.1 (*c* 0.32, H_2O), [lit.[5] $[\alpha]_D^{27}$ +11 (*c* 0.016, H_2O)].

18. *Spectral data of* **13**: hygroscopic white solid. ^{1}H NMR ($CDCl_3$): 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 (D_2O): δ 182.1, 180.0, 175.2, 58.9, 55.6, 45.6, 28.8; HRMS: Calcd for $C_7H_{10}N_2O_5$ (M^+) 202.0589. Found 202.0565; $[\alpha]_D^{24}$ −3.74 (*c* 0.09, H_2O).