Synthesis of conformationally constrained, orthogonally protected 3-azabicyclo[3.2.1]octane β-amino esters

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Dedicated to the memory of Professor Gábor Bernáth (1933-2009)

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Abstract
Novel azabicyclic β-amino acid derivatives were readily prepared from *diexo* or *diendo* norbornene β-amino acids. The 3-azabicyclo[3.2.1]octane skeleton was obtained by $NaIO_4$-mediated cleavage of the dihydroxylated β-amino ester intermediates, followed by reductive amination. Lipase-catalyzed enantioselective ring opening of racemic *exo*-norbornene β-lactam allowed preparation of the corresponding azabicyclic *exo* β-amino acid in enantiopure form.

Keywords: β-amino acids, dihydroxylation, ring opening, ring closure, enzymatic resolution

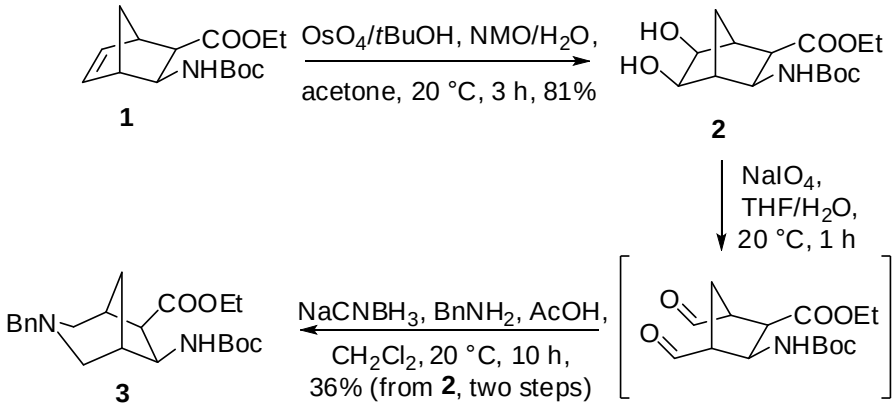
Introduction

Because of their importance in synthetic and medicinal chemistry and in peptide research, conformationally rigid, alicyclic β-amino acids have been subject to considerable interest during the past 20 years[1]. *N*-Heterocyclic β-amino acids have also attracted attention in view of their biological properties and their applications in peptide synthesis.[2] Bicyclic α- or β-amino acids in which the *N* atom of the amino function is part of the ring system are a class of compounds of appreciable importance. Thus, bicyclic α-amino acids with the N atom in the ring system, such as 7-azabicyclo[2.2.1]heptane-1-carboxylic acid, its derivatives and compounds with an 8-azabicyclo[3.2.1]octane skeleton are conformationally restricted analogs of proline, hydroxyprolines and related proline derivatives.[3,4] 7-Azabicyclo[2.2.1]heptane-2-carboxylic acid β-amino acids key compounds in novel β-peptide syntheses,[5] were recently reported to behave as conformationally restricted proline analogs, acting as efficient catalysts in organocatalytic aldol processes[6] Moreover, both bicyclic α- and β-amino acids with the *N* atom in the ring system serve as key precursors for the synthesis of medicinally valuable alkaloids such as anatoxin-*a*,[7]

epibatidine, epiboxidine etc.[8] A number of pharmacologically active 3-azabicyclo[3.2.1]octanes have been reported as bioactive molecules,[9] the most important of them probably being those with an amino or carboxyl function in their structure. 3-Azabicyclo[3.2.1]octane α-amino acids were recently synthetized in enantiomerically pure form,[9a] Because of the importance of the conformationally constrained alicyclic or heterocyclic β-amino acids, our work was directed toward the synthesis of novel 3-azabicyclo[3.2.1]octane skeleton β-amino acids.

Results and Discussion

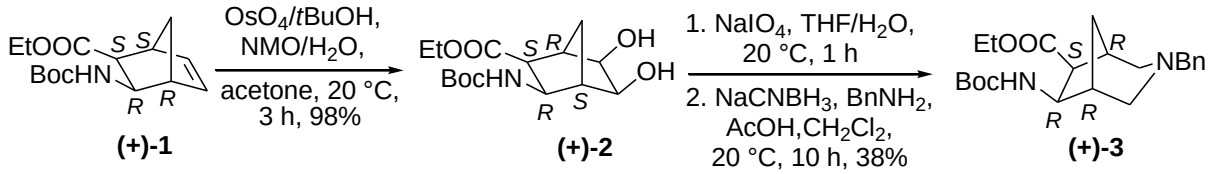
The synthetic route applied for the preparation of these azabicyclic β-amino esters is based on a simple method used for the synthesis of piperidine and azepane β-amino carboxylates.[2a,b] The starting compounds were exo and endo norbornene β-amino acids.[10] *Diexo*-*N*-Boc-protected norbornene amino ester **1** was transformed into the corresponding dihydroxy derivative **2** with *N*-methylmorpholine-*N*-oxide (NMO) as stoichiometric co-oxidant and OsO_4 as catalyst. A single dihydroxylated amino ester diastereomer was selectively obtained, in which the *cis* situation of the hydroxy groups relative to the methylene bridge was confirmed by NOESY experiment. NOE signals were observed between OH-5 (δ 4.63), OH-6 (δ 4.63) and H-7 (δ 1.81). Oxidative breaking of the vicinal diol C-C bond in **2** with $NaIO_4$ gave the corresponding dialdehyde. As this is unstable, its solution was submitted immediately, without isolation, to reductive amination with benzylamine in the presence of $NaBH_3CN$ and AcOH. The ring-closure reaction afforded the desired azabicyclic β-amino ester **3** (Scheme 1).



Scheme 1. Syntheses of racemic azabicyclic β-amino ester **3**.

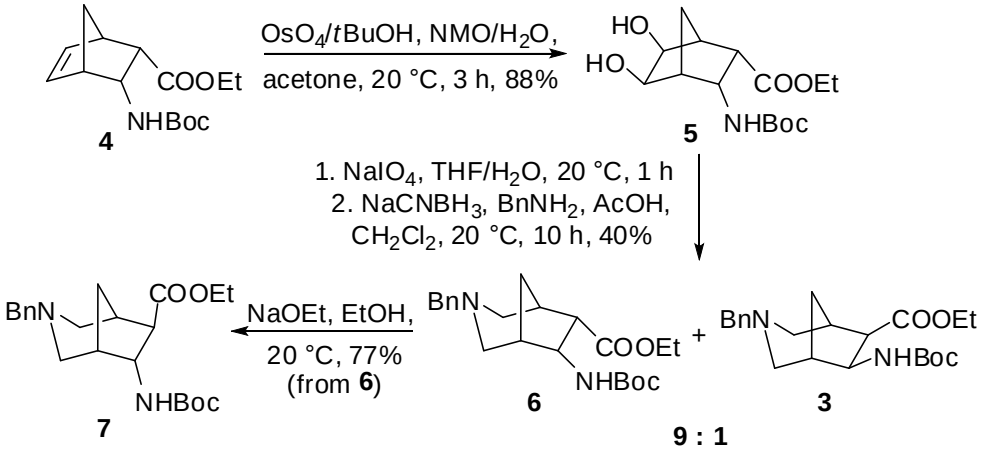
The above synthetic route was extended to the preparation of β-amino ester (+)-**3** in enantiomerically pure form (ee > 99%) from (+)-**1**, synthetized by a literature method.[11] Racemic norbornene β-lactam was subjected to enzymatic ring opening in the presence of CAL-B (lipase B from *Candida antarctica*, produced by the submerged fermentation of a genetically modified

Aspergillus oryzae microorganism and adsorbed on a macroporous resin) in iPr_2O.[11] The unreacted β-lactam enantiomer was transformed into the protected amino ester (+)-**1** via lactam ring opening, followed by N-Boc protection. Further transformations (dihydroxylation, ring-cleavage and ring-closure) were performed similarly as for the racemic substances, resulting in the enantiomerically pure bicyclic β-amino ester (+)-**3** (Scheme 2).



Scheme 2. Synthesis of enantiomeric azabicyclic β-amino ester (+)-**3**.

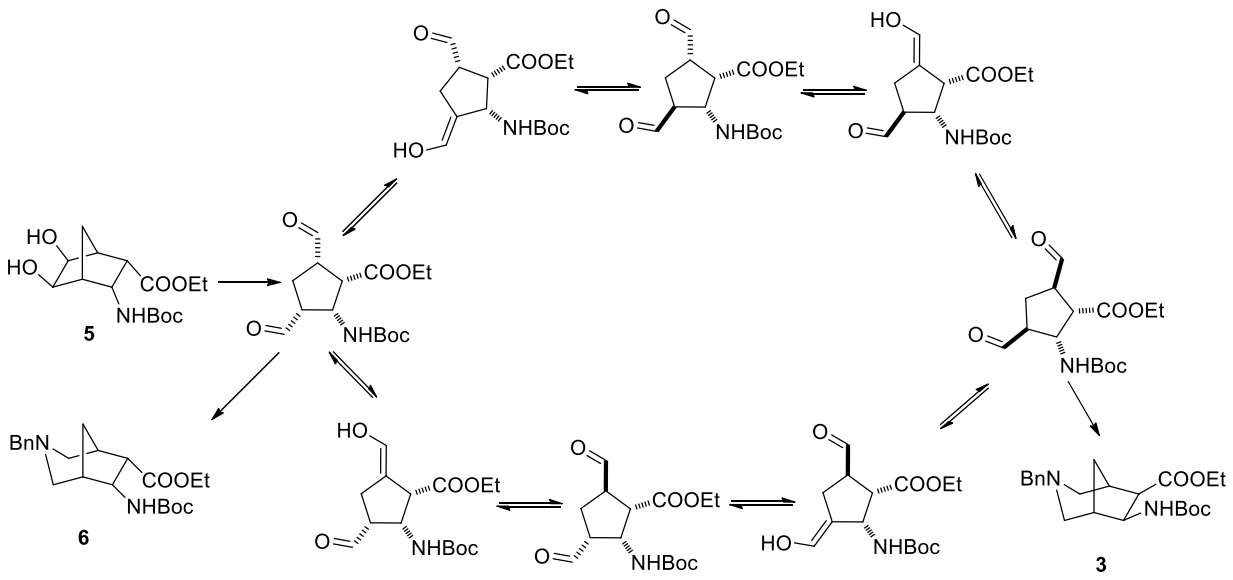
Via a synthetic procedure similar to that presented in Scheme 1, starting from *diendo* norbornene amino ester **4** through dihydroxylation, cleavage of the resulting diol and reductive amination two azabicyclic stereoisomers **6** and the earlier synthetized **3** were obtained in a ratio of 9:1 (Scheme 3). The NMR data confirmed that the major product was the desired heterocyclic *diendo* amino ester **6**, while the minor product was identified as the *diexo* compound **3** (Scheme 3).



Scheme 3. Syntheses of azabicyclic β-amino esters **3, 6** and **7**.

The detection of **3** in this reaction mixture was somewhat surprising as it demands a simultaneous configuration change at two positions (Scheme 3). The explanation may be that the keto-enol tautomerism of the dialdehyde intermediate generated from the oxidative cleavage of diol **5**, results in the configurational change of the heterocyclic amino ester (*diendo-diexo*), thereby accounting for the mixture of ring closure products (Scheme 4). The heterocyclic *diendo* amino ester **6** was subjected to isomerization in the presence of NaOEt in EtOH to afford a new

azabicyclic diastereomer **7**, a C-2 epimer of **6**, in good yield (77%) with almost full conversion (Scheme 3).



Scheme 4. Possible stereoisomers of the dialdehyde intermediate due to keto-enol tautomerism.

Experimental Section

General. The chemicals were purchased from Aldrich or Fluka. The solvents were used as received from the supplier. NMR spectra were recorded on a Bruker DRX 400 spectrometer. Chemical shifts are given in δ (ppm). Optical rotations were measured with a Perkin-Elmer 341 polarimeter. Melting points were determined with a Kofler apparatus. The mass spectra were recorded on a Finnigan MAT 95S spectrometer. Elemental analyses were performed with a Perkin-Elmer CHNS-2400 Ser II Elemental Analyzer. The ee value for (+)-**3** was determined by HPLC on a Chiral Pak IA 5 μ□□column (0.4 cm x 1 cm) [mobile phase: *n*-hexane/2-propanol (90/10); flow rate 0.5 mL/min; detection at 205 nm; retention time (min): 16.6 (antipode: 12.7)].

General procedure for Boc protection of amino esters

To a solution of ethyl *diexo*- or *diendo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylate hydrochloride[10] (2 g, 9.23 mmol) in THF (40 mL), Et_3N (1.86 g, 18.4 mmol) and di-*tert*-butyl dicarbonate (2.21 g, 10.1 mmol) were added at 0 °C. After stirring for 20 h at room temperature, the reaction mixture was taken up in EtOAc (40 mL) and the solution was washed with H_2O (3 × 80 mL), dried over Na_2SO_4 and concentrated under reduced pressure, giving amino ester **1** or **4**.

Ethyl *diexo*-(1*S,2*S**,3*R**,4*R**)-3-(*tert*-butoxycarbonylamino)bicyclo[2.2.1]hept-5-ene-2-carboxylate (1).** White crystals; 96% yield; mp. 141-143 °C. ^{1}H NMR (DMSO, 400 MHz) δ:

1.17 (t, 3H, *J* = 7.05 Hz, CH_3), 1.37 (s, 10H, *t*Bu, H-7), 2.12 (d, 1H, H-7, *J* = 9.06 Hz), 2.45 (d, 1H, H-2, *J* = 8.05 Hz), 2.54-2.60 (m, 1H, H-1), 2.83-2.87 (m, 1H, H-4), 3.77-3.81 (m, 1H, H-3), 3.89-4.00 (m, 1H, OCH_2), 4.00-4.11 (m, 1H, OCH_2), 6.16-6.23 (m, 2H, H-5 and H-6), 6.63 (d, 1H, NH, *J* = 8.81 Hz). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 27.7, 29.1, 45.1, 45.9, 48.1, 54.0, 60.6, 78.6, 137.9, 139.7, 155.8, 173.5. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 63.91; H, 8.20; N, 4.97.

Ethyl *diendo*-(1*R,2*S**,3*R**,4*S**)-3-(*tert*-butoxycarbonylamino)bicyclo[2.2.1]hept-5-ene-2-carboxylate (4).** White crystals; 83% yield; m.p. 86-88 °C. ^{1}H NMR (DMSO, 400 MHz) δ: 1.15 (t, 3H, *J* = 7.08 Hz, CH_3), 1.26-1.45 (m, 11H, *t*Bu, H-7), 2.88-2.92 (m, 1H, H-1), 2.97-3.01 (m, 1H, H-4), 3.13-3.21 (m, 1H, H-2), 3.88-4.05 (m, 2H, OCH_2), 4.38-4.49 (m, 1H, H-3), 6.62 (d, 1H, NH, *J* = 8.81 Hz), 6.15-6.21 (m, 1H, H-6), 6.28-6.34 (m, 1H, H-5). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 29.0, 46.5, 47.5, 47.8, 49.3, 54.5, 60.5, 78.8, 134.0, 138.7, 155.7, 172.7. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.00; H, 8.35; N, 5.11.

General procedure for dihydroxylation of N-Boc-protected amino esters

OsO_4 (1.43 mL, 0.08 mmol; 0.06 M solution in *t*BuOH) was added to a stirred solution of NMO (1.98 mL, 9.41 mmol; 50 wt.% in H_2O) and amino ester 1 or 4 (2.5 g, 8.88 mmol) in acetone (20 mL). After 3 h, the mixture was treated with saturated aqueous Na_2SO_3 (25 mL) and filtered through Celite, and the Celite was washed with CH_2Cl_2 (60 mL). The phases were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 25 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give the crude solid, which was recrystallized from *n*-hexane/EtOAc. The oily compound was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 1:3).

Ethyl *diexo*-(1*R,2*S**,3*R**,4*S**)-3-(*tert*-butoxycarbonylamino)-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxylate (2).** White crystals; 81% yield; m.p. 116-118 °C. ^{1}H NMR (DMSO, 400 MHz) δ: 1.14 (t, 3H, *J* = 7.08 Hz, CH_3), 1.35 (s, 9H, *t*Bu), 1.61 (d, 1H, H-7, *J* = 10.82 Hz), 1.75-1.83 (m, 2H, H-7 and, H-1), 2.05-20.10 (m, 1H, H-4), 2.46-3.00 (m, 1H, H-2), 3.47-3.57 (m, 2H, H-5 and H-6), 3.78-4.01 (m, 1H, H-3), 3.84-3.95 (m, 1H, OCH_2), 3.96-4.08 (m, 1H, OCH_2), 4.63 (brs, 2H, OH), 6.62 (d, 1H, NH, *J* = 8.81 Hz). ^{13}C NMR (DMSO, 400 MHz) δ: 14.8, 29.0, 29.9, 46.5, 49.2, 49.7, 53.0, 60.4, 71.9, 72.6, 78.5, 155.7, 172.3. MS: (ESI, pos): m/z = 338.2 (M+23). Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 56.89; H, 7.80; N, 4.47.

Ethyl *diendo*-(1*S,2*S**,3*R**,4*R**)-3-(*tert*-butoxycarbonylamino)-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxylate (5).** White crystals; 88% yield; m.p. 86-88 °C. ^{1}H NMR (DMSO, 400 MHz) δ: 1.13-1.21 (m, 4H, CH_3 and H-7), 1.38 (s, 9H, *t*Bu), 1.75 (d, 1H, H-7, *J* = 10.32 Hz), 2.03-2.12 (m, 1H, H-4), 2.19-2.23 (m 1H, H-1), 2.90-2.99 (m, 1H, H-2), 3.81-4.1 (m, 5H, OCH_2, H-3, H-5 and H-6), 4.45-4.63 (m, 2H, OH), 6.63 (d, 1H, NH, *J* = 7.55 Hz). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 29.0, 31.5, 44.2, 47.8, 49.0, 50.3, 60.8, 68.1, 69.5, 78.8, 156.0, 172.7. MS: (ESI, pos): m/z = 339.1 (M+23). Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.09; H, 8.12; N, 4.57.

General procedure for cleavage of dihydroxy compounds and ring closure with reductive amination

Dihydroxy compound **2** or **5** (315 mg, 1 mmol) was dissolved in THF/H_2O (11 mL, 10:1), and $NaIO_4$ (0.42 g, 2 mmol) was added to the solution. After stirring for 1 h at 20 °C under an Ar atmosphere, H_2O was added until the precipitation had dissolved. The mixture was extracted with CH_2Cl_2 (3 × 40 mL), the combined extract was 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 molecular sieve were added to the solution of the dialdehyde at 40 °C, which was next stirred for 10 min. A solution of $NaCNBH_3$ (63 mg, 1 mmol) and AcOH (0.057 mL, 1 mmol) in EtOH (2 mL) was added dropwise during 2 h under an Ar atmosphere. The stirring was continued for another 1 h at 40 °C. The reaction mixture was extracted in turn with 10% Na_2CO_3 (3 × 80 mL), and brine (80 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, (3: R_f 0.35 *n*-hexane/EtOAc, 2:1; 6: R_f 0.35 *n*-hexane/EtOAc, 4:1).

Ethyl *diexo*-(1*R,5*R**,6*S**,7*R**)-3-benzyl-7-(*tert*-butoxycarbonylamino)-3-azabicyclo[3.2.1]octane-6-carboxylate (3).** White crystals; 36% yield (two steps); m.p. 100-103 °C. ^{1}H NMR (DMSO, 400 MHz) δ: 1.11-1.21 (m, 4H, CH_3 and H-8), 1.36 (s, 9H, tBu), 1.95-2.02 (m, 3H, H-2, H-4, H-1), 2.08-2.22 (m, 1H, H-8), 2.30-2.35 (m, 1H, H-5), 2.52-2.61 (m, 1H, H-4), 2.62-2.76 (m, 1H, H-2), 3.03 (d, 1H, H-6, *J* = 8.31 Hz), 3.43 (s, 2H, $BnCH_2$), 3.80-3.95 (m, 1H, OCH_2), 3.96-4.09 (m, 1H, OCH_2), 4.22-4.26 (m, 1H, H-7), 6.76 (d, 1H, NH, *J* = 9.06 Hz), 7.20-7.38 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 29.1, 36.0, 39.4, 42.6, 53.7, 56.7, 58.5, 59.0, 60.3, 62.3, 78.4, 127.7, 129.1, 129.4, 139.6, 155.6, 173.4. MS: (EI, pos): m/z = 388.5 (M). Anal. Calcd for $C_{22}H_{32}N_2O_4$: C, 68.01; H, 8.30; N, 7.21. Found: C, 68.17; H, 8.15; N, 7.21.

Ethyl *diendo*-(1*S,5*S**,6*S**,7*R**)-3-benzyl-7-(*tert*-butoxycarbonylamino)-3-azabicyclo[3.2.1]octane-6-carboxylate (6).** White crystals; 36% yield; m.p. 78-80 °C. ^{1}H NMR (DMSO, 400 MHz) δ: 1.15 (t, 3H, CH_3 *J* = 7.08 Hz), 1.37 (s, 9H, *t*Bu), 1.41-1.49 (m, 1H, H-8), 1.52-1.61 (m, 1H, H-8), 1.97 (d, 1H, H-4, *J* = 10.93 Hz), 2.06-2.14 (m, 1H, H-1), 2.19 (d, 1H, H-2, *J* = 10.52 Hz), 2.24-2.32 (m, 1H, H-5), 2.53-2.57 (m, 1H, H-4), 3.06 (dd, 1H, H-6, J_1 = 11.14 Hz, J_2 = 5.70 Hz), 3.17-3.27 (m, 2H, $BnCH_2$, and H-2), 3.50 (d, 1H and $BnCH_2$, *J* = 12.56 Hz), 4.03 (m, 2H, OCH_2), 4.15-4.27 (m, 1H, H), 6.04 (d, 1H, NH, *J* = 9.92 Hz), 7.18-7.35 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 29.0, 35.9, 38.0, 47.2, 51.6, 54.8, 56.9, 60.2, 62.8, 78.3, 127,8, 129.1, 129.6, 139.2, 156.0, 171.9. MS: (ESI, pos): m/z = 389.3 (M+1). Anal. Calcd for $C_{22}H_{32}N_2O_4$: C, 68.01; H, 8.30; N, 7.21. Found: C, 67.88; H, 8.49; N, 7.11.

Isomerization of amino ester 6

Freshly prepared NaOEt (57 mg, 0.83 mmol) was added to a solution of 6 (250 mg, 0.64 mmol) in anhydrous EtOH (5 mL), and the mixture was stirred at room temperature for 48 h. The reaction mixture was then concentrated under reduced pressure and taken up in EtOAc (15 mL), and the organic layer was washed with H_2O (3 × 5 mL). The combined extract 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 (1*S,5*S**,6*R**,7*R**)-3-benzyl-7-(*tert*-butoxycarbonylamino)-3-azabicyclo[3.2.1]octane-6-carboxylate (7).** Colorless oil; 77% yield. ^{1}H NMR (DMSO, 400 MHz) δ: 1.17 (t, 3H, CH_3, *J* = 7.08 Hz), 1.32 (s, 9H, *t*Bu), 1.36-1.39 (m, 1H, H-8), 1.62-1.72 (m, 1H, H-8), 1.96-1.99 (m, 1H, H-2), 2.07-2.27 (m, 3H, H-5, H-4 and H-1), 2.52-2.83 (m, 3H, H-2, H-4 and H-6), 3.35 (d, 1H, $BnCH_2$, *J* = 12.2 Hz), 3.54 (d, 1H, $BnCH_2$, *J* = 12.2 Hz), 3.98-4.14 (m, 3H, OCH_2 and H-7), 5.87 (d, 1H, NH, *J* = 8.08 Hz), 7.20-7.39 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 13.4, 27.7, 34.1, 37.0, 38.2, 52.3, 55.2, 58.7, 59.5, 60.9, 78.0, 126.6, 128.1, 128.8, 138.0, 154.8, 174.6. Anal. Calcd for $C_{22}H_{32}N_2O_4$: C, 68.01; H, 8.30; N, 7.21. Found: C, 68.02; H, 8.46; N, 7.20.

Characterization of enantiomeric compounds

All the reactions were first optimized for racemic compounds. The ^{1}H and ^{13}C NMR spectroscopic data and elemental analyses on the enantiomeric derivatives were in accordance with those for the racemic compounds. Representative data on the enantiomers are as follows:

Ethyl (1*S*,2*S*,3*R*,4*R*)-3-(*tert*-butoxycarbonylamino)bicyclo[2.2.1]hept-5-ene-2-carboxylate [(+)-1]. White crystals; 99% yield; $[\alpha]_D$: + 90 (*c* 0.245, EtOH); m.p. 101-103 °C.

Ethyl (1*R*,2*S*,3*R*,4*S*)-3-(*tert*-butoxycarbonylamino)-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxylate [(+)-2]. Yellow oil; 98% yield; $[\alpha]_D$: + 41 (*c* 0,245, EtOH).

Ethyl (1*R*,5*R*,6*S*,7*R*)-3-benzyl-7-(*tert*-butoxycarbonylamino)-3-azabicyclo[3.2.1]octane-6-carboxylate [(+)-3]. White crystals; 38% yield; $[\alpha]_D$: + 53 (*c* 0,245, EtOH); ee > 99 %; m.p. 80-82 °C.

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