Tetrahedron: *Asymmetry* 20 (2009) 2220–2225

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Efficient synthesis of 3,4- and 4,5-dihydroxy-2-amino-cyclohexanecarboxylic acid enantiomers

Gabriella Benedek [a], Márta Palkó [a], Edit Wéber [a], Tamás A. Martinek [a], Enikő Forró [a], Ferenc Fülöp [a,b,*]

[a] *Institute of Pharmaceutical Chemistry, University of Szeged, H-6720 Szeged, Eötvös utca 6, Hungary*
[b] *Stereochemistry Research Group of the Hungarian Academy of Sciences, University of Szeged, H-6720 Szeged, Eötvös utca 6, Hungary*

ARTICLE INFO

Article history:
Received 23 July 2009
Accepted 2 September 2009
Available online 25 September 2009

ABSTRACT

An efficient method for the synthesis of (1*S*,2*R*,4*R*,5*S*)- and (1*R*,2*R*,4*R*,5*S*)-2-amino-4,5-dihydroxycyclohexanecarboxylic acids (−)-**6** and (−)-**9** and (1*R*,2*R*,3*S*,4*R*)- and (1*S*,2*R*,3*S*,4*R*)-2-amino-3,4-dihydroxycyclohexanecarboxylic acids (−)-**15** and (−)-**18** was developed by using the OsO_4-catalyzed oxidation of Boc-protected (1*S*,2*R*)-2-aminocyclohex-4-enecarboxylic acid (+)-**2** and (1*R*,2*S*)-2-aminocyclohex-3-enecarboxylic acid (+)-**11**. Good yields were obtained. The stereochemistry of the synthesized compounds was proven by NMR spectroscopy.

1. Introduction

Alicyclic β-amino acids[1,2] derived from β-lactams[3,4] have attracted the interest of a number of synthesis research groups as a consequence of their useful biological effects and occurrence in many pharmacologically relevant compounds.[5] Peptides containing β-amino acids can increase and modify biological activities and are not degradable by proteases, which can lead to peptide-based synthetic targets.[6] These compounds can be found in natural products, for example, cispentacin, (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid, an antifungal antibiotic, as is amipurimycin, which was isolated from *Streptomyces novoguineensis*.[5,7–9] The synthetic 4-methylene derivative of cispentacin (Icofungipen, PLD-118) is active in vitro against *Candida* species.[10,11] In recent years, the preparation of enantiopure β-amino acids has come into the foreground of interest, because of their widespread use in peptide, heterocyclic and combinatorial chemistries and drug research.[12–15]

Among the β-amino acids, the hydroxy-functionalized derivatives are of considerable importance in medicinal chemistry, because they occur in many important products, such as paclitaxel (Taxol) and docetaxel (Taxotere), which have chemotherapeutic effects.[16–18] Some cyclic hydroxylated β-amino acid derivatives have antibiotic (oryzoxymycin)[19–22] or antifungal activities, and are used as building blocks for pharmaceutically significant natural substances.[23]

A number of methods have recently been published for the stereoselective introduction of a mono-hydroxy functionality onto the cyclohexane or cyclopentane ring, for example, by iodolactonization of *cis*- and *trans*-2-aminocyclohexenecarboxylic acids or *cis*- and *trans*-2-aminocyclopentenecarboxylic acids, or via the corresponding dihydrooxazine or oxazoline derivatives.[24–29] Another method involves the hydroxylation of the 2-aminocyclohexenecarboxylic acid by functionalization of the olefinic bond through epoxidation.[29–31]

The OsO_4-catalyzed dihydroxylation of olefins provides one of the most efficient methods for the preparation of vicinal diols.[32–38] The $KMnO_4$-induced oxidation of the double bond is another well-known route to dihydroxy derivatives.[39]

Our present aim was the dihydroxylation of the olefinic bond of enantiopure and racemic, *cis*- and *trans*-2-amino-4-cyclohexenecarboxylic acids and *cis*- and *trans*-2-amino-3-cyclohexenecarboxylic acids, and the structural analysis of the new dihydroxy-substituted derivatives.

2. Results and discussion

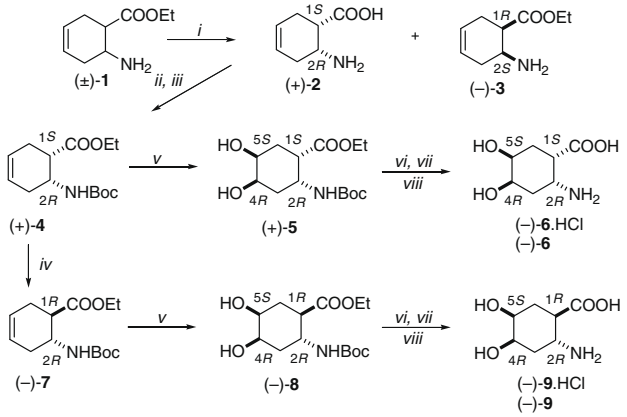
The starting (1*S*,2*R*)-2-aminocyclohex-4-enecarboxylic acid (+)-**2** and (1*R*,2*S*)-2-aminocyclohex-3-enecarboxylic acid (+)-**11** were synthesized from β-amino ester (±)-**1** and β-lactam (±)-**10** by highly enantioselective CAL-B-catalyzed hydrolysis with one equivalent of H_2O in *i*-Pr_2O at 65 °C.[40,41] The enantiopure amino acids (+)-**2** and (+)-**11** (ee >99%) were esterified in the presence of EtOH and $SOCl_2$ to give amino ester hydrochlorides, which were reacted with *tert*-butoxy pyrocarbonate to afford the *N*-Boc-protected amino esters (+)-**4** and (+)-**13**, respectively (Schemes 1 and 2).

The isomerization of (+)-**4** and (+)-**13** with NaOEt at room temperature resulted in *trans*-*N*-Boc amino esters (−)-**7** and (+)-**16**. The *trans*-configuration was confirmed by the NOE signal of relatively low intensity between H-1 and H-2 and the large ^3J(H-1, H-2) coupling at around 9–10 Hz.

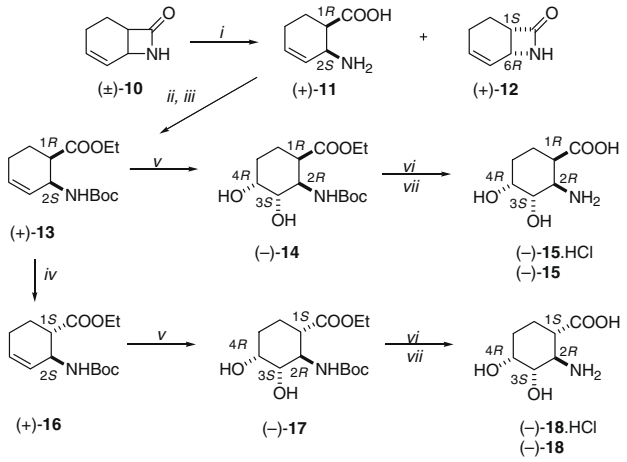
Dihydroxylation of protected esters (+)-**4**, (−)-**7** and (+)-**13**, (+)-**16** with a catalytic amount of OsO_4 and 4-methylmorpholine

* Corresponding author. Tel.: +36 62 545562; fax: +36 62 545705.
E-mail address: fulop@pharm.u-szeged.hu (F. Fülöp).

0957-4166/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.09.001



Scheme 1. Reagents and conditions: (i) CAL-B, H_2O (1 equiv), *i*-Pr_2O, 65 °C; (ii) $SOCl_2$, EtOH, 0 °C–Δ, 97%; (iii) Et_3N, Boc_2O, CH_2Cl_2, 2 h, rt, 89%; (iv) NaOEt, EtOH, 24 h, rt, 43%; (v) 2.0 w/w% OsO_4 solution in *t*-BuOH, NMO, acetone, 4 h, rt, 78–85%; (−)-**6**·HCl, (−)-**9**·HCl: (vi) LiOH, H_2O/THF, rt, 5 h, 92–96%; (vii) 10% HCl/H_2O, 24 h, Δ, 45–47%; (−)-**6**, (−)-**9**; (viii) microwave irradiation, H_2O, 150 °C, 1 h, 70–77%.



Scheme 2. Reagents and conditions: (i) CAL-B, H_2O (1 equiv), *i*-Pr_2O, 65 °C; (ii) $SOCl_2$, EtOH, 0 °C–Δ, 90%; (iii) Et_3N, Boc_2O, CH_2Cl_2, 2 h, rt, 82%; (iv) NaOEt, EtOH, 24 h, rt, 65%; (v) 2.0 w/w% OsO_4 solution in *t*-BuOH, NMO, acetone, 4 h, rt, 72–74%; (−)-**15**·HCl, (−)-**18**·HCl: (vi) 10% HCl/H_2O, 24 h, Δ, 43–49%; (−)-**15**, (−)-**18**; (vii) microwave irradiation, H_2O, 150 °C, 1 h, 72–74%.

N-oxide (NMO) as the stoichiometric co-oxidant afforded the desired products (+)-**5**, (−)-**8** and (−)-**14**, (−)-**17** as single diastereomers in good yields.

The dihydroxylations of (+)-**4** and (+)-**13** exhibit *anti* selectivity with regard to the ester and protected amino groups, on the sterically less-hindered side of the ring. The orientation of the hydroxy groups was deduced from the couplings and NOEs of their vicinal hydrogens. For (+)-**5**, H-4 and H-1 display large couplings (^3J = 9–10 Hz), indicating their axial positions. The singlet of H-5 suggests its equatorial position. NOE signals were observed between the axial 5-OH and the axial H-1 and H-3ax. Moreover, the signal between H-4 and the amide hydrogen confirms the *trans* orientation of the hydroxy groups relative to the ester and amide groups. For (−)-**14**, the coupling constants suggest equatorial H-3 and axial H-4 and H-1, and the NOEs prove the stereochemistry: the signal between 3-OH and H-1, H-4 and H-6ax and between the amide hydrogen and H-4 and H-6x.

Following the osmylation of the double bond in (−)-**7** or (+)-**16**, where the ester and amino groups are on opposite sides of the ring, the hydroxy groups project on the ester side, that is, *anti* relative to the amino group. In this case, H-1 and H-2 are in a *trans-diaxial* position, and the NOE signals between H-1 and the axial H-5 and between H-1 and the axial H-3 indicate the orientation of the hydroxy groups for (−)-**8** and (−)-**17**, respectively. This selectivity can be interpreted in terms of the steric bias of the substituents. The bulkier *N*-Boc-protecting group interacts unfavourably with the forming hydroxy groups, and hence osmylation will occur from the sterically less-hindered face.[32]

It is relevant that dihydroxylation by $KMnO_4$ results in the same diastereoselectivity as for osmylation, but the yields are not so good.[42]

The acidic hydrolysis of (−)-**14** and (−)-**17** resulted in the corresponding dihydroxy-amino acid hydrochlorides (−)-**15**·HCl and (−)-**18**·HCl in moderate yields.

For (+)-**5**, (−)-**8**, (±)-**5** and (±)-**8**, a different deprotection method was used in the last step of the synthesis: reaction first with LiOH in THF to deprotect the carboxylic group, followed by hydrolysis with HCl/H_2O. The yields were obviously the same.

In order to improve the yields of the final products, a new deprotection protocol was applied: dihydroxy compounds (+)-**5**, (−)-**8**, (−)-**14** and (−)-**17** and their racemic counterparts were subjected to microwave irradiation in H_2O at 150 °C for 1 h.[43,44]

Due to the possible isomerization after hydrolysis, we analyzed the structures of the deprotected dihydroxy-amino acids (−)-**6**, (−)-**9**, (−)-**15** and (−)-**18** as well. Because of the higher conformational flexibility of the compounds, some of the NMR signals were broadened; consequently the smaller coupling constants could not be determined exactly. For (−)-**9** and (−)-**18**, the small NOE signal between H-1 and H-2 and the large coupling ^3J(H-1, H-2) = 11–12 Hz suggest a *trans*-orientation for the carboxyl and amino groups, while for (−)-**6** and (−)-**15**, the small NOE couplings and the large NOE signals between H-1 and H-2 indicate *cis*-substituents. The orientations of the hydroxy groups can be deduced from the couplings and the NOE patterns of their vicinal hydrogens.

For (−)-**6**, whose conformational flexibility was pronounced, the stereochemistry was proved unequivocally by measurements in CD_3OD and in DMSO. In this case, the coupling constants suggest axial H-2 and H-5 and equatorial H-4. This would involve hydroxy groups on the opposite side of the ring from the amino group, which is supported by the absence of NOE signals between H-2 and H-4 and by the NOE cross peak between H-2 and one of the hydroxyl groups (Fig. 1).

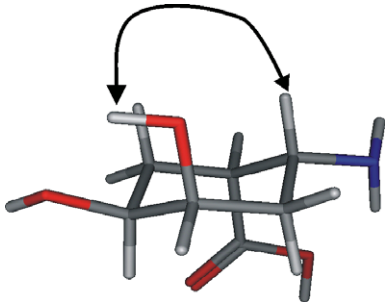


Figure 1. Molecular structure of (−)-**6**.

For (−)-**9**, H-1 and H-2 are in a *trans-diaxial* position (concluded from ^3J(H-1, H-2) = 12 Hz) and H-5 should also be axial, while H-4 is equatorial. NOE signals can be observed between H-1 and H-5 and between H-3ax and H-1 and H-5, which suggest that the hydroxy groups are *cis* relative to the carboxyl group (Fig. 2).

For (−)-**15**, whose spectra were measured in D_2O because of the overlapping signals in DMSO, the coupling constants indicate axial H-2 and H-3, and equatorial H-4, which requires *trans*-hydroxy groups relative to the amino and carboxyl groups. The NOE signal

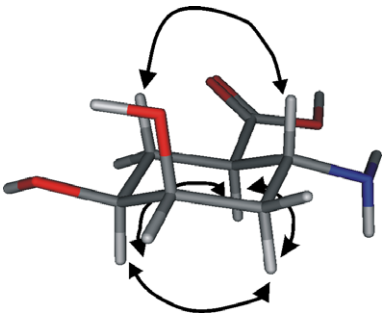


Figure 2. Molecular structure of (−)-**9**.

between H-3 and H-5ax is in accordance with this structure. For (−)-**18**, similar couplings and NOE signal patterns were observed for H-2, H-3 and H-4, which indicates that the hydroxy groups are on the opposite side of the cyclohexane ring from the amino group.

3. Conclusions

An effective route has been devised for the preparation of enantiopure 2-amino-4,5-dihydroxycyclohexanecarboxylic acids and 2-amino-3,4-dihydroxycyclohexanecarboxylic acids. Catalytic osmylation with OsO_4 and NMO as co-oxidants was used to introduce the dihydroxy functionality on the cyclohexene ring. After microwave irradiation of the protected amino acids, the appropriate products were obtained. These new β-amino acid derivatives can be used as enantiopure building blocks to produce peptides or heterocycles. The synthesis of further substances is also to be expected.

4. Experimental

4.1. General

The ^{1}H NMR spectra were recorded at 500 MHz or at 600 MHz while the ^{13}C NMR spectra at 125 MHz or at 150 MHz in DMSO-d_6, except for (−)-**6** (CD_3OD) and (−)-**15** (D_2O), which were recorded at ambient temperature, with Bruker DRX 500 and AV 600 spectrometers, respectively. Chemical shifts are given in δ (ppm) relative to TMS as the internal standard. Elemental analyses were performed with a Perkin–Elmer CHNS-2400 Ser II Elemental Analyzer. Melting points were measured with a Kofler melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. Microwave reactions were performed in a CEM Discover MW reactor. Ester (±)-**1** was prepared by hypochlorite-mediated Hoffman degradation of the carboxamide obtained by the ammonolysis of *cis*-1,2,3,6-tetrahydrophthalic anhydride,[47] while β-lactam (±)-**10** was formed by the addition of chlorosulfonyl isocyanate to 1,3-cyclohexadiene.[25] Amino acid (+)-**2** was esterified in the presence of EtOH and $SOCl_2$, and the amino group was then protected with di-*tert*-butyl dicarbonate to give Boc-protected ester (+)-**4**.[26] The ee values for the starting (1*S*,2*R*)-2-aminocyclohex-4-enecarboxylic acid (+)-**2** and (1*R*,2*S*)-2-aminocyclohex-3-enecarboxylic acid (+)-**11** (>99%) were determined after a simple and rapid double derivatization by using GC instrumentation equipped with CP-Chirasil L-Val columns.[45]

The ee values for the final products were determined by HPLC. For (−)-**9**·HCl, (−)-**15**·HCl and (−)-**18**·HCl, a Chirobiotic TAG 5μ column (0.46 cm × 25 cm) was used at room temperature; the mobile phase was MeOH containing 0.1% TEA and 0.1% AcOH; flow rate 1 mL/min; detection at 205 nm; retention times (min): (−)-**9**·HCl, 11.37 (antipode: 18.77); (−)-**15**·HCl, 16.11 (antipode: 14.43); (−)-**18**·HCl, 12.16 (antipode: 13.41). For (−)-**6**·HCl, a Chirobiotic T 5μ column (0.46 cm × 25 cm) was used at room temperature; the mobile phase was 0.1% aqueous triethylammonium acetate (TEEA)/EtOH = 20/80; flow rate 0.5 mL/min; detection at 205 nm; retention time (min): 22.77 (antipode: 21.08).[46] The ee values for compounds (−)-**6**, (−)-**9**, (−)-**15** and (−)-**18** were determined by the above-mentioned methods; the samples were derivatized with concentrated HCl.

4.2. Ethyl (1*R*,2*S*)-2-*tert*-butoxycarbonylaminocyclohex-3-enecarboxylate, (+)-13

At first, $SOCl_2$ (1.47 g, 12.4 mmol) was added dropwise with stirring to dry EtOH (11 mL) at −15 °C. To this mixture, (+)-**11** (2.00 g, 14.17 mmol) was added in one portion, followed by stirring for 30 min at 0 °C. After further stirring for 3 h at room temperature, the mixture was refluxed for an additional 1 h and then evaporated. The residue was recrystallized from EtOH/Et_2O to give a colourless crystalline product.

To the product (2.00 g, 9.7 mmol) in CH_2Cl_2 (50 mL), Et_3N (1.97 g, 19.4 mmol) and di-*tert*-butyl dicarbonate (2.33 g, 10.7 mmol) were added at 0 °C. The mixture was stirred at room temperature for 2 h, and then washed with water (2 × 20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic phase was dried (Na_2SO_4) and the solvents were evaporated off. The residue was recrystallized from *n*-hexane to give a white solid. Yield: 2.25 g (74%), mp 82–84 °C, $[\alpha]_D^{20}$ = +165.2 (*c* 0.55, EtOH). ^{1}H NMR (500 MHz, DMSO, 27 °C): δ = 1.16 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.36 (s, 9H, *t*-Bu), 1.61–1.68 (m, 1H, H-6eq), 1.76–1.84 (m, 1H, H6-ax), 1.88–1.96 (m, 1H, H-5ax), 2.02 (dt, *J* = 17.8, 5.4, 5.2 Hz, 1H, H-5eq), 2.62 (ddd, *J* = 12.4, 4.6, 3.0 Hz, 1H, H-1), 3.96–4.02 (m, 2H, CH_2CH_3), 4.35–4.39 (m, 1H, H-2), 5.53–5.59 (m, 1H, H-3), 5.73–5.78 (m, 1H, H-4), 6.73 (d, *J* = 9.4 Hz, 1H, N*H*) ppm. ^{13}C NMR (125 MHz, DMSO, 27 °C): δ = 13.5, 18.4, 23.4, 27.8, 43.2, 44.6, 59.1, 77.5, 126.0, 128.8, 154.6, 172.5 ppm. Anal. Calcd for $C_{14}H_{23}NO_4$ (269.34): C, 62.43; H, 8.61; N, 5.20. Found: C, 62.34; H, 8.59; N, 5.27.

4.3. General procedure for isomerization of Boc-protected *cis* amino esters, (+)-4 and (+)-13

Freshly prepared NaOEt (0.25 g, 3.7 mmol) was added to a solution of (+)-**4** or (+)-**13** (1.00 g, 3.7 mmol) in dry EtOH (12 mL), and the mixture was stirred for 24 h at room temperature. It was then concentrated under reduced pressure, taken up in EtOAc and washed with H_2O (2 × 20 mL). The combined organic phase was dried (Na_2SO_4) and the solvent was evaporated off. The residue was purified by column chromatography (*n*-hexane/EtOAc, 9:1) to give a white solid.

4.3.1. Ethyl (1*R*,2*R*)-2-*tert*-butoxycarbonylaminocyclohex-4-enecarboxylate, (−)-7

Yield: 0.43 g (43%), mp 45–47 °C, $[\alpha]_D^{20}$ = −23.7 (*c* 0.5, EtOH). ^{1}H NMR (500 MHz, DMSO, 27 °C): δ = 1.17 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.36 (s, 9H, *t*-Bu), 1.95–2.02 (m, 1H, H-3ax), 2.17 (dt, *J* = 17.3, 4.5, 4.5 Hz, 1H, H-3eq), 2.23–2.27 (m, 2H, H-6), 2.53 (dt, *J* = 10.7, 8.0, 8.0 Hz, 1H, H-1), 3.64–3.74 (m, 1H, H-2), 4.03 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 5.56–5.59 (m, 2H, H-4, H-5), 6.79 (d, *J* = 8.7 Hz, 1H, N*H*) ppm. ^{13}C NMR (125 MHz, DMSO, 27 °C): δ = 13.5, 27.1, 27.4, 31.1, 44.8, 46.5, 59.1, 77.9, 124.4, 124.8, 154.8, 174.3 ppm. Anal. Calcd for $C_{14}H_{23}NO_4$ (269.34): C, 62.43; H, 8.61; N, 5.20. Found: C, 62.27; H, 8.71; N, 5.17.

4.3.2. Ethyl (1*S*,2*S*)-2-*tert*-butoxycarbonylaminocyclohex-3-enecarboxylate, (+)-16

Yield: 0.65 g (65%), mp 75–78 °C, $[\alpha]_D^{20}$ = +103.6 (*c* 0.53, EtOH). ^{1}H NMR (600 MHz, DMSO, 27 °C): δ = 1.17 (t, *J* = 7.1 Hz, 3H,

CH_2CH_3), 1.63–1.69 (m, 1H, H-6ax), 1.82–1.89 (m, 1H, H-6eq), 1.36 (s, 9H, *t*-Bu), 1.95–2.02 (m, 2H, H-5), 2.42–2.47 (m, 1H, H-1), 3.97–4.11 (m, 2H, CH_2CH_3), 4.21 (d, J = 8.4 Hz, 1H, H-2), 5.42 (d, J = 9.8 Hz, 1H, H-3), 5.67–5.72 (m, 1H, H-4), 6.96 (d, J = 8.7 Hz, 1H, NH) ppm. ^{13}C NMR (150 MHz, DMSO, 27 °C): δ = 14.0, 23.3, 24.2, 28.2, 45.1, 48.0, 59.9, 77.7, 127.7, 128.7, 155.0, 173.8 ppm. Anal. Calcd for $C_{14}H_{23}NO_4$ (269.34): C, 62.43; H, 8.61; N, 5.20. Found: C, 62.45; H, 8.67; N, 5.22.

4.4. General procedure for dihydroxylation of *N*-Boc-protected esters, (+)-4, (−)-7, (+)-13 and (+)-16

At first, OsO_4 (1.02 mL 0.08 mmol; a 2.0% w/w solution in *t*-BuOH) was added to a stirred solution of *N*-methylmorpholine *N*-oxide (0.55 g, 4.7 mmol) and (+)-**4**, (−)-**7**, (+)-**13** or (+)-**16** (0.43 g, 1.6 mmol) in acetone (15 mL), and stirring was continued for a further 4 h. When the reaction was completed (monitored by TLC), the mixture was treated with aqueous Na_2SO_3 (20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layer was dried (Na_2SO_4). The solvent was removed by evaporation under reduced pressure to afford crystalline products (+)-**5**, (−)-**8** and (−)-**17**, which were recrystallized from *n*-hexane/EtOAc to give white crystalline solids. The oily compound (−)-**14** was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 1:1) to afford white crystals.

4.4.1. Ethyl (1*S*,2*R*,4*R*,5*S*)-2-*tert*-butoxycarbonylamino-4,5-dihydroxycyclohexanecarboxylate, (+)-5

Yield: 379 mg (78%), mp 136–137 °C, $[\alpha]_D^{20} = +27.3$ (c 0.49, EtOH). ^{1}H NMR (600 MHz, DMSO, 27 °C): δ = 1.14 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.36 (s, 9H, *t*-Bu), 1.51 (d, J = 11.8 Hz, 1H, H-3eq), 1.66 (ddd, J = 12.8, 5.0, 4.5 Hz, 1H, H-6eq), 1.73 (dd, J = 11.8, 9.4 Hz, 1H, H-3ax), 1.91 (dd, J = 12.8, 11.8 Hz, 1H, H-6ax), 2.75–2.82 (ddd, J = 10.5, 5.0, 4.2 Hz, 1H, H-1), 3.69 (d, J = 9.4 Hz, 1H, H-4), 3.72 (s, 1H, H-5), 3.93-4.04 (m, 2H, CH_2CH_3), 4.13 (s, 1H, H-2), 4.28 (s, 1H, OH), 4.35 (d, J = 2.5 Hz, 1H, OH), 6.79 (d, J = 5.9 Hz, 1H, NH) ppm. ^{13}C NMR (150 MHz, DMSO, 27 °C): δ = 13.9, 28.1, 28.3, 33.7, 39.9, 47.2, 59.5, 66.4, 67.2, 77.5, 154.9, 172.8 ppm. Anal. Calcd for $C_{14}H_{25}NO_6$ (303.35): C, 55.43; H, 8.31; N, 4.62. Found: C, 55.35; H, 8.29; N, 4.53.

4.4.2. Ethyl (1*R*,2*R*,4*R*,5*S*)-2-*tert*-butoxycarbonylamino-4,5-dihydroxycyclohexanecarboxylate, (−)-8

Yield: 413 mg (85%), mp 114–117 °C, $[\alpha]_D^{20} = -25.2$ (c 0.51, EtOH). ^{1}H NMR (600 MHz, DMSO, 27 °C): δ = 1.15 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.34 (s, 9H, *t*-Bu), 1.40 (dd, J = 12.2, 13.0 Hz, 1H, H-3ax), 1.55 (ddd, J = 12.4, 3.9, 3.6 Hz, 1H, H-6eq), 1.73 (ddd, J = 13.0, 4.0, 3.8 Hz, 1H, H-3eq), 1.83 (q, J = 12.4 Hz, 1H, H-6ax), 2.31 (ddd, J = 12.4, 12.3, 3.4 Hz, 1H, H-1), 3.36 (ddd, J = 11.0, 6.5, 5.5 Hz, 1H, H-5), 3.73 (s, 1H, H-4), 3.81–3.88 (m, 1H, H-2), 3.93–4.05 (m, 2H, CH_2CH_3), 4.42 (s, 1H, OH), 4.49 (d, J = 5.5 Hz, 1H, OH), 6.63 (d, J = 9.3 Hz, 1H, NH) ppm. ^{13}C NMR (150 MHz, DMSO, 27 °C): δ = 14.5, 28.6, 30.9, 37.8, 45.8, 47.8, 60.0, 68.5, 69.7, 77.5, 155.2, 172.6 ppm. Anal. Calcd for $C_{14}H_{25}NO_6$ (303.35): C, 55.43; H, 8.31; N, 4.62. Found: C, 55.60; H, 8.35; N, 4.54.

4.4.3. Ethyl (1*R*,2*R*,3*S*,4*R*)-2-*tert*-butoxycarbonylamino-3,4-dihydroxycyclohexanecarboxylate, (−)-14

Yield: 359 mg (74%), mp 49–51 °C $[\alpha]_D^{20} = -43.2$ (c 0.54, EtOH). ^{1}H NMR (600 MHz, DMSO, 27 °C): δ = 1.13 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.36 (s, 9H, *t*-Bu), 1.39–1.48 (m, 2H, H-5), 1.49–1.56 (m, 1H, H-6eq), 1.76 (td, J = 12.4, 6.2, 6.2 Hz, 1H, H-6ax), 2.73 (td, J = 12.2, 4.1, 4.1 Hz, 1H, H-1), 3.48 (s, 1H, H-3), 3.63 (dt, 1H, J = 10, 5.6, 5.6 Hz, H-4), 3.90–4.05 (m, 2H, CH_2CH_3), 4.10 (dt, J = 9.8, 4.5, 4.5 Hz, 1H, H-2), 4.28 (d, J = 5.7 Hz, 1H, OH), 4.72 (d, J = 3.4 Hz, 1H, OH), 6.73 (d, J = 9.8 Hz, 1H, NH) ppm. ^{13}C NMR (150 MHz, DMSO, 27 °C): δ = 13.7, 20.2, 26.3, 27.8, 39.4, 52.6, 59.2, 65.8, 70.9, 78.1, 155.2, 174.0 ppm. Anal. Calcd for $C_{14}H_{25}NO_6$ (303.35): C, 55.43; H, 8.31; N, 4.62. Found: C, 55.49; H, 8.37; N, 4.65.

4.4.4. Ethyl (1*S*,2*R*,3*S*,4*R*)-2-*tert*-butoxycarbonylamino-3,4-dihydroxycyclohexanecarboxylate, (−)-17

Yield: 349 mg (72%), mp 153–156 °C, $[\alpha]_D^{20} = -12$ (c 0.28, EtOH). ^{1}H NMR (600 MHz, DMSO, 27 °C): δ = 1.16 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.32 (d, J = 13.3 Hz, 1H, H-5ax), 1.35 (s, 9H, *t*-Bu), 1.42–1.47 (m, 1H, H-6eq), 1.67 (ddd, J = 13.5, 6.9, 3.5 Hz, 1H, H-5eq), 1.81 (dq, J = 13.1, 12.9, 12.9, 3.3 Hz, 1H, H-6ax), 2.28 (dt, J = 12.3, 12.3, 3.7 Hz, 1H, H-1), 3.18–3.23 (m, 1H, H-3), 3.73 (q, J = 10.20 Hz, 1H, H-2), 3.80 (s, 1H, H-4), 3.93–4.04 (m, 2H, CH_2CH_3), 4.20 (d, J = 7.0 Hz, 1H, OH), 4.45 (s, 1H, OH), 6.54 (d, J = 9.4 Hz, 1H, NH) ppm. ^{13}C NMR (150 MHz, DMSO, 27 °C): δ = 14.5, 22.6, 28.7, 30.0, 48.5, 52.2, 60.1, 69.0, 73.6, 77.5, 155.7, 173.6 ppm. Anal. Calcd for $C_{14}H_{25}NO_6$ (303.35): C, 55.43; H, 8.31; N, 4.62. Found: C, 55.47; H, 8.40; N, 4.69.

4.5. General synthesis of stereoisomeric 2-amino-4,5-dihydroxycyclohexanecarboxylic acid hydrochlorides, (−)-6·HCl and (−)-9·HCl, and 2-amino-3,4-dihydroxycyclohexanecarboxylic acid hydrochlorides, (−)-15·HCl and (−)-18·HCl

Dihydroxy ester (−)-**14** or (−)-**17** (364 mg, 1.2 mmol) was dissolved in aqueous HCl (10%; 20 mL) and the mixture was refluxed for 24 h. The solvent was then evaporated off to afford the crude amino acid hydrochloride, which was recrystallized from EtOH/Et_2O to give a pale-yellow crystalline solid. Compounds (+)-**5** and (−)-**8** were first hydrolyzed with LiOH in H_2O/THF at room temperature for 5 h and subsequently treated with aqueous HCl by the above-mentioned method.

4.5.1. (1*S*,2*R*,4*R*,5*S*)-2-Amino-4,5-dihydroxycyclohexanecarboxylic acid hydrochloride, (−)-6·HCl

Yield: 119 mg (47%), mp 240–243 °C (dec.), $[\alpha]_D^{20} = -7.3$ (c = 0.324, H_2O); ee >99%. ^{1}H NMR (600 MHz, CD_3OD, 40 °C): δ = 2.03–2.12 (m, 3H, H-3, H-3, H-6ax), 2.17 (dt, J = 13.6, 4.7, 4.7 Hz, H-6eq), 3.12 (q, J = 4.8 Hz, 1H, H-1), 3.74 (dt, J = 9.8, 4.7, 4.7 Hz 1H, H-2), 3.77 (d, J = 10.0 Hz, 1H, H-5), 3.99 (dt, J = 5.0, 2.9, 2.9 Hz, 1H, H-4) ppm. ^{13}C NMR (150 MHz, MeOD, 40 °C): δ = 28.5, 31.7, 39.6, 46.0, 67.0, 67.6, 174.2 ppm. Anal. Calcd for $C_7H_{14}ClNO_4$ (211.64): C, 39.72; H, 6.67; N, 6.62. Found: C, 39.79; H, 6.57; N, 6.65.

4.5.2. (1*R*,2*R*,4*R*,5*S*)-2-Amino-4,5-dihydroxycyclohexanecarboxylic acid hydrochloride, (−)-9·HCl

Yield: 114 mg (45%), mp 222–225 °C (dec.), $[\alpha]_D^{20} = -48.8$ (c = 0.46, H_2O); ee >99%. ^{1}H NMR (500 MHz, DMSO, 27 °C): δ = 1.58 (t, J = 12.4 Hz, 1H, H-3ax), 1.67 (q, J = 12.2 Hz, 1H, H-6ax), 1.79–1.84 (m, 1H, H-6eq), 2.06 (dt, J = 12.6, 4.0, 4.0 Hz, 1H, H-3eq), 2.55 (t, J = 12.4 Hz, 1H, H-1), 3.36–3.47 (m, 2H, H-2, H-5), 3.79 (s, 1H, H-4), 4.69–4.86 (m, 2H, OH), 8.06 (s, 3H, NH) ppm. ^{13}C NMR (125 MHz, DMSO, 27 °C): δ = 30.3, 33.7, 43.9, 45.3, 66.9, 69.0, 173.8 ppm. Anal. Calcd for $C_7H_{14}ClNO_4$ (211.64): C, 39.72; H, 6.67; N, 6.62. Found: C, 39.77; H, 6.67; N, 6.58.

4.5.3. (1*R*,2*R*,3*S*,4*R*)-2-Amino-3,4-dihydroxycyclohexanecarboxylic acid hydrochloride, (−)-15·HCl

Yield: 109 mg (43%), mp 224 °C (dec.), $[\alpha]_D^{20} = -84.8$ (c = 0.55, H_2O); ee >99%. ^{1}H NMR (600 MHz, D_2O, 27 °C): δ = 1.51–1.60 (dd, J = 14.8, 12.0 Hz 1H, H-5ax), 1.74–1.79 (m, 1H, H-5eq), 1.87 (tt, J = 14.2, 14.2, 4.2, 4.2 Hz, 1H, H-6ax), 1.93–2.01 (m, 1H, H6-eq), 3.11 (q, J = 4.2 Hz, 1H, H-1), 3.50 (dd, J = 10.7, 4.6 Hz, 1H, H-2), 3.99 (dd, J = 10.7, 3.20 Hz, 1H, H-3), 4.04 (q, J = 3.1 Hz, 1H, H-4) ppm. ^{13}C NMR (150 MHz, D_2O, 27 °C): δ = 20.6, 26.8, 41.3, 50.7,

68.5, 68.5, 173.8 ppm. Anal. Calcd for $C_7H_{14}ClNO_4$ (211.64): C, 39.72; H, 6.67; N, 6.62. Found: C, 39.65; H, 6.54; N, 6.71.

4.5.4. (1*S*,2*R*,3*S*,4*R*)-2-Amino-3,4-dihydroxycyclohexanecarboxylic acid hydrochloride, (−)-18·HCl

Yield: 124 mg (49%), mp 214 °C (dec.), $[\alpha]_D^{20} = -61.5$ (c = 0.5, H_2O); ee >99%. ^{1}H NMR (600 MHz, DMSO, 27 °C): δ = 1.47 (s, 1H, H-5ax), 1.62–1.69 (m, 1H, H-6), 1.69–1.74 (m, 2H, H-5eq, H-6), 2.47–2.51 (m, 1H, H-1), 3.23–3.29 (m, 1H, H-2), 3.45 (dd, J = 12.9, 4.2 Hz, 1H, H-3), 3.85 (s, 1H, H-4), 4.89 (s, 1H, O*H*), 5.42 (br s, 1H, O*H*), 7.90 (br s, 3H, N*H*), 12.70 (br s, 1H, COO*H*) ppm. ^{13}C NMR (150 MHz, DMSO, 27 °C): δ = 22.5, 29.6, 44.6, 51.4, 67.4, 71.4, 173.7 ppm. Anal. Calcd for $C_7H_{14}ClNO_4$ (211.64): C, 39.72; H, 6.67; N, 6.62. Found: C, 39.55; H, 6.83; N, 6.64.

4.6. General synthesis of stereoisomeric 2-amino-4,5-dihydroxycyclohexanecarboxylic acids (−)-6, (−)-9 and 2-amino-3,4-dihydroxycyclohexanecarboxylic acids, (−)-15 and (−)-18

Dihydroxy esters (+)-**5**, (−)-**8**, (−)-**14** or (−)-**17** (0.2 g, 0.66 mmol) were dissolved in water (4 mL) in a CEM-Discover microwave pressure tube. The reaction mixture was then stirred at 150 °C for 60 min under a maximum microwave irradiation of 150 W. After cooling, the mixtures were diluted with acetone (6 mL) and the products crystallized out. The crude amino acids were recrystallized from H_2O/acetone to afford pale-yellow crystalline solids.

4.6.1. (1*S*,2*R*,4*R*,5*S*)-2-Amino-4,5-dihydroxycyclohexanecarboxylic acid, (−)-6

Yield: 81 mg (70%), mp 248–250 °C (dec.), $[\alpha]_D^{20} = -11.7$ (c = 0.35, H_2O); ee >99%. ^{1}H NMR (500 MHz, D_2O, 27 °C): δ = 1.86–1.93 (m, 1H, H-6), 1.96–2.08 (m, 3H, H-3, H-3, H-6), 2.78 (q, J = 4.7 Hz, 1H, H-1), 3.61 (dt, J = 9.8, 4.7, 4.7 Hz 1H, H-2), 3.70 (d, J = 8.7 Hz, 1H, H-5), 3.98–4.01 (m, 1H, H-4) ppm. ^{13}C NMR (125 MHz, D_2O, 27 °C): δ = 29.3, 31.8, 41.1, 46.7, 67.9, 67.9, 179.1 ppm. Anal. Calcd for $C_7H_{13}NO_4$ (175.18): C, 47.99; H, 7.48; N, 8.00. Found: C, 48.07; H, 7.62; N, 8.15.

4.6.2. (1*R*,2*R*,4*R*,5*S*)-2-Amino-4,5-dihydroxycyclohexanecarboxylic acid, (−)-9

Yield: 89 mg (77%), mp 236–240 °C (dec.), $[\alpha]_D^{20} = -56$ (c = 0.37, H_2O); ee >99%. ^{1}H NMR (500 MHz, DMSO, 27 °C): δ = 1.40 (t, J = 12.4 Hz, 1H, H-3ax), 1.47 (q, J = 12.4 Hz, 1H, H-6ax), 1.77 (dt, J = 3.0, 12.4, 12.4 Hz, 1H, H-1), 1.88–1.95 (m, 2H, H-6eq, H-3eq), 2.98 (dt, J = 3.0, 11.7, 11.7 Hz,1H, H-2), 3.35 (dt, J = 11.6, 4.0. 3.4 Hz, 1H, H-5), 3.76 (s, 1H, H-4), 4.25–4.54 (m, 2H, O*H*), 8.51 (s, 2H, N*H*) ppm. ^{13}C NMR (125 MHz, DMSO, 27 °C): δ = 30.3, 36.6, 43.9, 47.0, 68.2, 70.5, 176.5 ppm. Anal. Calcd for $C_7H_{13}NO_4$ (175.18): C, 47.99; H, 7.48; N, 8.00. Found: C, 47.55; H, 7.58; N, 8.05.

4.6.3. (1*R*,2*R*,3*S*,4*R*)-2-Amino-3,4-dihydroxycyclohexanecarboxylic acid, (−)-15

Yield: 86 mg (74%), mp 227–230 °C (dec.), $[\alpha]_D^{20} = -81.4$ (c = 0.35, H_2O); ee >99%. ^{1}H NMR (500 MHz, D_2O, 47 °C): δ = 1.98 (dd, J = 14.8, 12.0 Hz 1H, H-5ax), 2.15–2.28 (m, 2H, H-5eq, H-6ax), 2.34–2.43 (m, 1H, H-6eq), 3.27 (s, 1H, H-1), 3.92 (d, J = 10.3, 4.7 Hz, 1H, H-2), 4.39 (d, J = 10.3 Hz, 1H, H-3), 4.50 (s, 1H, H-4) ppm. ^{13}C NMR (125 MHz, D_2O, 47 °C): δ = 21.6, 27.8, 42.6, 52.2, 69.3, 69.4, 174.9 ppm. Anal. Calcd for $C_7H_{13}NO_4$ (175.18): C, 47.99; H, 7.48; N, 8.00. Found: C, 48.12; H, 7.51; N, 7.89.

4.6.4. (1*S*,2*R*,3*S*,4*R*)-2-Amino-3,4-dihydroxycyclohexanecarboxylic acid, (−)-18

Yield: 83 mg (72%), mp 258 °C (dec.), $[\alpha]_D^{20} = -5.2$ (c = 0.38, H_2O); ee >99%. ^{1}H NMR (500 MHz, D_2O, 27 °C): δ = 1.66–1.76 (m, 2H, H-5, H-6), 1.96–2,02 (m, 2H, H-5, H-6), 2.38–2.44 (m, 1H, H-1), 3.49 (t, 11.0 Hz, 1H, H-2), 3.74 (d, J = 10.5 Hz, 1H, H-3), 4.16 (s, 1H, H-4) ppm. ^{13}C NMR (125 MHz, D_2O, 27 °C): δ = 22.6, 29.3, 46.8, 53.0, 68.8, 71.8, 174.7 ppm. Anal. Calcd for $C_7H_{13}NO_4$ (175.18): C, 47.99; H, 7.48; N, 8.00. Found: C, 48.04; H, 7.35; N, 7.93.

4.7. Racemic compounds

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

4.7.1. Ethyl (1*S**,2*R**,4*R**,5*S**)-2-*tert*-butoxycarbonylamino-4,5-dihydroxycyclohexane-carboxylate, (±)-5

White crystals, mp 76–78 °C.

4.7.2. (1*S**,2*R**,4*R**,5*S**)-2-Amino-4,5-dihydroxycyclohexane-carboxylic acid hydrochloride, (±)-6·HCl

Pale-yellow crystals, mp 227 °C (dec.).

4.7.3. (1*S**,2*R**,4*R**,5*S**)-2-Amino-4,5-dihydroxycyclohexane-carboxylic acid, (±)-6

Pale-yellow crystals, mp 231 °C (dec.).

4.7.4. Ethyl (1*R**,2*R**,4*R**,5*S**)-2-*tert*-butoxycarbonylamino-4,5-dihydroxycyclohexane-carboxylate, (±)-8

White crystals, mp 99–101 °C.

4.7.5. (1*R**,2*R**,4*R**,5*S**)-2-Amino-4,5-dihydroxycyclohexane-carboxylic acid hydrochloride, (±)-9·HCl

Pale-yellow crystals, mp 220 °C (dec.).

4.7.6. (1*R**,2*R**,4*R**,5*S**)-2-Amino-4,5-dihydroxycyclohexane-carboxylic acid, (±)-9

Pale-yellow crystals, mp 251 °C (dec.).

4.7.7. Ethyl (1*R**,2*S**)-2-*tert*-butoxycarbonylaminocyclohex-3-enecarboxylate, (±)-13

White crystals, mp 67–69 °C.

4.7.8. Ethyl (1*R**,2*R**,3*S**,4*R**)-2-*tert*-butoxycarbonylamino-3,4-dihydroxycyclohexane-carboxylate, (±)-14

White crystals, mp 123–125 °C.

4.7.9. (1*R**,2*R**,3*S**,4*R**)-2-Amino-3,4-dihydroxycyclohexane-carboxylic acid hydrochloride, (±)-15·HCl

Pale-yellow crystals, mp 213 °C (dec.).

4.7.10. (1*R**,2*R**,3*S**,4*R**)-2-Amino-3,4-dihydroxycyclohexane-carboxylic acid, (±)-15

Pale-yellow crystals, mp 233 °C (dec.).

4.7.11. Ethyl (1*S**,2*S**)-2-*tert*-butoxycarbonylaminocyclohex-3-enecarboxylate, (±)-16

White solid, mp 71–74 °C.

4.7.12. Ethyl (1*S**,2*R**,3*S**,4*R**)-2-*tert*-butoxycarbonylamino-3,4-dihydroxycyclohexane-carboxylate, (±)-17

White crystals, mp 165–168 °C.

4.7.13. (1*S**,2*R**,3*S**,4*R**)-2-Amino-3,4-dihydroxycyclohexane-carboxylic acid hydrochloride, (±)-18·HCl

Pale-yellow crystals, mp 225 °C (dec.).

4.7.14. (1*S**,2*R**,3*S**,4*R**)-2-Amino-3,4-dihydroxycyclohexanecarboxylic acid, (±)-18

Pale-yellow crystals, mp 275 °C (dec.).

Acknowledgements

The authors acknowledge the receipt of Grants K 71938 and T 049407 from the Hungarian Scientific Research Fund (OTKA), and a Bolyai Fellowship for E.F.

References

1. *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Soloshonok, V. A., Eds., 2nd ed.; Wiley-VHC: New York, 2005.
2. Kuhl, A.; Hahn, M. G.; Dumic, M.; Mittendorf, J. *Amino Acids* **2005**, *29*, 89–100.
3. Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921–1949.
4. Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. *Curr. Med. Chem.* **2004**, *11*, 1889–1920.
5. Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181–2204.
6. Fülöp, F.; Martinek, T. A.; Tóth, K. G. *Chem. Soc. Rev.* **2006**, *35*, 323–334.
7. Konishi, M.; Nishio, M.; Saitoh, K.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1989**, *42*, 1749–1755.
8. Oki, T.; Hirano, M.; Tomatsu, K.; Numata, K.; Kamei, H. *J. Antibiot.* **1989**, *42*, 1756–1762.
9. Iwamoto, T.; Tsujii, E.; Ezaki, M.; Fujie, A.; Hashimoto, S.; Okuhara, M.; Kohsaka, M.; Imanaka, H.; Kawabata, K.; Inamoto, Y.; Sakane, K. *J. Antibiot.* **1990**, *43*, 1–7.
10. Hamersak, Z.; Roje, M.; Avdagic, A.; Sunjic, V. *Tetrahedron: Asymmetry* **2007**, *18*, 635–644.
11. Hasenoehrl, A.; Galic, T.; Ergovic, G.; Marsic, N.; Skerlev, M.; Mittendorf, J.; Geschke, U.; Schmidt, A.; Schoenfeld, W. *Antimicrob. Agents Chemother.* **2006**, 3011–3018.
12. Price, J. L.; Horne, W. S.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 6376–6377.
13. Hetényi, A.; Szakonyi, Z.; Mándity, I. M.; Szolnoki, É.; Tóth, G. K.; Martinek, A. T.; Fülöp, F. *Chem. Commun.* **2009**, 177–179.
14. Kanizsai, I.; Gyónfalvi, S.; Szakonyi, Z.; Sillanpää, R.; Fülöp, F. *Green Chem.* **2007**, *9*, 357–360.
15. Kapferer, P.; Vasella, A. *Helv. Chim. Acta* **2004**, *87*, 2764–2789.
16. Wuts, P. G. M.; Gu, R. L.; Northuis, J. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2117–2123.
17. Roy, O.; Pattenden, G.; Pryde, D. C.; Wilson, C. *Tetrahedron* **2003**, *59*, 5115–5121.
18. Nicolaou, K. C. *Tetrahedron* **2003**, *59*, 6683–6738.
19. Hashimoto, T.; Kondo, S.; Takita, T.; Hamada, M.; Takeuchi, T.; Okami, Y.; Umezawa, H. *J. Antibiot.* **1968**, *21*, 653–658.
20. Hashimoto, T.; Takahashi, S.; Naganawa, H.; Takita, T.; Maeda, T. K.; Umezawa, H. *J. Antibiot.* **1972**, *25*, 350–355.
21. Hashimoto, T.; Kondo, S.; Naganawa, H.; Takita, T.; Maeda, K.; Umezawa, H. *J. Antibiot.* **1974**, *27*, 86–87.
22. Bunnage, M. E.; Ganesh, T.; Masesane, I. B.; Orton, D.; Steel, P. G. *Org. Lett.* **2003**, *5*, 239–242.
23. Palkó, M.; Kiss, L.; Fülöp, F. *Curr. Med. Chem.* **2005**, *12*, 3063–3083.
24. Fülöp, F.; Palkó, M.; Forró, E.; Dervarics, M.; Martinek, T. A.; Sillanpää, R. *Eur. J. Org. Chem.* **2005**, 3214–3220.
25. Szakonyi, Z.; Gyónfalvi, S.; Forró, E.; Hetényi, A.; De Kimpe, N.; Fülöp, F. *Eur. J. Org. Chem.* **2005**, 4017–4023.
26. Benedek, G.; Palkó, M.; Wéber, E.; Martinek, T. A.; Forró, E.; Fülöp, F. *Eur. J. Org. Chem.* **2008**, 3724–3730.
27. Songis, O.; Didierjean, C.; Martinez, J.; Calmés, M. *Tetrahedron: Asymmetry* **2008**, *19*, 2135–2139.
28. Matsushima, Y.; Kino, J. *Eur. J. Org. Chem.* **2009**, 1619–1624.
29. Kiss, L.; Forró, E.; Fülöp, F. *Tetrahedron Lett.* **2006**, *47*, 2855–2858.
30. Kiss, L.; Szatmári, I.; Fülöp, F. *Lett. Org. Chem.* **2006**, *3*, 463–467.
31. Kiss, L.; Forró, E.; Sillanpää, R.; Fülöp, F. *J. Org. Chem.* **2007**, *72*, 8786–8790.
32. Paquette, L. A.. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: Chichester, 1995; Vol. 6. pp 3801–3808.
33. Coldham, I.; Price, K. N.; Rathmell, R. E. *Org. Biomol. Chem.* **2003**, *1*, 2111–2119.
34. Padwa, A.; Zhang, H. *J. Org. Chem.* **2007**, *72*, 2570–2582.
35. Jayakanthan, K.; Vankar, Y. D. *Org. Lett.* **2006**, *8*, 247–250.
36. Wipf, P.; Wang, X. *Tetrahedron Lett.* **2000**, *41*, 8747–8751.
37. Donohoe, T. J.; Blades, K.; Helliwell, M.; Moore, P. R.; Winter, J. J. G. *J. Org. Chem.* **1999**, *64*, 2980–2981.
38. Chola, J.; Masesane, I. B. *Tetrahedron Lett.* **2008**, *49*, 5680–5682.
39. Kiss, L.; Kazi, B.; Forró, E.; Fülöp, F. *Tetrahedron Lett.* **2008**, *49*, 339–342.
40. Forró, E.; Fülöp, F. *Tetrahedron: Asymmetry* **2004**, *15*, 2875–2880.
41. Forró, E.; Fülöp, F. *Chem. Eur. J.* **2007**, *22*, 6397–6401.
42. Cha, J. K.; Kim, N.-. S. *Chem. Rev.* **1995**, *95*, 1761–1795.
43. Dandepally, R. S.; Williams, L. A. *Tetrahedron Lett.* **2009**, *50*, 1071–1074.
44. Wang, G.; Li, C.; Li, J.; Jia, X. *Tetrahedron Lett.* **2009**, *50*, 1438–1440.
45. Forró, E. *J. Chromatogr., A.* **2009**, *1216*, 1025–1029.
46. Berkecz, R.; Ilisz, I.; Benedek, G.; Fülöp, F.; Armstrong, D. W.; Péter, A. *J. Chromatogr., A.* **2009**, *1216*, 927–932.
47. Bernáth, G.; Stájer, G.; Szabó, E. A.; Fülöp, F.; Sohár, P. *Tetrahedron* **1985**, *41*, 1353–1365.