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Synthesis of orthogonally protected azepane β-amino ester enantiomers

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ABSTRACT

A simple and convenient route is presented for the preparation of regio- and stereoisomers of novel azepane β-amino esters, starting from bicyclic β-lactam isomers. The synthetic procedure consists of dihydroxylation of the olefinic bond of the alicyclic amino esters, followed by $NaIO_4$-mediated cleavage of the diol intermediate and reductive ring closure, which furnishes novel regioisomeric 5-aminoazepane-4-carboxylate and 3-aminoazepane-4-carboxylates. This method also allows the preparation of amino esters with an azepane skeleton in enantiomerically pure form.

Introduction

Biologically active, conformationally restricted alicyclic β-amino acids have aroused significant interest among chemists and biochemists over the past two decades. These types of compounds are found in many natural products, β-lactams and antibiotics. The incorporation of conformationally constrained β-amino acids into biologically active peptides is of considerable importance in the preparation of peptide-based drug molecules.[1]

In recent years, conformationally rigid cyclic β-amino acids with a heteroatom in the ring have received considerable attention as a consequence of their biological potential. As a result of their natural occurrence, biological activities, and chemical interest, the number of investigations on these medicinally interesting molecules has increased rapidly. The largest group of such heterocyclic β-amino acid derivatives are those with one N 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 have been reported to exhibit interesting biological (e.g., antimicrobial) activities.[2] β-Amino acids possessing a pyrrolidine skeleton have been presented as potent influenza neuraminidase inhibitors.[3] Both pyrrole β-amino acids and 4-aminopiperidine-3-carboxylic acids can be incorporated into peptides with a 14-helical structure.[4] Iduronic acid-type 1-*N*-iminosugars, six-membered derivatives with an N atom in the ring, display antimetastatic and enzyme inhibitory activities.[5] Furthermore, enamino 1-carboxylates containing a piperidine skeleton are important elements in the synthesis of selective small opioid receptor antagonists.[6] Their enantiomers have been used for the preparation of cinchona alkaloids.[7] It was recently reported that the pyrrole β-amino acid moiety is a key element in the structure of several tumor necrosis factor-α converting enzyme inhibitors.[8] β-Aminopiperidine carboxylates have been prepared in optically pure form by lithium amide-promoted asymmetric conjugate addition-cyclization.[9] We previously reported an efficient ring expansion method for the synthesis of novel β-amino acid derivatives containing a piperidine skeleton, starting from alicyclic 2-aminocyclopentenecarboxylates, via oxidative ring opening followed by reductive ring closure.[10]

Despite the wide occurrence and importance of five- and six-membered *N*-heterocyclic β-amino acid derivatives, larger ring analogues do not appear to have been described thus far. Our goal was to fill this gap by synthesizing enantiomerically pure β-amino acid derivatives based on azepane. The construction of ring systems containing more than six members suffers in general from difficulties and limitations such as low yields and unwanted side-products.

The synthetic routes to naturally occurring compounds with functionalized azepane rings generally involve: (a) intramolecular metathesis of secondary aminodienes;[11] (b) pinacol-type intermolecular cyclization of carbonylhydrazones with a protected amino function inserted in the chain;[12] (c) intramolecular nucleophilic displacement with ring closure of a leaving group by an amino function;[13] (d) intermolecular simultaneous nucleophilic substitution with an amine of two leaving groups at the end of a six-carbon chain;[14] and (e) intermolecular reductive amination of functionalized dialdehydes followed by ring closure.[10,15]

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In a first approach to the synthesis of the desired enantiomerically pure β-amino acid derivatives, racemic bicyclic lactam **1**[16a] was submitted to enzymatic ring opening in the presence of CAL-B (lipase B from *Candida antarctica*, produced by the submerged fermentation of a genetically modified *Aspergillus oryzae* microorganism and adsorbed on a macroporous resin) in iPr$_2$O.[16b] The unreacted β-lactam (−)-**1**[16b] (ee >99%) was transformed into the amino ester hydrochloride (−)-**3** via lactam ring opening (for the opposite enantiomer, see Ref. 16a). Amine protection then gave *N*-Boc-protected ethyl 2-aminocyclohex-3-enecarboxylate (−)-**4** (Scheme 1). The azepane ring construction was based on functionalization of the C–C double bond of amino ester (−)-**4** through ring opening and closure with ring expansion. With this aim, 2-aminocyclohexenecarboxylate (−)-**4** was first subjected to dihydroxylation. Oxidation of the C–C double bond was achieved by OsO_4-mediated *cis*-dihydroxylation, using *N*-methylmorpholine *N*-oxide (NMO) as the stoichiometric co-oxidant. The reaction afforded a single dihydroxylated diastereomer (+)-**5** in good yield (88%). Based on our earlier studies,[10,16c] it may be assumed that OsO_4 attacks the olefin from the opposite side relative to the ester and carbamate function, and therefore the hydroxy groups on C-3 and C-4 are trans relative to the carboxylate on C-1 and the amino group on C-2 (numbering for the cyclohexane skeleton) (Scheme 1).

The next step was oxidative ring cleavage of the diol. Treatment of (+)-**5** with $NaIO_4$ gave the corresponding dialdehyde, which was immediately submitted, without isolation, to reductive amination with benzylamine in the presence of $NaBH_3CN$ and AcOH. This afforded the desired azepane β-amino ester (−)-**6** (36% yield for the two steps; Scheme 1). The diastereoisomeric trans derivative (−)-**7** was prepared by epimerization of (−)-**6** at C-4 in the presence of NaOEt (Scheme 1). The relatively low yield of this reaction was due to the poor conversion of the starting material, which was recovered during column chromatographic purification. The ee values for (−)-**6** and (−)-**7** were found to be >99% (HPLC).[17]

The bicyclic β-lactam **8**[18a] allowed the synthesis of a new type of β-amino acid derivative with an azepane framework, that is, regioisomers of (−)-**6** and (−)-**7**. Racemic azetidinone **8** was converted into amino acid (−)-**9** by enzymatic hydrolysis with CAL-B in iPr$_2$O. The optically active (ee >99%) β-amino acid (−)-**9**[18b] was transformed, via amino ester (−)-**11**,[18a] into enantiomerically pure *N*-Boc-protected β-amino ester (−)-**12**[19] (Scheme 2). In the subsequent steps, the procedure presented in Scheme 1 was followed: dihydroxylation, diol cleavage, then reductive amination with ring closure, giving (−)-**14**, and following epimerization, (+)-**15**, both with ee's >99% (HPLC).[17]

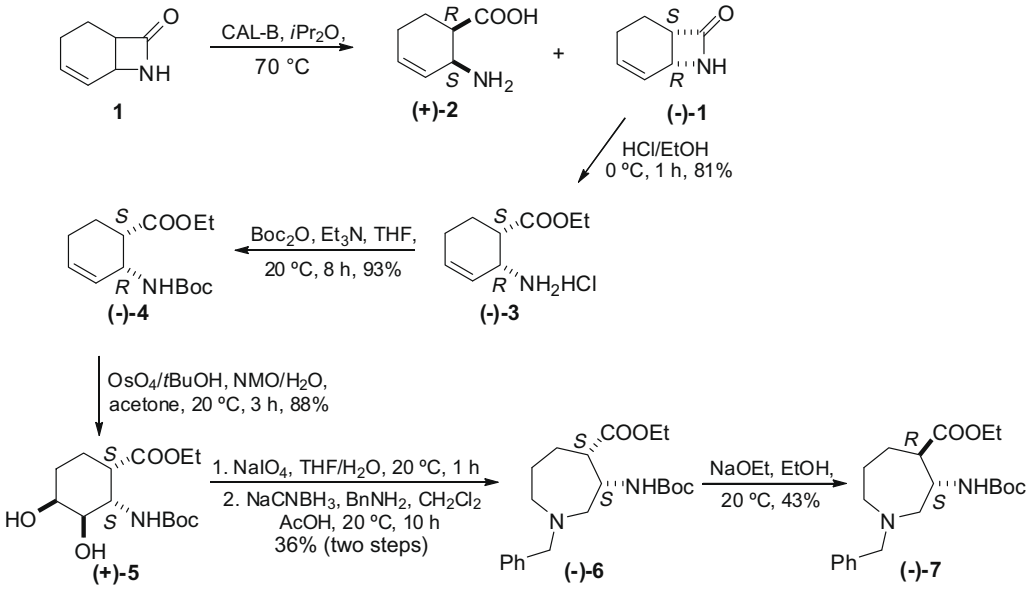
In conclusion, four novel azepane β-amino ester diastereomers have been prepared in enantiomerically pure form, starting from racemic bicyclic β-lactam isomers **1** and **8**, via dihydroxylation of β-aminocyclohexenecarboxylate regioisomers, followed by ring cleavage and ring closure on reductive amination.

Cleavage of dihydroxy compounds and ring closure with reductive amination; general procedure

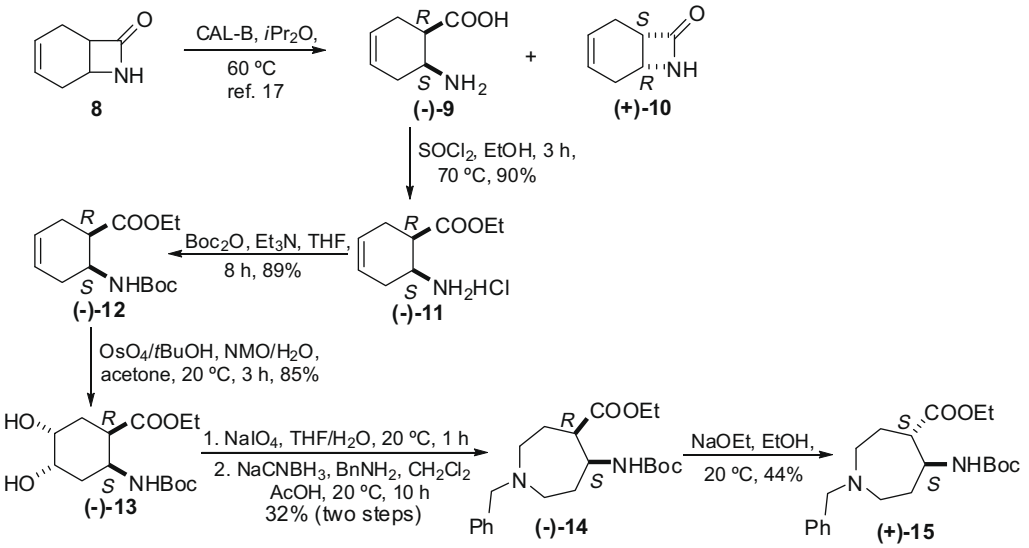
$NaIO_4$ (420 mg, 2 mmol) was added to a stirred solution of amino ester (+)-**5** or (−)-**13** (303 mg, 1 mmol) in THF/H_2O (16.5 mL, 10/1). After stirring for 1 h at rt under an Ar atmosphere, H_2O was added until the precipitate dissolved. The mixture was then extracted with CH_2Cl_2 (3 × 40 mL), the combined extract dried over Na_2SO_4 and the resulting dialdehyde solution was immediately used for the next reaction without isolation. Benzylamine (0.11 mL, 1 mmol) and oven-dried 3 Å MS were added to the solution of the dialdehyde and the mixture was stirred at 40 °C for 10 min. A solution of $NaCNBH_3$ (62 mg, 1 mmol) and AcOH (1 equiv) in EtOH (2 mL) was added dropwise under an Ar atmosphere over 2 h, and stirring was continued for another 1 h at 40 °C. The reaction mixture was washed with 10% Na_2CO_3 (3 × 80 mL) and brine (80 mL), and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 3/1).

Ethyl (3*S*,4*S*)-1-benzyl-3-(*tert*-butoxycarbonylamino)azepane- 4-carboxylate [(−)-6]

White crystals; yield: 36% (two steps); mp 76–78 °C; $[\alpha]_D^{20}$ −5.2 (*c* 0.31, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.24 (t, 3H, CH_3, J = 7.08 Hz,), 1.40 (s, 9H, CH_3), 1.44–1.56 (m, 1H, CH_2), 1.70–1.87 (m, 2H, CH_2), 1.89–2.00 (m, 1H, CH_2), 2.44–2.54 (m, 1H, H-4), 2.56–2.83 (m, 4H, 2 × N–CH_2), 3.60 (m, 2H, N–CH_2Ph), 4.05–4.20 (m, 3H, OCH_2, H-3), 5.35 (br s, 1H, N–H), 7.19–7.33 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.6, 24.7, 26.7, 29.5, 50.2,



Scheme 1. Synthesis of azepane amino esters (−)-**6** and (−)-**7**.



Scheme 2. Synthesis of azepane amino esters (−)-**14** and (+)-**15**.

51.0, 54.4, 57.5, 60.8, 64.0, 79.3, 127.4, 128.7, 129.3, 139.7, 155.5, 174.1; MS: (ESI): m/z = 377 (M+1). Anal. Calcd for $C_{21}H_{32}N_2O_4$: C, 66.99; H, 8.57; N, 7.44. Found: C, 66.69; H, 8.30; N, 7.20.

Ethyl (4*R*,5*S*)-1-benzyl-5-(*tert*-butoxycarbonylamino)azepane-4-carboxylate [(−)-14]

Yellow oil; yield: 32% (two steps); $[\alpha]_D^{20}$ −5.0 (c 0.31, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.23 (t, 3H, CH_3, J = 7.05 Hz), 1.42 (s, 9H, CH_3), 1.67–1.81 (m, 2H, CH_2), 1.91–2.19 (m, 2H, CH_2), 2.35–2.51 (m, 1H, H-4), 2.58–2.72 (m, 2H, N–CH_2), 2.77–2.89 (m, 1H, N–CH_2), 2.82–2.91 (m, 1H, N–CH_2), 3.56–3.70 (m, 2H, NCH_2Ph), 4.08–4.19 (m, 3H, OCH_2 and H-5), 5.77 (br s, 1H, N–H), 7.20–7.35 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.6, 28.3, 28.8, 32.8, 47.9, 51.3, 51.9, 52.7, 60.7, 63.9, 79.2, 127.4, 128.7, 129.1, 139.9, 155.7, 173.9; MS: (ESI): m/z = 377 (M+1). Anal. Calcd for $C_{21}H_{32}N_2O_4$: C, 66.99; H, 8.57; N, 7.44. Found: C, 66.64; H, 8.22; N, 7.17.

Isomerization of the azepane amino esters; general procedure

Freshly prepared NaOEt (86 mg, 1.27 mmol) was added to a solution of (−)-**6** or (−)-**14** (400 mg, 1.06 mmol) in anhydrous EtOH (15 mL), and the mixture was stirred at rt for 72 h, and then concentrated under reduced pressure. The residue was taken up in EtOAc (25 mL) and the organic layer was washed with H_2O (3 × 10 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified from the unreacted starting material by column chromatography on silica gel (n-hexane/EtOAc: 5/1).

Ethyl (3*S*,4*R*)-1-benzyl-3-(*tert*-butoxycarbonylamino)azepane-4-carboxylate [(−)-7]

Yellowish oil; yield: 38%; $[\alpha]_D^{20}$ −27.5 (c 0.325, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.24 (t, 3H, CH_3, J = 7.3 Hz), 1.38 (s, 9H, CH_3), 1.61–1.76 (m, 2H, CH_2), 1.76–1.98 (m, 2H, CH_2), 2.34–2.45 (m, 1H, H-4), 2.59–2.90 (m, 4H, 2 × N–CH_2), 3.48–3.68 (m, 2H, N–CH_2Ph), 3.90–4.03 (m, 1H, H-3), 4.12 (m, 2H, OCH_2), 5.27 (br s, 1H, N–H), 7.23–7.35 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.6, 26.1, 26.8, 28.8, 50.3, 50.7, 56.2, 56.9, 60.8, 64.2, 79.3, 127.6, 128.8, 129.5, 139.8, 155.4, 173.8; MS: (ESI): m/z = 377 (M+1). Anal. Calcd for $C_{21}H_{32}N_2O_4$: C, 66.99; H, 8.57; N, 7.44. Found: C, 66.71; H, 8.27; N, 7.19.

Ethyl (4*S*,5*S*)-1-benzyl-5-(*tert*-butoxycarbonylamino)azepane-4-carboxylate [(+)-15]

Yellowish oil; yield: 44%; $[\alpha]_D^{20}$ +3 (c 0.315, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.19 (t, 3H, CH_3, J = 7.3 Hz), 1.39 (s, 9H, CH_3), 1.71–2.03 (m, 4H, CH_2), 2.43–2.53 (m, 1H, H-4), 2.58–2.74 (m, 4H, N–CH_2), 3.55 (m, 2H, N–CH_2Ph), 4.04–4.13 (m, 2H, OCH_2), 4.14–4.25 (m, 1H, H-5), 5.34 (br s, 1H, N–H), 7.12–7.38 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.6, 28.3, 28.8, 30.1, 49.2, 49.3, 51.4, 52.5, 60.9, 63.5, 70.2, 127.5, 128.7, 129.2, 139.4, 155.6, 174.7; MS: (ESI): m/z = 377 (M+1). Anal. Calcd for $C_{21}H_{32}N_2O_4$: C, 66.99; H, 8.57; N, 7.44. Found: C, 66.70; H, 8.33; N, 7.29.

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17. The ee value for (−)-**6** was determined by HPLC on a Chiralcel® OD 5 μm column (0.46 cm × 25 cm) [mobile phase: *n*-hexane/2-propanol (95/5); flow rate 0.5 mL/min; detection at 205 nm; retention time (min): 11.1 (antipode: 12.8)]. The ee values for (−)-**7**, (−)-**14**, and (+)-**15** were determined by HPLC on a Chiral Pak IA 5 μm column (0.4 cm × 1 cm) {detection at 205 nm; [mobile phase: *n*-hexane/2-propanol (90/10); flow rate 0.5 mL/min; retention times (min) for (−)-**7**: 13.0 (antipode: 15.1); for (+)-**15**: 16.7 (antipode: 14.0)]; and [mobile phase: *n*-hexane/2-propanol (97/3); flow rate 0.3 mL/min; retention time (min) for (−)-**14**: 35.1 (antipode: 30.2)]}.
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