Amino Acids (2012) 43:415–421
DOI 10.1007/s00726-011-1097-6

ORIGINAL ARTICLE

New 1,3-amino alcohols derived from enantiopure bridgehead β-aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acids

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Received: 24 June 2011 / Accepted: 19 September 2011 / Published online: 4 October 2011

Abstract Constrained enantiopure bicyclic β-amino acids derived from the asymmetric Diels–Alder reaction of the (*R*)-benzyl-4-(3-acryloyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)-benzoate and the 1-(benzyloxycarbonylamino)cyclohexadiene provide original templates for the construction of new rigid enantiopure 1,3-amino alcohols.

Keywords Bicyclic β-amino acid derivatives · Cyclic amino alcohols · Constrained chiral β-amino acids · Reduction

Introduction

Synthesis of enantiopure amino alcohols is of great importance in synthetic organic chemistry since they are a well established source of ligands for asymmetric synthesis (Blaser 1992; Ager et al. 1996; Lait et al. 2007) including enantioselective borane reduction of prochiral ketones (Corey et al. 1987; Corey and Helal 1998; Deloux and Screbnik 1993; Li et al. 1999; Krzemiński and Wojtczak 2005; Krzemiński and Zaidlewicz 2003; Hobuss et al. 2008) or enantioselective addition of dialkylzinc (Kitamura et al. 1986; Kossenjans and Martens 1998; Garcia Martinez et al. 2002; Oliveira and Costa 2004; Szakonyi et al. 2006; Binder et al. 2009; Scarpi et al. 2009; Wu et al. 2009). Apart from this property, enantiopure amino alcohols are also important derivatives for the synthesis of various chemical compounds. They constitute convenient starting materials for the synthesis of various 1,3-heterocycles for example (Ager et al. 1996; Fülöp et al. 1997; Gyonfalvi et al. 2003; Kivelä et al. 2003, 2005). Although 1,2-amino alcohols have received much attention because they are generally readily accessible in enantiomerically pure form from natural precursors (Gyonfalvi et al. 2003; Reetz et al. 1987; Delair et al. 1994; Masui and Shiori 1998; Laczkowski et al. 2009; Kiss and Fülöp 2009), the synthesis and the use of chiral 1,3-amino alcohols are still undergoing development and remain a challenge (Lait et al. 2007; Didier et al. 1991; Barluenga et al. 1993; Bartoli et al. 1994; Kossenjans and Martens 1999; Kochi et al. 2003; Raghavan et al. 2004; Murai et al. 2005; Balazs et al. 2007).

This prompted us to synthesize new constrained 1,3-amino alcohols from some enantiopure bicyclic β-amino acids recently developed in our group (Songis et al. 2007, 2008a, b). These bicyclic β-amino acids were obtained by using the asymmetric Diels–Alder cycloaddition between the chiral acrylate (*R*)-**1** (Akkari et al. 2004; Calmès et al. 2005) and the 1-(benzyloxycarbonylamino)cyclohexadiene **2** (Fig. 1).

The resulting Diels–Alder cycloadducts were obtained in high yield and moderate selectivity using optimized conditions mainly contained the two diastereoisomers **3** (60%) and **4** (30%). These two major Diels–Alder adducts (3′*R*,1*S*,2*R*,4*R*)-**3** and (3′*R*,1*R*,2*R*,4*S*)-**4** (Fig. 2), resulting from an endo and an exo selectivity on the same Cα Si face of the chiral dienophile (*R*)-**1** respectively, were isolated in pure form after column chromatography on silica gel. Stereochemistry of the endo adduct **3**, that crystallized from diethyl ether/petroleum ether, has been confirmed unambigously by X-ray diffraction analysis (Songis et al. 2007).

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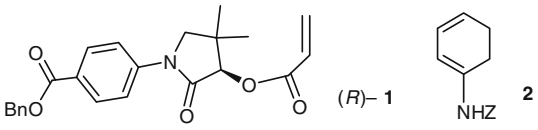


Fig. 1 Chiral acrylate (*R*)-**1** and protected aminodiene **2**

Removal of the chiral auxiliary of (3′*R*,1*S*,2*R*,4*R*)-**3** and (3′*R*,1*R*,2*R*,4*S*)-**4** afforded the two bicyclic *β*-amino acids (1*S*,2*R*,4*R*)-**5** and (1*R*,2*R*,4*S*)-**6**. Then, the palladium-catalyzed hydrogenation/hydrogenolysis of both carboxylic acids **5** and **6** yielded the corresponding saturated bicyclic-*β*-amino acid (*R*)-**7** (Fig. 3).

These three bicyclic compounds bearing an amino group at the bridgehead and possessing the particular structural properties of constrained cyclic amino acids (Fülöp 2001; Park and Kurth 2002; Kiss et al. 2009) represent useful templates for the construction of new rigid enantiopure amino alcohols. Here, we proposed the synthesis of original rigid bicyclic amino alcohols from compounds **5**, **6** and **7**.

Experimental

Materials

All reagents were used as purchased from commercial suppliers without further purification. Solvents were dried and purified by conventional methods prior to use. The enantiopure compounds (1*S*,2*R*,4*R*)-**5**, (1*R*,2*R*,4*S*)-**6** and (2*R*)-**7** were prepared as previously described (Songis et al. 2007, 2008a, b).

Techniques

Melting points were determined with a Kofler Heizbank apparatus and are uncorrected. Optical rotations were measured with a Perkin Elmer 341 polarimeter. ^{1}H or ^{13}C NMR spectra (DEPT, $^{1}H/^{13}C$ 2D-correlations) were recorded with a Bruker A DRX 400 spectrometer using the solvent as internal reference. Data are reported as follows: chemical shifts (δ) in parts per million, coupling constants (J) in hertz (Hz). The ESI mass spectra were recorded with a platform II quadrupole mass spectrometer (Micromass, Manchester, UK) fitted with an electrospray source. HRMS

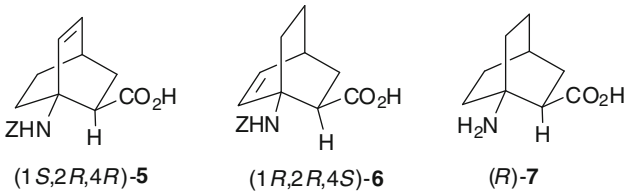


Fig. 3 Bicyclic *β*-amino acids **5**, **6** and **7**

were recorded in positive mode using NBA (3-nitrobenzylalcohol or GT (Glycerol/thioglycerol) as matrix. HPLC analyses were performed with a Waters model 510 instrument or a Beckman System Gold 126 instrument with variable detector using: column A SymmetryShield™ RP-18, 3.5 μ (50 mm × 4.6 mm), flow 1 ml/min, H_2O (0.1% TFA)/CH_3CN (0.1% TFA), gradient 0 → 100% (15 min) and 100% (4 min); column B Chromolith® SpeedROD RP-18e, 2 μ, (50 × 4.6 mm), flow 3 ml/min, H_2O (0.1% TFA)/CH_3CN (0.1% TFA), gradient 0 → 100% (4 min) and 100% (1 min).

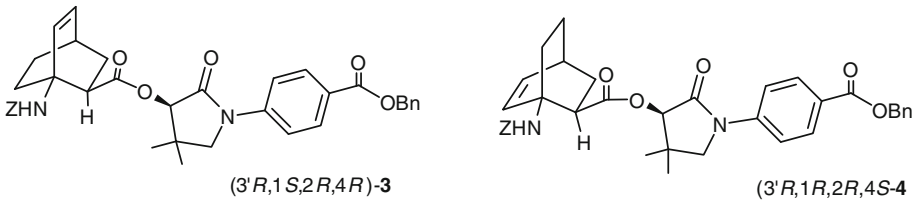
*General procedure for the reduction of compounds **5, 6, 14** and **16***

To a stirred solution of the N-protected amino acid (1 equiv) in THF was added at room temperature benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) (1 equiv) and *N*,*N*-diisopropylethylamine (DIEA) (1.5 equiv). The resulting solution was stirred for 10 min, then $NaBH_4$ (3 equiv) was added by portionwise at 0°C. After stirring at room temperature until completion of the reaction (monitored by HPLC, column A or B), the solvent was evaporated and the residue was dissolved in ethyl acetate (20 ml). This organic layer was washed with 0.1 N HCl (2 × 5 ml), dried over Na_2SO_4 and concentrated in vacuo.

*(1S,2R,4R)-(1-Benzyloxycarbonylaminobicyclo[2.2.2]oct-5-ene-2-yl)methanol (**8**)*

Synthesized according to the general procedure from the N-Z amino acid (1*S*,2*R*,4*R*)-**5** (170 mg, 0.56 mmol, 1 equiv) in THF (4 ml), BOP reagent (255 mg, 0.56 mmol, 1 equiv), DIEA (0.15 ml, 0.85 mmol, 1.5 equiv) and $NaBH_4$ (64 mg, 1.68 mmol, 3 equiv). After stirring for 40 min at

Fig. 2 Major Diels–Alder adducts **3** and **4**



room temperature, concentration of the solvent and washings, the residue was purified by column chromatography on silica gel, using dichloromethane/ethyl acetate (9/1) as eluent to yield the expected compound (1*S*,2*R*,4*R*)-**8** as a colourless oil (99 mg, 0.35 mmol, 62% yield); $[\alpha]_D^{20} = -16$ ($c = 1.1$ in CH_2Cl_2), t_R (HPLC, column B) 2.19 min, MS (ESI) *m/z* 244.3 [(M-CO_2 + H)$^+$], 288.2 [(M + H)$^+$], 575.3 [(2 M + H)$^+$], ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 0.63–0.79 (m, 1H, *H*CH), 1.25–1.36 (m, 1H, *H*CH), 1.39–1.54 (m, 2H 2*H*CH), 1.66–1.75 (m, 1H, *H*CH), 1.86–1.97 (m, 2H, *H*CH and C*H*-CH_2-OH), 2.38–2.44 (m, 1H, 4-H), 2.62–2.46 (br s, 1H, O*H*), 3.20–3.42 (m, 2H, CH_2-OH), 4.97 (d, $J = 12.5$ Hz, 1H, O*H*CHC_6H_5), 5.02 (d, $J = 12.5$ Hz, 1H, O*H*CHC_6H_5), 6.11–6.21 (m, 2H, 6-H and 5-H), 6.26–6.42 (br s, 1H, N*H*), 7.18–7.26 (m, 5H, CH-arom); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ 24.2 (*C*H_2), 28.5 (*C*-4), 29.9 (*C*H_2), 30.9 (*C*H_2), 42.5 (2-*C*), 56.3 (1-*C*), 64.8 (*C*H_2OH), 65.2 (O*C*$H_2C_6H_5$), 126.9, 127.1, 127.4 (*C*H-arom), 132.1 and 132.6 (*C*H=), 135.7 (*C*-arom), 154.8 (*C*O); HRMS (ESI) Calcd for $C_{17}H_{22}NO_3$ (MH$^+$) 288.1600, found 288.1599.

*(1R,2R,4S)-(1-Benzyloxycarbonylaminobicyclo[2.2.2]oct-5-ene-2-yl)methanol (**9**)*

Synthesized according to the general procedure from the N-Z amino acid (1*S*,2*R*,4*R*)-**6** (170 mg, 0.56 mmol, 1 equiv) in THF (4 ml) containing BOP reagent (255 mg, 0.56 mmol, 1 equiv), DIEA (0.15 ml, 0.85 mmol, 1.5 equiv) and $NaBH_4$ (64 mg, 1.68 mmol, 3 equiv). After stirring for 40 min at room temperature, the residue obtained after treatment was purified by column chromatography on silica gel, using dichloromethane/ethyl acetate (9/1) as eluent to yield the expected compound (1*S*,2*R*,4*R*)-**9** as a colourless oil (108 mg, 0.38 mmol, 67% yield); $[\alpha]_D^{20} = -46$ ($c = 1$ in CH_2Cl_2), t_R (HPLC, column A) 8.5 min, MS (ESI) *m/z* 288.4 [(M + H)$^+$], ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 0.72–0.86 (m, 1H, *H*CH), 1.28–1.45 (2 m, 2H, CH_2), 1.48–1.58 (m, 1H, *H*CH), 1.60–1.78 (m, 2H, CH_2), 1.80–1.95 (m, 1H, C*H*-CH_2-OH), 2.02–2.30 (br s, 1H, O*H*), 2.34–2.42 (m, 1H, 4-*H*), 3.56–3.72 (m, 2H, CH_2-OH), 4.97 (d, $J = 12.5$ Hz, 1H, O*H*CHC_6H_5), 5.02 (d, $J = 12.5$ Hz, 1H, O*H*CHC_6H_5), 6.10 (dd, $J = 6.7$ and 8.3 Hz, 1H, 5-*H*), 6.42 (br d, 2H, N*H* and 6-*H*), 7.18–7.32 (m, 5H, C*H*-arom); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ 24.7 (*C*H_2), 26.4 (*C*H_2), 29.3 (*C*-4), 30.4 (*C*H_2), 41.4 (2-*C*), 56.5 (1-*C*), 64.8 (*C*H_2OH), 66.2 (*C*$H_2C_6H_5$), 127.9, 128.1, 128.4 (*C*H-arom), 131.4 (*C*H=), 136.9 (*C*-arom), 138.6 (*C*H=), 155.4 (*C*O); HRMS (ESI) calculated for $C_{17}H_{22}NO_3$ (MH$^+$) 288.1600, found 288.1594.

*(R)-(1-Benzyloxycarbonylaminobicyclo[2.2.2]octane-2-yl)methanol (**15**)*

Synthesized according to the general procedure from N-Z-amino acid (*R*)-**14** (100 mg, 0.33 mmol, 1 equiv) in THF (4 ml), BOP reagent (145 mg, 0.33 mmol, 1 equiv), DIEA (86 µl, 0.49 mmol, 1.5 equiv) and $NaBH_4$ (37 mg, 0.99 mmol, 3 equiv). After stirring for 40 min at room temperature, the residue obtained after treatment was purified by column chromatography on silica gel, using dichloromethane/ethyl acetate (9/1) as eluent to yield the pure expected compound (*R*)-**15** as a colourless oil (64 mg, 0.22 mmol, 65% yield); $[\alpha]_D^{20} = -37$ ($c = 1.5$ in CH_2Cl_2); t_R (HPLC, column B) 2.0 min; MS (ESI) *m/z* 246.2 [(M-CO_2 + H)$^+$], 290.3 [(M + H)$^+$], 312.1 [(M + Na)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 1.16–1.21 (m, 1H, *H*CH), 1.55–1.95 (2 m, 9H, 3CH_2, 2*H*CH and 4-*H*), 2.10–2.18 (m, 2H, *H*CH and 2-*H*), 3.59 (dd, $J = 5.1$ and 11.1 Hz, 1H, *H*CH-OH), 3.78 (dd, $J = 7.8$ and 11.1 Hz, 1H, *H*CH-OH), 5.08 (s, 2H, O*C*$H_2C_6H_5$), 7.28–7.36 (m, 5H, C*H*-arom); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ 24.5 (4-*C*), 25.9 (*C*H_2), 26.0 (*C*H_2), 26.4 (*C*H_2), 30.7 (*C*H_2), 32.0 (*C*H_2), 41.1 (2-*C*), 52.9 (1-*C*), 64.9 (*C*H_2), 66.0 (*C*H_2), 128.1, 128.2, 128.6 (*C*H-arom), 135.9 (*C*-arom), 155.4 (*C*O); HRMS (ESI) calculated for $C_{17}H_{24}NO_3$ (MH$^+$) 290.1756, found 290.1755.

*(R)-(1-Butyloxycarbonylaminobicyclo[2.2.2]octane-2-yl)methanol (**17**)*

Synthesized according to the general procedure from *N*-Boc-amino acid (*R*)-**16** (100 mg, 0.37 mmol, 1 equiv) in THF (4 ml), BOP reagent (145 mg, 0.33 mmol, 1 equiv), DIEA (86 µl, 0.49 mmol, 1.5 equiv) and $NaBH_4$ (37 mg, 0.99 mmol, 3 equiv). After stirring for 40 min at room temperature, the residue obtained after treatment was purified by column chromatography on silica gel, using cyclohexane/ethyl acetate (7/3) as eluent to yield the pure expected compound (*R*)-**17** as a colourless oil (66 mg, 0.23 mmol, 62% yield); $[\alpha]_D^{20} = -106$ ($c = 0.7$ in CH_2Cl_2); MS (ESI) *m/z* 156.2[(M-BOC + H)$^+$], 200.2 [(M-(CH_2 = $C(CH_3)_2$) + H)$^+$], 256.2 [(M + H)$^+$], 278.2 [(M + Na)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 1.18–1.26 (m, 1H, *H*CH), 1.41 (s, 9H, C(CH_3)$_3$), 1.51–1.82 (2 m, 8H, 2CH_2, 3*H*CH and 4-*H*), 1.88–1.98 (m, 2H, 2*H*CH), 2.12–2.18 (m, 1H, 2-*H*), 3.58 (dd, $J = 4.8$ and 11.2 Hz, 1H, *H*CH-OH), 3.73 (dd, $J = 7.2$ and 11.2 Hz, 1H, *H*CH-OH); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ 23.9 (4-*C*), 25.3 (*C*H_2), 25.8 (*C*H_2), 26.0 (*C*H_2), 26.5 (C(*C*H_3)$_3$), 27.9 (*C*H_2), 30.2 (*C*H_2), 40.9 (2-*C*), 51.9 (1-*C*), 64.6 (*C*H_2), 78.5 (*C*(CH_3)$_3$), 128.1, 128.2, 128.6 (*C*H-arom), 154.9 (*C*O); HRMS (ESI) calculated for $C_{14}H_{26}NO_3$ (MH$^+$) 256.1913, found 290.1919.

*(1R,3S,6R,7R)-7-(Benzyloxycarbonylamino)-4-oxa-8-tricyclo[4.3.1.0^{3,7}]decan-5-one (**11**)*

Tributyltin hydride (0.32 ml, 1.17 mmol, 2 equiv) and azobis(isobutyronitrile) (20 mg, 0.12 mmol, 0.2 equiv) were added to a solution of the iodolactone (1*R*,2*R*,3*R*,6*R,7R*)-**10**[12] (250 mg, 0.58 mmol) in dry toluene (4 ml) under argon. After heating by microwave irradiation at 80°C for 1 h, the solvent was concentrated in vacuo and the γ-lactone (1*R*,3*S*,6*R,7R*)-**11** was obtained as a white solid by precipitation from hexane (160 mg, 0.53 mmol, 90% yield); m.p. 143°C; $[\alpha]_D^{20} = +37$ ($c = 0.55$, AcOEt); t_R (HPLC, column A) 8.7 min; MS (ESI) *m/z* 302.2 [$(M + H)^+$]; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 1.65 (t, $J = 8.3$ Hz, 2H, 8-*H*), 1.85–2.01 (m, 5H, 1-*H*, 2-*H* and 10-*H*), 2.05–2.22 (m, 2H, 9-*H*), 2.77 (d, $J = 9.2$ Hz, 1H, 6-*H*), 4.91 (s br, 1H, 3-*H*), 5.03 (s, 2H, CH_2O), 5.35 (s, 1H, N*H*), 7.28–7.38 (m, 5H, *H*-arom); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ 21.1 (9-*C*), 23.7 (1-*C*), 27.5 (8-*C*), 28.6 (10-*C*), 33.6 (2-*C*), 42.8 (6-*C*), 58.8 (7-*C*), 66.7 (*C*H_2O), 80.6 (3-*C*), 128.1, 128.2, 128.3, 128.4, 128.6 (*C*H-arom), 136.1 (*C*-arom), 154.9 (NH*C*OO), 179.9 (*C*OO); HRMS (ESI) calculated for $C_{17}H_{20}NO_4$ (MH^+) 302.1392, found 302.1406.

*(1R,2R,4R,6S)-1-(Benzyloxycarbonylamino)-6-hydroxybicyclo[2.2.2]octane-2-carboxylic acid (**12**)*

A solution of LiOH· H_2O (27 mg, 0.64 mmol, 1.6 equiv) in water (0.5 ml) was added dropwise to a solution of the γ-lactone (1*R*,3*S*,6*R,7R*)-**11** (120 mg, 0.40 mmol, 1 equiv) in THF/H_2O (2/1) (2 ml) and the mixture was stirred at room temperature till completion of the hydrolysis ($\sim$14 h) (monitored by HPLC, column A). The solvent was removed in vacuo and the residue was dissolved in ethyl acetate/saturated aqueous $NaHCO_3$ (4 ml/20 ml). The aqueous phase was acidified (pH 2) and extracted with dichloromethane (4 × 10 ml). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo to yield the expected pure hydroxyl β-amino acid (1*R*,2*R*,4*R,6S*)-**12** as a white solid (102 mg, 0.32 mmol, 88% yield), melting point 98°C; $[\alpha]_D^{20} = -48$ ($c = 3$ in CH_3CN); t_R (HPLC, column A) 8.1 min; t_R (HPLC, column B) 1.9 min; MS (ESI) *m/z* 276.1 [$(M\text{-}CO_2 + H)^+$], 320.1 [$(M + H)^+$], 342.0[$(M + Na)^+$]; ^{1}H NMR (400 MHz, CD_3CN, 25°C) δ 1.52–1.62 (m, 4H, 3-*H*, 5-*H*, 8-*H*), 1.75 (q, $J = 3.0$ Hz, 1H, 4-*H*,), 1.92–2.06 (m, 2H, 7-*H*,), 2.12–2.28 (m, 2H, 3-*H*, and 5-*H*,), 3.29 (dd, $J = 9.9$ and 7.4 Hz, 1H, 6-*H*,), 3.96 (dd, $J = 9.9$ and 3.0 Hz, 1H, 2-*H*,), 5.02 (d, $J = 12.7$ Hz, 1H, *H*CHO), 5.09 (d, $J = 12.7$ Hz, 1H, *H*CHO), 6.80 (s, 1H, N*H*), 7.31–7.42 (m, 5H, *H*-arom); ^{13}C NMR (100 MHz, CD_3CN, 25°C) δ 23.9 (4-*C*), 24.5 (8-*C*), 29.0 (5-*C*), 29.7 (7-*C*), 37.2 (3-*C*), 42.2 (6-*C*), 55.2 (1-*C*), 65.5 (*C*H_2O), 70.1 (2-*C*), 127.6, 127.8, 128.4 (*C*H-arom), 137.4 (*C*-arom), 155.1 (NH*C*OO), 177.1 (*C*OOH); HRMS (ESI) calculated for $C_{17}H_{22}NO_5$ (MH^+) 320.1498, found 320.1492.

*(1R,2R,4R,6S)-1-(Benzyloxycarbonylamino)-6-(hydroxymethyl)bicyclo[2.2.2]octane-2-ol (**13**)*

To a stirred solution of the N-protected lactone (1*R*,3*S*,6*R,7R*)-**11** (80 mg, 0.23 mmol, 1 equiv) in a mixture of 2-propanol (4 ml) and H_2O (1.2 ml) was added $NaBH_4$ (43 mg, 5 equiv) by portion wise at room temperature. After stirring at the same temperature until completion of the reaction (48 h) (monitored by HPLC, column B), the solvents were concentrated in vacuo. The residue was dissolved in ethyl acetate (10 ml) and washed successively with HCl 0.1 N and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to yield the expected dihydroxylated compound (1*R*,2*R*,4*R*,6*S*)-**13** as a colourless oil (43 mg, 0.14 mmol, 62% yield); $[\alpha]_D^{20} = -9$ ($c = 1.1$ in CH_3OH); t_R (HPLC, column B) 1.7 min; MS (ESI) *m/z* 306.3 [$(M + H)^+$]; ^{1}H NMR (400 MHz, CD_3OD, 25°C) δ 1.11–1.31 (m, 2H, CH_2), 1.32–1.75 (m, 5H, 2CH_2 and *H*CH), 1.88–2.20 (m, 2H, 3-*H*), 2.24–2.36 (br m, 1H, 6-*H*), 3.46 (dd, $J = 4.6$ and 11.2 Hz, 1H, *H*CH-OH), 3.54 (dd, $J = 4.1$ and 11.2 Hz, 1H, *H*CH-OH), 3.80 (br d, $J = 7.2$ Hz, 1H, 2-*H*), 4.89 (d, $J = 12.5$ Hz, 1H, *H*CHC_6H_5), 4.96 (d, $J = 12.5$ Hz, 1H, *H*CHC_6H_5), 7.17–7.25 (m, 5H, H-arom); ^{13}C NMR (100 MHz, CD_3OD, 25°C) δ 26.3 (4-*C*), 26.3 (*C*H_2), 30.5 (*C*H_2), 31.2 (*C*H_2), 39.0 (*C*H_2), 39.8 (6-C), 57.3 (1-*C*), 63.0 (*C*H_2OH), 67.0 (*C*$H_2C_6H_5$), 71.4 (2-*C*), 128.9, 128.9, 129.5 (*C*H-arom), 138.4 (*C*-arom), 157.1 (NH*C*OO); HRMS (ESI) calculated for $C_{17}H_{24}NO_4$ (MH^+) 306.1705, found 306.1705.

*(R)-1-(Benzyloxycarbonylamino)bicyclo[2.2.2]octane-2-carboxylic acid (**14**)*

To a stirred solution of the (*R*)-1-Aminobicyclo[2.2.2]octane-2-carboxylic acid (*R*)-**7** (110 mg, 0.65 mmol, 1 equiv) in a mixture of aqueous $NaHCO_3$ (164 mg, 1.95 mmol, 3 equiv) (2 ml) and THF (3 ml), was slowly added benzyl chloroformate (138 µl, 0.97 mmol, 1.5 equiv) at 0°C. After stirring for 12 h at room temperature, THF was eliminated at reduced pressure, the mixture was diluted with aqueous $NaHCO_3$ (10 ml) and washed with ethyl acetate (10 ml). The aqueous phase was acidified to pH 2 and extracted with (3 × 10 ml). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The expected pure compound (*R*)-**14** was obtained as a colourless oil after column chromatography on silica gel using dichloromethane/ethyl acetate 5/5 as eluent (173 mg, 0.57 mmol, 88% yield); $[\alpha]_D^{20} = -78$ ($c = 2.4$ in CH_2Cl_2); t_R (HPLC, column A) 9.3 min; MS (ESI) *m/z* 304.0

[(M + H)$^+$]; ^{1}H NMR (400 MHz, CD_3CN, 25°C) δ 1.50–80 (m, 7H, 4-H, 7-H, 2CH_2, HC*H*), 1.82–2.00 (m, 3H, CH_2, HC*H*), 2.28–2.38 (m, 1H, 7-H), 3.36 (ddd, J = 10.5 Hz, 6.2 Hz and 2.0 Hz, 1H, 2-H), 4.99 (d, J = 12.8 Hz, 1H, O*H*CHC$_6$H$_5$), 5.07 (d, J = 12.8 Hz, 1H, O*H*CHC$_6$H$_5$), 5.50 (s, 1H, N*H*) 7.30–7.42 (m, 5H, *H*-arom); ^{13}C NMR (100 MHz, CD_3CN, 25°C) δ 23.8 (4-*C*), 25.4, 25.5, 27.1, 29.7, 30.3 (3-*C*, 5-*C*, 6-*C*, 7-*C*, 8-*C*), 42.8 (2-*C*), 51.5 (1-*C*), 65.3 (O*C*H$_2$), 127.5, 127.7, 128.4 (*C*H-arom), 137.6 (*C*-arom), 154.9, 175.5 (*C*O); HRMS (ESI) calculated for $C_{17}H_{22}NO_4$ (MH$^+$) 304.1549, found 304.1550.

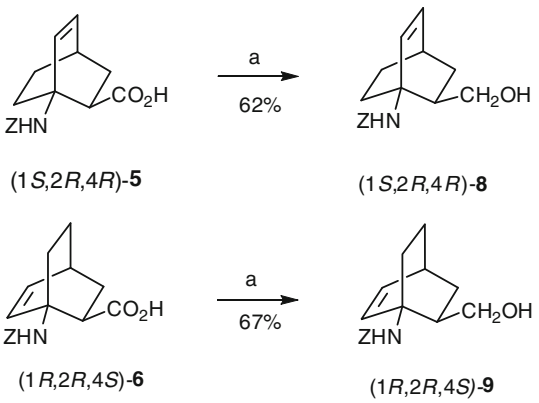
*(R)-1-(tert-Butyloxycarbonylamino)bicyclo[2.2.2]octane-2-carboxylic acid (**16**)*

(*R*)-1-Aminobicyclo[2.2.2]octane-2-carboxylic acid (*R*)-**7** (100 mg, 0.60 mmol, 1 equiv) was added to acetonitrile (50 ml) followed by trimethylammonium hydroxide (TMAH) (162 mg, 1.2 mmol, 1.5 equiv). After stirring for 2–3 h at room temperature (until a homogeneous mixture was obtained) the di-*tert*-butyldicarbonate (520 mg, 2.4 mmol, 4 equiv) was added. Stirring was continued for an additional 12 h at room temperature and acetonitrile was eliminated at reduce pressure. The residue was diluted with water (10 ml) and the aqueous layer was washed with ethyl acetate (10 ml), acidified to pH 3 and extracted with dichloromethane (3 × 10 ml). The organic layer was dried over Na_2SO_4 and concentrated in vacuo.

The expected pure compound (*R*)-**16** obtained as a white solid (131 mg, 0.49 mmol, 81% yield), was used without further purification; m. p. 124°C; $[\alpha]_D^{20} = -42$ (c = 1.1 in CH_2Cl_2); MS (ESI) *m/z* 270.2 [(M + H)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 1.42–1.55 (m, 10H, C(C*H*$_3$)$_3$ and *H*CH), 1.60–1.70 (m, 5H, 2CH_2 and *H*CH), 1.72–1.82 (m, 2H, CH_2), 1.88–2.12 (m, 2H, CH_2), 2.34–2.50 (m, 1H, 7-*H*), 3.28–3.44 (m, 1H, 2-*H*), 6.27 (br s, 1H, N*H*) 9.37 (br s, 1H, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ 23.6 (4-*C*), 25.7, 25.8 and 27.8 (3CH_2), 28.3(C(*C*H$_3$)$_3$), 29.6 (*C*H$_2$), 30.4 (7-*C*), 43.2 (2-*C*), 51.9 (1-*C*), 80.9 (*C*(CH$_3$)$_3$), 178.9 (*C*O); HRMS (ESI) calculated for $C_{14}H_{24}N_4O$ (MH$^+$) 270.1705, found 270.1702.

Results and discussion

The synthesis of the bicyclo amino alcohols **8** and **9** is reported in Scheme 1. Compound (1*S*,2*R*,4*R*)-**5** was converted into the corresponding N-Z bicyclic 1,3-amino alcohol (1*S*,2*R*,4*R*)-**8** using the method developed by McGeary (1998). Compound **5** was treated with BOP/DIEA to activate the carboxylic acid function and then rapidly reduced using $NaBH_4$ to provide the N-Z amino alcohol derivative (1*S*,2*R*,4*R*)-**8** in good yield.



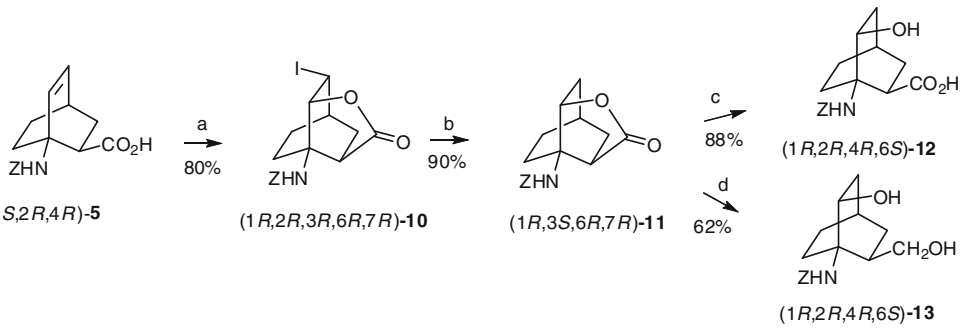
Scheme 1 Reagents and conditions: *a* BOP/DIEA/$NaBH_4$/THF

Starting from the compound (1*R*,2*R*,4*S*)-**6** a similar treatment yielded the N-Z bicyclic 1,3-amino alcohol (1*R*,2*R*,4*S*)-**9**. Structures of compounds **8** and **9** were characterized by ^{1}H and ^{13}C NMR and LC/MS analysis.

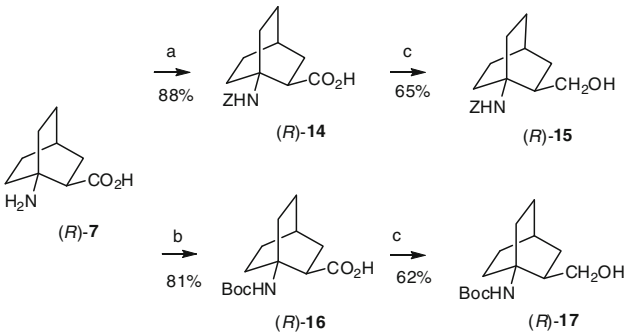
In a second set of experiments, we synthesized compounds **12** and **13** from the intermediate lactone **11** (Scheme 2). Stereoselective iodolactonisation was the first step of the synthesis of (1*R*,2*R*,4*R*,6*S*)-1-N-Z-amino-6-hydroxybicyclo[2.2.2]octane-2-carboxylic acid **12** and of the (1*R*,2*R*,4*R*,6*S*)-dihydroxylated compound **13**. The reaction of (1*S*,2*R*,4*R*)-N-Z-aminobicyclo[2.2.2]oct-5-ene-2-carboxylic acid **5** with I_2/KI in slightly alkaline conditions yielded the iodolactone (1*R*,2*R*,3*R*,6*R*,7*R*)-**10** with excellent regio- and stereoselectivity (Songis et al. 2008b). This iodolactone was isolated in pure form in 80% yield after column chromatography on silica gel. Compound **10** was then treated with tributyltin hydride and a catalytic amount of azobisisobutyronitrile at 80°C for 1 h under microwave activation. The corresponding lactone (1*R*,3*S*,6*R*,7*R*)-**11** was obtained in 85% yield. The hydroxyl β-amino acid (1*R*,2*R*,4*R*,6*S*)-**12** was obtained from compound **11** in good yield, using aqueous LiOH in THF at room temperature.

Furthermore, direct reduction of the lactone **11** using sodium borohydride yielded the dihydroxylated compound (1*R*,2*R*,4*R*,6*S*)-**13**. Compounds **10–13** were characterized by ^{1}H, ^{13}C NMR and LC/MS analyses.

In the last investigated pathway (Scheme 3), the amino group of the saturated (*R*)-1-aminobicyclo[2.2.2]octane-2-carboxylic acid (*R*)-**7** was first converted into its N-Z or *N*-Boc derivative (*R*)-**14** and (*R*)-**16,** respectively. The benzyloxycarbonyl group was introduced in good yield using conventional methods. On the other hand, for the N-*tert*-butoxycarbonyl protection of (*R*)-**7**, the efficient method developed for sterically hindered amino acid by Khalil et al. (1996) had to be used, to increase the low yield obtained when using standard conditions. Then, reduction of the carboxylic acid function with BOP/$NaBH_4$ yielded the enantiopure N-protected 1,3-amino alcohol (*R*)-**15** and (*R*)-**17** (Scheme 3).



Scheme 2 Reagents and conditions: *a* I_2, KI, $NaHCO_3$, DCM, H_2O, *b* Bu_3SnH/AIBN/toluene, *c* LiOH, THF, H_2O, rt, (*d*) $NaBH_4$/iPrOH/H_2O



Scheme 3 Reagents and conditions: *a* Benzylchloroformate/$NaHCO_3$/THF/H_2O, *b* Boc_2O/Me_3NHOH/THF/H_2O, *c* BOP/DIEA/$NaBH_4$/THF

Conclusions

In this study, we have established original syntheses of five enantiopure bicyclic 1,3-amino alcohols bearing an amino group at the bridgehead. Opposite enantiomers could be obtained by the same synthetic routes by using the chiral acrylate (*S*)-**1**. These syntheses constitute the first preparation of such compounds and further studies concerning their application are currently in progress.

Acknowledgments The authors gratefully acknowledge the CNRS and the MESR for their financial support.

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