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# A new strategy for the preparation of heterocyclic β-amino esters: orthogonally protected β-amino esters with a piperidine skeleton

Loránd Kiss,[a] Brigitta Kazi,[a] Enikő Forró[a] and Ferenc Fülöp[a,b,*]

[a]*Institute of Pharmaceutical Chemistry, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary*
[b]*Research Group of Heterocyclic Chemistry, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary*

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**Abstract**—A simple strategy is presented for the introduction of a nitrogen atom into the carbocycle of an aminocyclopentenecarboxylic ester via dihydroxylation of the olefinic bond, followed by $NaIO_4$-mediated cleavage of the diol intermediate and ring expansion, resulting in new regioisomeric 3-amino-4-piperidinecarboxylic acid derivatives. This method permits the preparation of amino esters with a piperidine skeleton in enantiomerically pure form.
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## 1. Introduction

As a consequence of their biological effects, conformationally constrained alicyclic β-amino acids have generated great interest among chemists and biochemists. Such structures are found in many natural products, β-lactams and antibiotics. The incorporation of conformationally restricted β-amino acids into biologically active peptides is of considerable interest as concerns the preparation of peptide-based drug molecules.[1]

In recent years, conformationally rigid heterocyclic β-amino acids have received appreciable attention in view of their biological potential. As a result of their natural occurrence, biological activities and chemical interest, the number of investigations of these medicinally valuable molecules has increased rapidly. One of the largest groups of such heterocyclic β-amino acid derivatives is that with one nitrogen atom in the ring. β-Peptides containing 3-aminopyrrolidine-4-carboxylic acid and 3-aminopyrrolidine-2-carboxylic acid structural moieties have been shown to adopt helical secondary structures, and they have been reported to display interesting biological (e.g., antimicrobial) activities.[2] β-Amino acids with a pyrrolidine skeleton have been used for the synthesis of glycosylated hexapeptides,[3] and have been described as potent influenza neuraminidase inhibitors.[4] Both five-membered nitrogen-containing heterocyclic β-amino acids and six-membered 4-aminopiperidine-3-carboxylic acids can be incorporated into peptides with a 14-helical structure.[5] Iduronic acid-type 1-*N*-iminosugars, six-membered derivatives with a nitrogen atom in the ring, exhibit antimetastatic and enzyme inhibitory activities.[6] Enamino 1-carboxylates with a piperidine skeleton are important elements in the synthesis of selective small opioid receptor antagonists.[7] Furthermore, 4-amino-1-oxyl-2,2,6,6-tetramethylpiperidine-3-carboxylic acid, a β-amino acid with a piperidine skeleton has been synthesized in enantiomerically pure form from 2,2,6,6-tetramethyl-4-piperidone.[8] Enamino carboxylate enantiomers with a piperidine skeleton have been used for the preparation of cinchona alkaloids.[9] In addition, β-amino piperidine carboxylates have been synthesized in optically pure form via lithium amide-promoted asymmetric conjugate addition-cyclization.[10]

Our aim was to develop a route for the synthesis of the diastereomers of six-membered β-amino carboxylates with one nitrogen atom in the ring. The β-amino esters **2a**–**c**[11a] with a cyclopent-3-ene skeleton, prepared from β-lactam **1**, were considered to be suitable starting

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* Corresponding author. Tel.: +36 62 545564; fax: +36 62 545705; e-mail: fulop@pharm.u-szeged.hu

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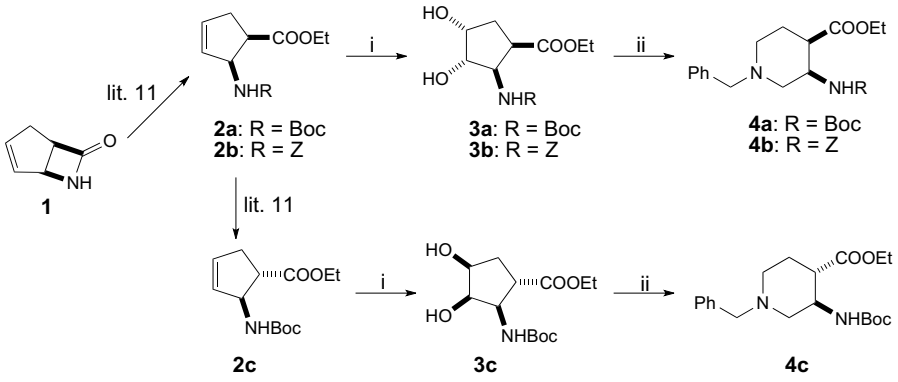
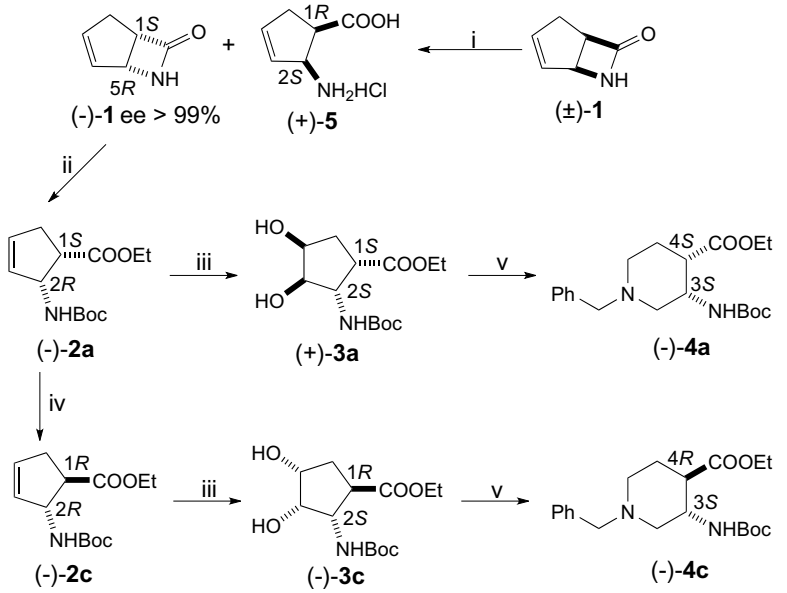



**Scheme 1.** Synthesis of racemic piperidine-4-carboxylates **4a**–**c**. Reagents and conditions: (i) $KMnO_4$, $CH_2Cl_2$, $BnEt_3NCl$, 0 °C, 2 h, **3a**: 47%, **3b**: 44%, **3c**: 48%; (ii) (a) $NaIO_4$, $THF/H_2O$, rt, 1 h; (b) $NaCNBH_3$, 1 equiv AcOH, $CH_2Cl_2$/THF, $BnNH_2$, rt, 4 h, **4a**: 16% (two steps), **4b**: 22% (two steps), **4c**: 17% (two steps).

materials for this purpose. The synthetic approach was based on the ring cleavage of *cis*-2-aminocylopentenecarboxylates **2a**,**b** and *trans*-2-aminocylopentenecarboxylate **2c**, followed by ring expansion (Scheme 1). In the first step, amino esters **2a**–**c** were subjected to $KMnO_4$-mediated dihydroxylation in the presence of various phase transfer catalysts (e.g., tetrabutylammonium chloride, 18-crown-6 ether or benzyltriethylammonium chloride). It was found that the dihydroxy derivatives **3a**–**c** were formed in the highest yields in the presence of benzyltriethylammonium chloride. During the $KMnO_4$ oxidation process, only one *cis*-functionalized dihydroxy β-amino carboxylate **3a**–**c** was obtained, diastereoselectively, from the *cis* amino esters **2a**,**b** and the *trans* derivative **2c**. No other diastereomer was detected in the crude reaction mixture. The relative stereochemistry was assigned on the basis of NOESY experiments. The two hydroxy groups are presumably formed on the opposite side to the carboxylate at C-1 in the cyclopentane skeleton.

The next step in the synthetic route was the oxidation of the diol with $NaIO_4$. The C–C bond cleavage of compounds **3a**–**c** was accomplished in $THF/H_2O$ at room temperature for 1 h under an argon atmosphere. After extraction with $CH_2Cl_2$ the resulting dialdehyde was subjected to reductive ring closure in the presence of $NaCNBH_3$, 1 equiv of AcOH and benzylamine at room temperature for 4 h. Through reductive amination in the final step, the ring closure furnished the desired heterocyclic β-amino esters with a piperidine skeleton. It is noteworthy that the reduction could not be performed in the presence of $NaBH_4$; only $NaCNBH_3$ proved to be a suitable reductant agent in this reaction.




**Scheme 2.** Synthesis of ethyl 1-benzyl-3-(*tert*-butoxycarbonylamino)piperidine-4-carboxylate enantiomers (−)-**4a**, (−)-**4c**. Reagents and conditions: (i) Lipolase, $iPr_2O$, 70 °C, 4 h; (ii) (a) EtOH/HCl, 0 °C, 1 h, 83%; (b) $Boc_2O$, TEA, THF, rt, 12 h, 77%; (iii) $KMnO_4$, $CH_2Cl_2$, $BnEt_3NCl$, 0 °C, 2 h, (+)-**3a**: 46%, (−)-**3c**: 50%; (iv) NaOEt, EtOH, rt, 18 h, 68%; (v) (a) $NaIO_4$, $THF/H_2O$, rt, 1 h; (b) $NaCNBH_3$, 1 equiv AcOH, $CH_2Cl_2$/THF, $BnNH_2$, rt, 4 h, (−)-**4a**: 28% (two steps), (−)-**4c**: 30% (two steps).

Amino esters **4a** and **4c** were also synthesized for the enantiomeric substances (Scheme 2).

The starting compound (1*S*,5*R*)-**1** was prepared through the Lipolase (lipase B from *Candida Antarctica*)-catalyzed enantioselective ring opening of 7-azabicyclo[4.2.0]oct-3-en-8-one, using a slightly modified literature procedure.[11b] The enantioselective ring cleavage of (±)-**1** was performed successfully ($E > 200$) on a 10 g scale by adding the enzyme in portions to the reaction mixture. Following the route presented above the preparation of (−)-**4a** and (−)-**4c** was accomplished in enantiomerically pure form (Scheme 2). An advantage of the procedure is that the known stereocentres of the starting materials are unaffected during the synthetic steps, which allows the determination of the absolute configurations of the chiral centres in the final products.

In conclusion, a simple strategy has been developed for the preparation of cyclic β-amino ester diastereomers containing a piperidine skeleton, based on dihydroxylation of a β-aminocyclopentene carboxylate, cleavage of the resulting dihydroxy compound, followed by reduction and amine-mediated ring expansion. We are currently studying the application of such transformations for the synthesis of other heterocyclic β-amino acids in both racemic and enantiomerically pure forms.

## 2. Experimental

Compound characterizations are given only for enantiomeric substances.

### 2.1. Ethyl (1*S*,2*S*,3*R*,4*S*)-2-(*tert*-butoxycarbonylamino)-3,4-dihydroxycyclopentanecarboxylate [(+)-3a]

White solid, mp 117–120 °C, yield 46%, $[\alpha]_D^{25}$ +110 (*c* 0.17, EtOH). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta = 1.27$ (t, $J = 7.14$ Hz, 3H, $CH_3$), 1.48 (s, 9H, $CH_3$), 2.08–2.14 (m, 1H, $CH_2$), 2.16–2.24 (m, 1H, $CH_2$), 3.24–3.34 (m, 1H, H-1), 3.98–4.04 (m, 1H, H-3), 4.08–4.22 (m, 4H, $OCH_2$, H-2, H-4), 5.55 (s, 1H, NH); $^{13}$C NMR ($CDCl_3$, 400 MHz): $\delta = 14.8$, 29.0, 34.4, 42.6, 57.5, 61.8, 70.9, 79.6, 81.1, 157.2, 175.1; Anal. Calcd. for $C_{13}H_{23}NO_6$: C, 53.97; H, 8.01; N, 4.84. Found: C, 53.64; H, 7.90; N, 4.59.

### 2.2. Ethyl (1*R*,2*S*,3*R*,4*S*)-2-(*tert*-butoxycarbonylamino)-3,4-dihydroxycyclopentanecarboxylate [(−)-3c]

Colourless oil, yield: 50%, $[\alpha]_D^{25}$ −20 (*c* 0.15, EtOH). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta = 1.25$ (t, $J = 7.25$ Hz, 3H, $CH_3$), 1.44 (s, 9H, $CH_3$), 1.97 (m, 1H, $CH_2$), 2.07–2.18 (m, 1H, $CH_2$), 2.89–2.99 (m, 1H, H-1), 4.06–4.12 (m, 1H, H-2), 4.12–4.18 (m, 3H, $OCH_2$, H-3), 4.25–4.32 (m, 1H, H-4), 5.14 (d, $J = 8.05$ Hz, 1H, NH); $^{13}$C NMR ($CDCl_3$, 400 MHz): $\delta = 14.5$, 28.7, 34.1, 47.5, 56.4, 31.4, 72.3, 77.4, 80.3, 156.2, 175.1; Anal. Calcd. for $C_{13}H_{23}NO_6$: C, 53.97; H, 8.01; N, 4.84. Found: C, 53.62; H, 7.88; N, 4.54.

### 2.3. Ethyl (3*S*,4*S*)-1-benzyl-3-(*tert*-butoxycarbonylamino)piperidine-4-carboxylate [(−)-4a]

Colourless oil, yield: 28% (two steps), $[\alpha]_D^{25}$ −17 (*c* 0.24, EtOH). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta = 1.25$ (t, $J = 7.09$ Hz, 3H, $CH_3$), 1.41 (s, 9H, $CH_3$), 1.66–1.74 (m, 1H, $CH_2$), 1.89–2.08 (m, 2H, H-4 and $CH_2$), 2.22–2.30 (m, 1H, $NCH_2$), 2.45–2.53 (m, 1H, $NCH_2$), 2.71–2.82 (m, 2H, $NCH_2$), 3.48 (s, 2H, $NCH_2Ar$), 4.07–4.15 (m, 2H, $OCH_2$), 4.17–4.25 (m, 1H, H-3), 5.33–5.40 (m, 1H, NH), 7.25–7.33 (m, 5H, ArH); $^{13}$C NMR ($CDCl_3$, 400 MHz): $\delta = 14.8$, 29.1, 45.1, 48.0, 52.4, 58.7, 61.3, 63.3, 78.3, 79.8, 127.8, 128.9, 129.5, 138.7, 154.6, 173.6; Anal. Calcd. for $C_{20}H_{30}N_2O_4$: C, 66.27; H, 8.34; N, 7.73. Found: C, 65.91; H, 8.03; N, 7.30.

### 2.4. Ethyl (3*S*,4*R*)-1-benzyl-3-(*tert*-butoxycarbonylamino)piperidine-4-carboxylate [(−)-4c]

Colourless oil, yield: 30% (two steps), $[\alpha]_D^{25}$ −13 (*c* 0.13, EtOH). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta = 1.25$ (t, $J = 7.09$ Hz, 3H, $CH_3$), 1.42 (s, 9H, $CH_3$), 1.82–2.00 (m, 2H, $CH_2$), 2.10–2.31 (m, 2H, H-4, $NCH_2$), 2.32–2.65 (m, 2H, $NCH_2$), 2.71–2.83 (m, 1H, $NCH_2$), 3.41–3.50 (m, 1H, $NCH_2Ar$), 4.00–4.1 (m, 1H, H-3), 4.11–4.19 (m, 2H, $OCH_2$), 4.83–4.97 (m, 1H, NH), 7.25–7.33 (m, 5H, ArH); $^{13}$C NMR ($CDCl_3$, 400 MHz): $\delta = 14.2$, 28.4, 48.3, 51.1, 57.1, 59.3, 60.6, 62.7, 70.2, 77.6, 127.1, 128.3, 128.9, 138.1, 154.9, 173.1; Anal. Calcd. for $C_{20}H_{30}N_2O_4$: C, 66.27; H, 8.34; N, 7.73. Found: C, 65.95; H, 8.01; N, 7.36.

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