Tetrahedron 68 (2012) 4438–4443

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Selective syntheses of novel highly functionalized β-aminocyclohexanecarboxylic acids

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ARTICLE INFO

Article history:
Received 4 October 2011
Received in revised form 24 November 2011
Accepted 21 December 2011
Available online 27 December 2011

Keywords:
Selective functionalization
β-Amino acid
Foldamer building block
Oxirane ring opening

ABSTRACT

Highly functionalized β-aminocyclohexanecarboxylate regio- and stereoisomers were synthetized from racemic unsaturated bicyclic β-lactams via enzymatic resolution, selective transformation of the C–C double bond by stereoselective epoxidation, and regioselective oxirane ring opening with azide or cyanide as nucleophile.

1. Introduction

Highly functionalized cyclic amino acids are an important class of bioactive compounds of increasing interest that have been a target of research in organic and medicinal chemistry during the past 10 years. Highly functionalized cyclic amino acids (e.g., oryzoxymycin,[1] tamiflu,[2] zanamivir and 2,3-didehydro-2-deoxy-*N*-acetylneuraminic acid[3]) exhibit strong antiviral, antifungal or antibacterial activities (Fig. 1). Modified derivatives[3b,d,4] and other multisubstituted cyclohexane amino acids[4a,5] have recently been at the focus of interest in synthetic and medicinal chemistry in view of their enormous pharmacological potential.

Stereoselective epoxidation of a functionalized cyclohexene ring and regioselective oxirane ring opening reactions are efficient and powerful strategies towards the synthesis of multifunctionalized cyclohexanes.[6,7] Stereoselective epoxidation and regioselective oxirane ring opening were earlier applied successfully for the synthesis of highly functionalized cyclohexane[8] or cyclopentane[9] amino acid derivatives.

2. Results and discussion

Our goal in the present work was the synthesis of highly functionalized β-aminocyclohexanecarboxylates, with the focus on the

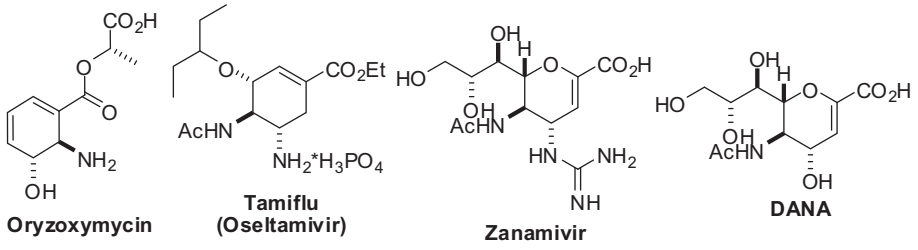

Fig. 1. Some highly functionalized bioactive cyclic amino acids.

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doi:10.1016/j.tet.2011.12.065

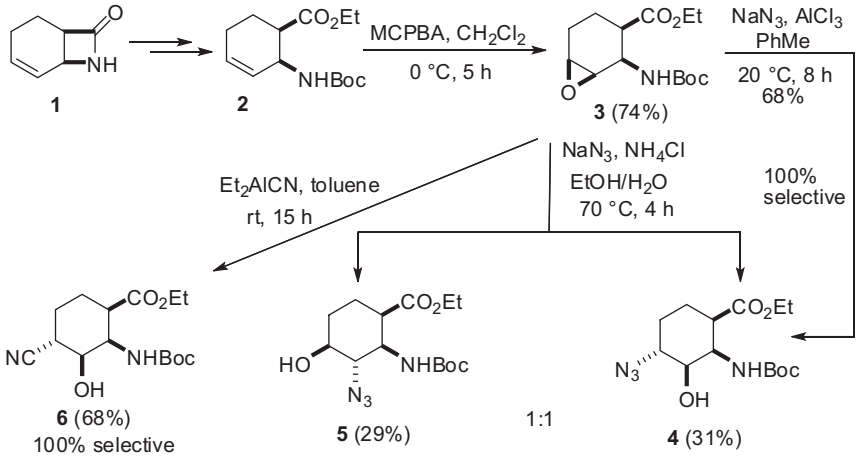
stereoselective epoxidation of the cyclohexene ring C–C double bond, followed by regioselective oxirane ring opening with azide or cyanide as nucleophile.

In the first part of our investigation, in order to synthetize multifunctionalized cyclohexanecarboxylic acids, β-amino-cyclohexenecarboxylate **2** derived from bicyclic lactam **1** was subjected to epoxidation with *m*-chloroperbenzoic acid (MCPBA), which furnished *cis*-selectively amino ester epoxide **3**[8,9] in 74% isolated yield. An azido function was introduced onto the ring of the β-amino ester with NaN_3 in $EtOH/H_2O$ in the presence of NH_4Cl at 70 °C. The azide attack occurred on both C-3 and C-4, giving the azido ester regioisomers **4** (31%) and **5** (29%) in approximately 1:1 ratio (^1H NMR) (Scheme 1). The structures of **4** and **5** were determined by evaluating their 2D COSY and HSQC spectra besides the ^1H NMR and ^{13}C NMR data.

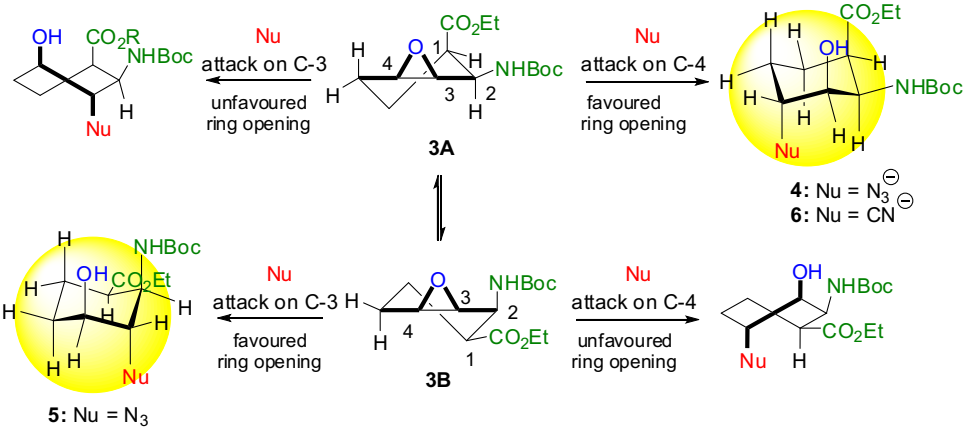
As a result of the conformational equilibrium of **3A** (with NHBoc equatorial and CO_2Et axial) and **3B** (with CO_2Et equatorial and NHBoc axial),[8d] the oxirane ring opens via the trans-diaxial chair conformation at both C-3 and C-4, leading to azido esters **4** and **5** (Scheme 2). Oxirane ring opening of **3** with NaN_3 was accomplished by carrying out the reaction in toluene at room temperature with 1 equiv of $AlCl_3$ as additive. Interestingly, the reaction proceeded 100% regioselectively, with the azide attack occurring on C-4, yielding azido aminocyclohexanecarboxylate **4** as the sole product (Scheme 1). This regioselectivity of the oxirane ring opening may be explained by the diaxial chair conformation being favoured during the nucleophile attack. In the presence of $AlCl_3$, most probably due to the ability of Al to coordinate to the oxirane *O*-atom and the ester carbonyl *O*-atom (C]O group), the conformational equilibrium **3A**–**3B** is shifted towards **3A**. Azide attack on C-4 in the oxirane leads to a favoured ring opening since it generates a trans-diaxial chair conformation. In contrast, attack on C-3 would contribute to a trans-diaxial twisted chair conformation, which explains why the 3-azido derivative is not formed under the latter conditions (Scheme 2).

Selective introduction of a nitrile function onto the cyclohexane skeleton in epoxyamino ester **3** was achieved on treatment with Et_2AlCN in toluene at room temperature. As a result of the coordinating ability of Al with the carbonyl *O*-atom and oxirane *O*-atom, the favoured nitrile attack on the preferred conformer **3A** resulted 100% regioselectively in the corresponding 4-cyano-substituted amino ester **6** in 68% yield (Scheme 1).

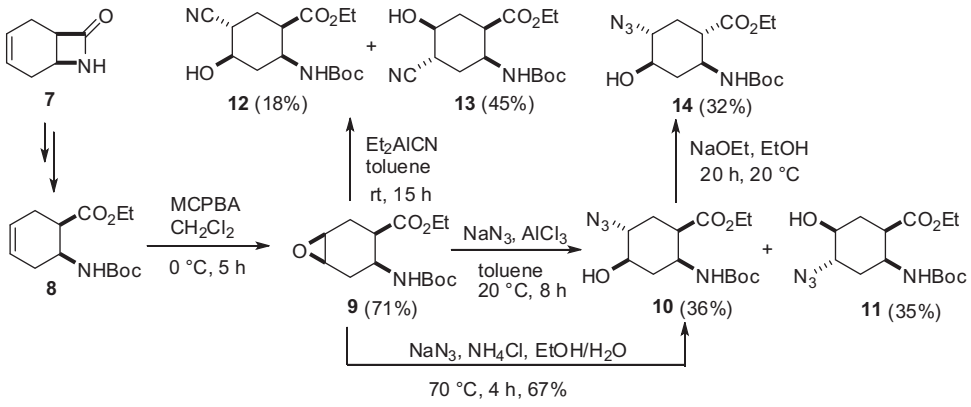
In order to synthetize other novel highly functionalized β-aminocyclohexanecarboxylate stereoisomers, we investigated the transformation through selective epoxidation and oxirane ring opening of bicyclic β-lactam **7**, a regioisomer of **1**. Epoxyamino ester **9** prepared from lactam **7** via *N*-Boc ester **8** was regioselectively transformed on treatment with NaN_3/NH_4Cl in $EtOH/H_2O$ at 70 °C to 5-azido-substituted aminocyclohexanecarboxylate **10** in 67% yield (Scheme 3). The 100% regioselectivity of this transformation is a result of the shifted conformational equilibrium from **9B** to **9A**, in which NHBoc has an axial arrangement[8c,d] and whose oxirane ring opening at C-5 led through the trans-diaxial chair conformation to



Scheme 1.



Scheme 2.



Scheme 3.

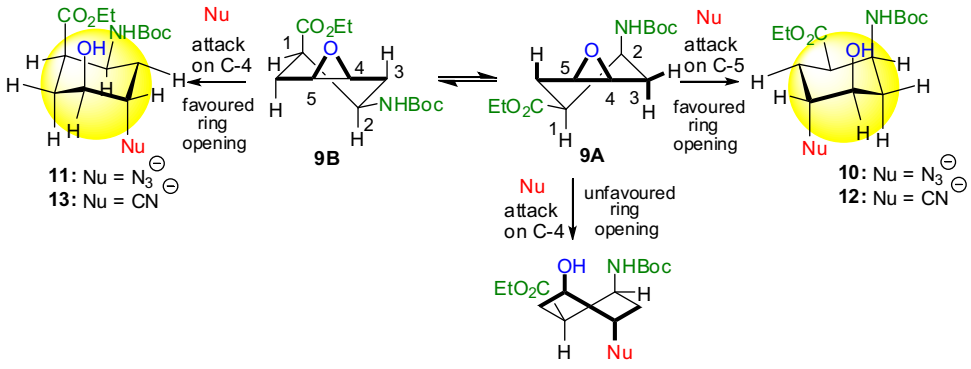
azido ester **10**. Azide attack on C-4 in **9A** under these conditions would generate an unfavoured trans-diaxial twisted chair conformation (Scheme 4).

On change of the oxirane ring opening reaction conditions to $NaN_3/AlCl_3$/toluene (considering the coordinating capability of Al, with an increased contribution of **9B**), due to the conformational equilibrium **9A**–**9B**, the azide attack on both C-4 and C-5 is favoured, and azido esters **10** and **11** were formed in approximately 1:1 ratio (^1H NMR) (Schemes 3 and 4).

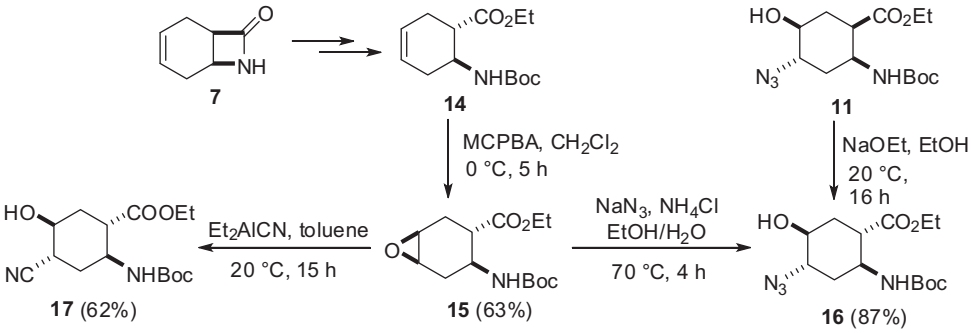
In the presence of Et_2AlCN, both conformational arrangements **9A** and **9B** contribute, while nitrile attack can occur on C-4 and C-5, affording the nitrile-substituted β-aminocyclohexanecarboxylates **12** and **13** in 1:2.5 ratio (Scheme 3). A new azido ester stereoisomer **14** could be prepared from **10** by epimerization with NaOEt in EtOH (Scheme 3).

Epoxyamino ester **15** derived from lactam **7**, in which the carboxylate and amino moieties are in a trans relationship, offered a possibility for the synthesis of other novel multifunctionalized β-aminocyclohexanecarboxylic ester isomers.

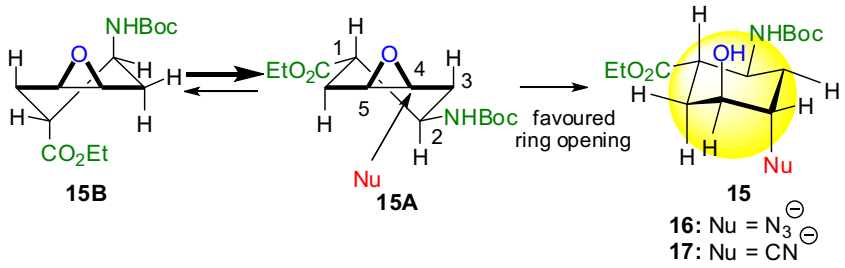
Opening of the oxirane ring in amino ester **15** with either NaN_3/NH_4Cl/EtOH or Et_2AlCN as nucleophile afforded aminocyclohexanecarboxylic ester **16** or **17** 100% regioselectively with the N_3 or CN group in position-4 (Scheme 5). Since the diequatorial (carboxylate and carbamate) arrangement predominates as the favoured conformation of **15**, attack of the nucleophile through the trans-diaxial chair conformation will be preferred on C-4 (Scheme 6). It is noteworthy that the oxirane ring opening of **15** in the $NaN_3/AlCl_3$/toluene system gave, as expected, azido ester **16**, which could also be prepared by epimerization at C-1 from the earlier synthetized *cis*-amino ester **11** (Scheme 5).



Scheme 4.



Scheme 5.



Scheme 6.

The synthetic procedures for the synthesis of azido or nitrile-substituted 2-aminocyclohexanecarboxylate regio- and stereoisomers were extended to the preparation of these multifunctionalized cyclohexanes in enantiomerically pure form. The syntheses were accomplished by starting from enantiopure β-aminocyclohexenecarboxylic acid (+)-**18**. For this purpose, the racemic bicyclic β-lactam **1** was first subjected to enzymatic resolution with CAL-B in *t*-BuOMe to yield optically pure amino acid (+)-**18**. This was converted by esterification with EtOH/$SOCl_2$ via (+)-**19**, followed by *N*-Boc protection, to (+)-**2**. The amino ester was then functionalized by selective epoxidation, followed by oxirane ring opening. On treatment with NaN_3/NH_4Cl in EtOH/H_2O, epoxyamino ester (+)-**3** afforded enantiomerically pure azido ester stereoisomers (−)-**4** and (+)-**5** in 38% and 34% yields, respectively (Scheme 7).

When subjected to reaction with Et_2AlCN, epoxyamino ester enantiomer (+)-**3** underwent regioselective oxirane ring opening to give the 4-cyano-substituted β-amino ester enantiomer (−)-**6** in 59% yield (Scheme 7).

In conclusion, a series of highly functionalized β-aminocyclohexanecarboxylate stereo- and regioisomers containing new stereogenic centres were efficiently synthetized by diastereoselective epoxidation and regioselective oxirane ring opening with azide or cyanide as nucleophile. Since these substituents may be regarded as masked amines or carboxylates, the synthesis might furnish orthogonally protected diaminocyclohexanecarboxylates or aminocyclohexanedicarboxylates, respectively. In view of the considerable importance of multifunctionalized cyclic amino acid derivatives, the compounds synthetized in this work may be of value as precursors for potentially pharmacologically active products.

3. Experimental

3.1. General

The epoxidation reactions were performed according to the earlier-published procedures.[8c,d]

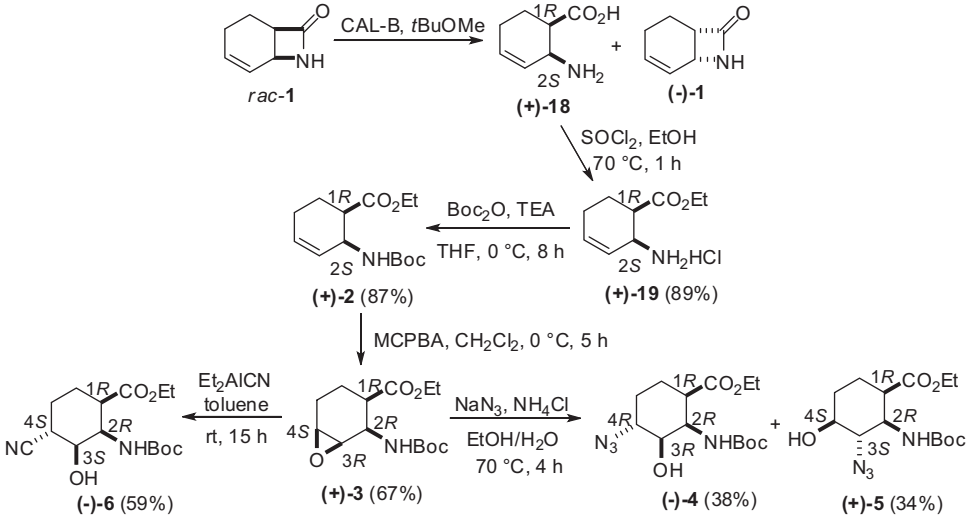
3.2. General procedure for the azidolysis of epoxyamino esters

Method A: To a solution of epoxiamino ester (2 mmol) in EtOH (20 mL), NaN_3 (4 mmol), H_2O (1 mL) and NH_4Cl (40 mg) were added. The mixture was then stirred at 70 °C for 4 h and concentrated at reduced pressure. The residue was taken up in EtOAc (25 mL) and washed with water (2×15 mL). The organic layer was next dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (*n*-hexane/acetone 4:1).

Method B: To a solution of epoxyamino ester (2 mmol) in dry toluene (20 mL), NaN_3 (4 mmol) and $AlCl_3$ (2 mmol) were added and the mixture was stirred at 20 °C for 8 h. It was then diluted with CH_2Cl_2 (25 mL) and washed with water (2×15 mL). The organic layer was next dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (*n*-hexane/acetone 4:1).

3.3. General procedure for oxirane ring opening with nitrile

To a solution of epoxyamino ester (2 mmol) in dry toluene (15 mL), a 50% solution of Et_2AlCN (2.2 mmol) in toluene was added and the mixture was stirred at 20 °C for 15 h. Water (5 mL) was



Scheme 7.

then added and the mixture was extracted with CH_2Cl_2 (2×15 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc 3:1).

3.3.1. Ethyl (1R,2R*,3R*,4S*)-2-(tert-butoxycarbonylamino)-3,4-epoxycyclohexanecarboxylate [(±)-**3**].* White solid; mp 87–90 °C; yield: 74%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.29 (t, 3H, CH_3, J=7.20 Hz), 1.46 (s, 9H, CH_3), 1.50–1.56 (m, 1H, CH_2), 1.74–1.80 (m, 2H, CH_2), 2.12–2.21 (m, 1H, CH_2), 2.45–2.50 (m, 1H, H-1), 3.29–3.38 (m, 2H, H-3 and H-4), 4.11–4.20 (m, 2H, OCH_2), 5.52–5.56 (m, 1H, H-2), 5.63 (br s, 1H, N–H); ^{13}C NMR (400 MHz, DMSO): δ=14.8, 17.3, 24.0, 29.0, 43.4, 45.9, 53.7, 54.0, 60.6, 78.9, 155.7, 172.7. IR (KBr): ν_{max} 1161, 1514, 1718, 1731, 2954, 2981, 3357. Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.70; H, 7.82; N, 4.65.

3.3.2. Ethyl (1R,2R*,3R*,4R*)-4-azido-2-(tert-butoxycarbonylamino)-3-hydroxycyclohexane carboxylate [(±)-**4**].* White solid; mp 89–90 °C; yield: 31% or 68% (see Scheme 1). ^{1}H NMR (400 MHz, DMSO): δ=1.18 (t, 3H, CH_3, J=7.20 Hz), 1.47 (s, 9H, CH_3), 1.49–1.57 (m, 1H, CH_2), 1.70–1.78 (m, 2H, CH_2), 2.50–2.57 (m, 2H, CH_2 and H-1), 3.48–3.54 (m, 1H, H-3), 3.59–3.66 (m, 1H, H-4), 3.98–4.12 (m, 2H, OCH_2), 4.30–4.38 (m, 1H, H-2), 5.29 (br s, 1H, O–H), 6.53 (br s, 1H, N–H); ^{13}C NMR (400 MHz, DMSO): δ=14.8, 21.0, 29.0, 29.1, 45.1, 53.9, 60.6, 61.5, 73.9, 78.5, 156.5, 172.8. MS: (ESI) m/z=351 (M+23). IR (KBr): ν_{max}: 1532, 1700, 1720, 2109, 2982, 3368, 3458. Anal. Calcd for $C_{14}H_{24}N_4O_5$: C, 51.21; H, 7.37; N, 17.06. Found: C, 51.40; H, 7.08; N, 16.86.

3.3.3. Ethyl (1R,2R*,3S*,4S*)-3-azido-2-(tert-butoxycarbonylamino)-4-hydroxycyclohexanecarboxylate [(±)-**5**].* White solid; mp 88–90 °C; yield: 29%. ^{1}H NMR (400 MHz, DMSO): δ=1.19 (t, 3H, CH_3, J=7.20 Hz), 1.46 (s, 9H, CH_3), 1.52–1.81 (m, 4H, CH_2), 2.95–3.00 (m, 1H, H-1), 3.25–3.45 (m, 2H, H-2 and H-4), 3.61–3.68 (m, 1H, H-3), 4.08–4.16 (m, 2H, OCH_2), 5.36 (br s, 1H, O–H), 6.98 (br s, 1H, N–H); ^{13}C NMR (400 MHz, DMSO): δ=14.9, 23.7, 29.1, 30.1, 43.9, 52.9, 60.8, 66.9, 72.9, 78.9, 155.8, 173.4. MS: (ESI) m/z=351 (M+23). IR(KBr): ν_{max} 1515, 1693, 1725, 2099, 2934, 2981, 3378. Anal. Calcd for $C_{14}H_{24}N_4O_5$: C, 51.21; H, 7.37; N, 17.06. Found: C, 50.92; H, 7.02; N, 16.88.

3.3.4. Ethyl (1R,2R*,3S*,4S*)-2-(tert-butoxycarbonylamino)-4-cyano-3-hydroxycyclohexanecarboxylate [(±)-**6**].* White solid; mp 185–187 °C; yield: 68%. ^{1}H NMR (400 MHz, DMSO): δ=1.18 (t, 3H, CH_3, J=7.15 Hz), 1.40 (s, 9H, CH_3), 1.45–1.60 (m, 3H, CH_2), 1.81–1.90 (m, 1H, CH_2), 2.58–2.63 (m, 1H, H-1), 2.92–2.99 (m, 1H, H-4), 3.58–3.63 (m, 1H, H-3), 3.95–4.01 (m, 2H, OCH_2), 4.36–4.41 (m, 1H, H-2), 5.52 (br s, 1H, O–H), 6.62 (br s, 1H, N–H); ^{13}C NMR (400 MHz, DMSO): δ=14.8, 20.8, 27.0, 29.1, 31.5, 44.9, 52.9, 60.7, 70.3, 78.6, 122.9, 158.0, 172.5. MS: (ESI) m/z=335 (M+23). IR (KBr): ν_{max} 1532, 1700, 1718, 2246, 2981, 3363, 3456. Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.42; H, 7.52; N, 8.67.

3.3.5. Ethyl (1R,2S*,4R*,5S*)-2-(tert-butoxycarbonylamino)-4,5-epoxycyclohexanecarboxylate [(±)-**9**].* Colourless oil; yield: 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.30 (t, 3H, CH_3, J=7.20 Hz), 1.44 (s, 9H, CH_3), 2.08–2.31 (m, 3H, CH_2), 2.45–2.53 (m, 1H, CH_2), 2.60–2.67 (m, 1H, H-1), 3.20–3.23 (m, 2H, H-4 and H-5), 4.06–4.11 (m, 1H, H-2), 4.13–4.26 (m, 2H, OCH_2), 5.53 (br s, 1H, N–H); ^{13}C NMR (400 MHz, DMSO): δ=14.7, 24.1, 29.0, 29.5, 46.1, 48.2, 51.1, 52.2, 60.8, 79.0, 155.0, 173.1. IR (KBr): ν_{max} 1161, 1515, 1718, 1731, 2954, 2981, 3358. Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.72; H, 7.89; N, 4.59.

3.3.6. Ethyl (1R,2S*,4R*,5R*)-5-azido-2-(tert-butoxycarbonylamino)-4-hydroxycyclohexanecarboxylate [(±)-**10**].* White solid; mp 68–70 °C; yield: 36% or 67% (see Scheme 3). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.33 (t, 3H, CH_3, J=7.20 Hz), 1.46 (s, 9H, CH_3), 1.63–1.70 (m, 1H, CH_2), 1.80–1.89 (m, 1H, CH_2), 2.08–2.15 (m, 1H, CH_2), 2.40–2.43 (m, 1H, CH_2), 2.93–2.99 (m, 1H, H-1), 2.40–2.46 (m, 1H, H-2), 3.61–3.68 (m, 1H, H-5), 3.80–3.96 (m, 1H, H-4), 4.19–4.27 (m, 2H, OCH_2), 5.56 (br s, 1H, N–H); ^{13}C NMR (400 MHz, DMSO): δ=14.9, 29.0, 35.7, 39.9, 42.3, 48.6, 60.9, 63.1, 71.5, 78.7, 155.6, 173.3. MS: (ESI) m/z=351 (M+23). IR (KBr): ν_{max} 1525, 1659, 1720, 2102, 2983, 3357, 3376. Anal. Calcd for $C_{14}H_{24}N_4O_5$: C, 51.21; H, 7.37; N, 17.06. Found: C, 50.90; H, 7.01; N, 16.89.

3.3.7. Ethyl (1R,2S*,4S*,5S*)-4-azido-2-(tert-butoxycarbonylamino)-5-hydroxycyclohexanecarboxylate [(±)-**11**].* White solid; mp 134–136 °C, yield: 35%. ^{1}H NMR (400 MHz, DMSO): δ=1.20 (t, 3H, CH_3, J=7.4 Hz), 1.36 (s, 9H, *t*-Bu), 1.73–2.04 (m, 4H, CH_2), 2.68–2.80 (m, 1H, H-1), 3.34–3.42 (m, 1H, H-5), 3.84–4.01 (m, 2H, OCH_2), 4.04–4.09 (m, 1H, H-4), 4.16–4.21 (m, 1H, H-2), 5.17 (br s, 1H, O–H), 7.00 (br s, 1H, N–H); ^{13}C NMR (400 MHz, DMSO): δ=14.8, 29.0, 31.9, 32.0, 44.3, 48.4, 60.7, 63.1, 73.2, 78.7, 155.8, 172.4. MS: (ESI) m/z=351 (M+23). IR (KBr): ν_{max} 1522, 1700, 1717, 2102, 2975, 3353. Anal. Calcd for $C_{14}H_{24}N_4O_5$: C, 51.21; H, 7.37; N, 17.06. Found: C, 50.86; H, 7.04; N, 17.30.

3.3.8. Ethyl (1R,2S*,4R*,5S*)-2-(tert-butoxycarbonylamino)-5-cyano-4-hydroxycyclohexanecarboxylate [(±)-**12**].* White solid; mp 136–138 °C; yield: 18%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24 (t, 3H, CH_3, J=7.20 Hz), 1.42 (s, 9H, CH_3), 1.80–1.89 (m, 2H, CH_2), 2.18–2.24 (m, 1H, CH_2), 2.42–2.55 (m, 1H, CH_2), 2.71–2.79 (m, 1H, H-1), 2.98–3.03 (m, 1H, H-5), 3.91–3.99 (m, 2H, H-2 and H-4), 4.20–4.28 (m, 2H, OCH_2), 5.52 (br s, 1H, N–H); ^{13}C NMR (400 MHz, $CDCl_3$): δ=14.5, 28.7, 34.1, 36.5, 36.7, 42.5, 58.4, 61.7, 69.6, 80.2, 121.6, 158.2, 170.6. MS: (ESI) m/z=335 (M+23). IR (KBr): ν_{max} 1525, 1683, 1716, 2252, 2977, 3358, 3452. Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.40; H, 7.98; N, 8.65.

3.3.9. Ethyl (1R,2S*,4R*,5S*)-2-(tert-butoxycarbonylamino)-4-cyano-5-hydroxycyclohexanecarboxylate [(±)-**13**].* White solid; mp 172–174 °C; yield: 45%. ^{1}H NMR (400 MHz, DMSO): δ=1.18 (t, 3H, CH_3, J=7.15 Hz), 1.39 (s, 9H, CH_3), 1.61–1.90 (m, 4H, CH_2), 2.63–2.74 (m, 1H, H-1), 2.83–2.90 (m, 1H, H-4), 3.52–3.60 (m, 1H, H-5), 3.95–4.02 (m, 2H, OCH_2), 4.15–4.21 (m, 1H, H-2), 5.50 (br s, 1H, O–H), 7.01 (br s, 1H, N–H); ^{13}C NMR (400 MHz, $CDCl_3$): δ=14.8, 29.0, 31.7, 32.5, 33.8, 44.2, 43.0, 60.7, 69.3, 78.4, 122.8, 156.0, 172.3. MS: (ESI) m/z=335 (M+23). IR (KBr): ν_{max} 1521, 1701, 1710, 2252, 2975, 3348, 3479. Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.96; H, 7.50; N, 8.69.

3.3.10. Ethyl (1S,2S*,4R*,5S*)-2-(tert-butoxycarbonylamino)-3,4-epoxycyclohexanecarboxylate [(±)-**15**].* White solid; mp 96–98 °C; yield: 63%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.29 (t, 3H, CH_3, J=7.20 Hz), 1.46 (s, 9H, CH_3), 1.90–1.99 (m, 1H, CH_2), 2.21–2.26 (m, 2H, CH_2), 2.33–2.42 (m, 1H, CH_2), 2.68–2.74 (m, 1H, H-1), 3.20–3.23 (m, 1H, H-4), 3.28–3.32 (m, 1H, H-5), 4.03–4.09 (m, 1H, H-2), 4.14–4.23 (m, 2H, OCH_2), 5.14 (br s, 1H, N–H); ^{13}C NMR (400 MHz, $CDCl_3$): δ=15.5, 24.4, 28.7, 29.1, 41.7, 46.4, 51.6, 52.1, 61.3, 79.8, 156.8, 173.5. IR (KBr): ν_{max} 1161, 1514, 1716, 1731, 2954, 2981, 3350. Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.70; H, 7.84; N, 4.55.

3.3.11. Ethyl (1S,2S*,4S*,5S*)-4-azido-2-(tert-butoxycarbonylamino)-5-hydroxycyclohexanecarboxylate [(±)-**16**].* Colourless oil; yield: 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.29 (t, 3H, CH_3, J=7.20 Hz), 1.47 (s, 9H, CH_3), 1.80–1.88 (m, 1H, CH_2), 1.98–2.06 (m, 2H, CH_2), 2.21–2.28 (m, 1H, CH_2), 2.80–2.88 (m, 1H, H-1), 3.35–3.70 (m, 1H, H-2), 3.82–3.89 (m, 1H, H-4), 4.09–4.14 (m, 1H, H-5), 4.14–4.23 (m, 2H, OCH_2), 4.67 (br s, 1H, N–H); ^{13}C NMR (400 MHz, DMSO): δ=14.9, 29.0, 31.3, 31.6, 43.7, 46.8, 60.8, 62.3, 66.7, 78.5, 155.6, 174.0. MS: (ESI) m/z=351 (M+23). IR (KBr): ν_{max} 1528, 1700, 1719, 2105, 2934, 2980, 3374. Anal.

Calcd for $C_{14}H_{24}N_4O_5$: C, 51.21; H, 7.37; N, 17.06. Found: C, 50.89; H, 7.01; N, 16.88.

3.3.12. Ethyl (1S,2S*,4R*,5S*)-2-(tert-butoxycarbonylamino)-4-cyano-5-hydroxycyclohexanecarboxylate [(±)-**17**].* Colourless oil; yield: 62%. ^{1}H NMR (400 MHz, DMSO): δ=1.18 (t, 3H, CH_3, J=7.15 Hz), 1.36 (s, 9H, CH_3), 1.62–2.00 (m, 4H, CH_2), 2.65–2.70 (m, 1H, H-1), 2.98–3.03 (m, 1H, H-4), 3.70–3.76 (m, 1H, H-2), 3.89–3.94 (m, 1H, H-5), 4.01–4.12 (m, 2H, OCH_2), 5.45 (br s, 1H, O–H), 6.51 (br s, 1H, N–H); ^{13}C NMR (400 MHz, DMSO): δ=14.9, 29.1, 32.7, 32.8, 33.2, 43.5, 47.6, 60.9, 64.7, 78.7, 121.7, 158.0, 173.8. MS: (ESI) m/z=335 (M+23). IR (KBr): ν_{max} 1528, 1716, 1720, 2244, 2937, 2980, 3376. Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.41; H, 7.49; N, 8.65.

3.4. Characterization of the enantiomers

The ee values for **4** and **5** were determined by using HPLC on a Chiralpak IA 5μ column (0.4 cm×1 cm), for **4** (enantiomer, ee 98%) [mobile phase: *n*-hexane/2-propanol (95:5); flow rate 0.5 mL min^{-1}; detection at 205 nm; retention time (min): 46.65 (antipode: 44.75)]; for **5** (enantiomer, ee 98%) [mobile phase: *n*-hexane/2-propanol (90:10); flow rate 0.5 mL min^{-1}; detection at 205 nm; retention time (min): 15.59 (antipode: 19.85)].

The ee value for **6** (99%) was determined by using GC on a Chromopack Chiralsil-Dex CB column (25 m) after derivatization with hexanoic anhydride in the presence of pyridine containing 10% DMAP [190 °C; 140 kPa; retention time (min): 30.89].

*3.4.1. Ethyl (1R,2S)-2-aminocyclohex-3-enecarboxylate hydrochloride [(+)-**19**].* White solid; mp 155–159 °C; yield: 89%. $[\alpha]_D^{25}$ +108 (*c* 0.38, EtOH).

*3.4.2. Ethyl (1R,2S)-2-(tert-butoxycarbonylamino)cyclohex-3-enecarboxylate [(+)-**2**].* White solid; mp 64–65 °C (*n*-hexane); yield: 87%. $[\alpha]_D^{25}$ +178 (*c* 0.35, EtOH).

*3.4.3. Ethyl (1R,2R,3R,4S)-2-(tert-butoxycarbonylamino)-3,4-epoxycyclohexanecarboxylate [(+)-**3**].* A white solid; mp 85–87 °C (*n*-hexane); yield: 67%. $[\alpha]_D^{25}$ +40 (*c* 0.7, EtOH).

*3.4.4. Ethyl (1R,2R,3R,4R)-4-azido-2-(tert-butoxycarbonylamino)-3-hydroxycyclohexanecarboxylate [(−)-**4**].* White solid; mp 84–86 °C (*n*-hexane); yield: 38%. $[\alpha]_D^{25}$ −29 (*c* 2.2, EtOH).

*3.4.5. Ethyl (1R,2R,3S,4S)-3-azido-2-(tert-butoxycarbonylamino)-4-hydroxycyclohexanecarboxylate [(+)-**5**].* A white solid; mp 90–92 °C (*n*-hexane); yield: 34%. $[\alpha]_D^{25}$ +1.8 (*c* 1.3, EtOH).

*3.4.6. Ethyl (1R,2R,3S,4S)-2-(tert-butoxycarbonylamino)-4-cyano-3-hydroxycyclohexanecarboxylate [(−)-**6**].* White solid; mp 183–186 °C (*n*-hexane); yield: 59%. $[\alpha]_D^{25}$ −55.7 (*c* 1.1, EtOH).

Acknowledgements

We are grateful to the Hungarian Research Foundation (OTKA No. T81371) for financial support and acknowledge the receipt of Bolyai János Fellowships for L.K. and E.F. We also thank TÁMOP-4.2.1/B-09/1/KONV-2010-0005.

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