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2-Azidoethoxy derivatives of 2-aminocyclohexanecarboxylic acids (ACHC): interesting building blocks for the synthesis of cyclic β-peptide conjugates

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ABSTRACT

Oligomers of cyclic-β-aminoacids possess a high resistance to peptidase-catalyzed hydrolysis and display a high intrinsic tendency to adopt regular secondary structures. These characteristics are attractive to develop new biologically active substances. However, cyclic-β-peptides often show limited solubility in water and cannot be conjugated to biologically relevant fragments, such as oligosaccharides, which are often essential for full biological activity of natural α-peptides. In this article, we report the synthesis of one *trans*- and one *cis*-2-aminocyclohexanecarboxylic acid (ACHC), both functionalized with a hydroxy group, to increase the solubility in water, and an azidoethoxy group to allow the synthesis of cyclic-β-peptide conjugates by a 'click reaction'.

1. Introduction

In the past few years, oligomers of β-aminoacids have become a subject of considerable interest.[1–5] These unnatural peptides possess a high resistance to peptidase-catalyzed hydrolysis[6,7] and often present discrete and predictable folding propensities (foldamers).[8–11] Usually, β-peptides with cyclic β-aminoacid residues display a higher intrinsic tendency to adopt a regular secondary structure (helix, sheet and turn) than acyclic residues do.[12–15] However, up to now, most of these results have been obtained in organic solvents, because cyclic β-aminoacids and the resulting peptides often show a limited solubility in water. Only some examples of β-peptides with a helical conformation in aqueous solution have been obtained by modification of the cyclic framework with appropriate hydrophilic substituents.[12]

Cyclic-β-aminoacids have also been exploited as scaffolds in the synthesis of glycomimetic compounds. Our group demonstrated the use of (1*S*,2*R*)-2-aminocyclohexanecarboxylic acid as a scaffold to prepare a mimic of Lewis-x trisaccharide where sugars or sugar-like fragments are connected avoiding glycosidic bonds.[16] These modifications of the oligosaccharide structure are used to improve metabolic stability and activity and to simplify the synthesis of the final glycomimetic compounds.

Introduction of additional substituents on cyclic β-aminoacid frameworks has also been actively sought after.[17,18] Beside improving (water) solubility, additional substituents can be exploited to allow conjugation of β-peptides or other β-aminoacid-containing molecules to additional elements. For instance, β-peptides could be connected to biologically relevant fragments, such as oligosaccharides, which are often essential for full biological activity of natural α-peptides. In our glycomimetic research program, functionalized cyclic β-aminoacids are required to achieve polyvalent presentation of derived oligosaccharide mimics on dendrimers and other polymeric scaffolds, a topic of current high interest in the field of carbohydrate mimicry.[19,20]

Herein, we report the practical synthesis of enantiomerically pure and orthogonally protected derivatives of *trans*- and *cis*-2-aminocyclohexanecarboxylic acids (ACHC) **2** and **3**, functionalized in the cyclohexane ring with a hydroxy group, to increase solubility in water, and with a functional 2-azidoethyl linker to be used as a conjugation handle. Azides give access to various efficient approaches for bioconjugation,[21] including the 1,3-dipolar cycloaddition known as the 'click reaction'.[22]

2. Results and discussion

Compounds **2** and **3** were prepared in a few synthetic steps from commercially available tetrahydrophthalic anhydride **1** through the known protected β-cyclohexenecarboxylic acids **4**[23] and **6**.[24] Key to our strategy was the stereoselective synthesis of epoxides **5** and **7** and their regio- and stereoselective opening by metal-catalyzed alcoholysis (Scheme 1).

The synthesis of **2** (Scheme 2) began with Bölm desymmetrization[25,26] of **1** in the presence of quinidine. The resulting *cis*-hemiester **8** (93% ee) was epimerized to the trans-isomer **9** using

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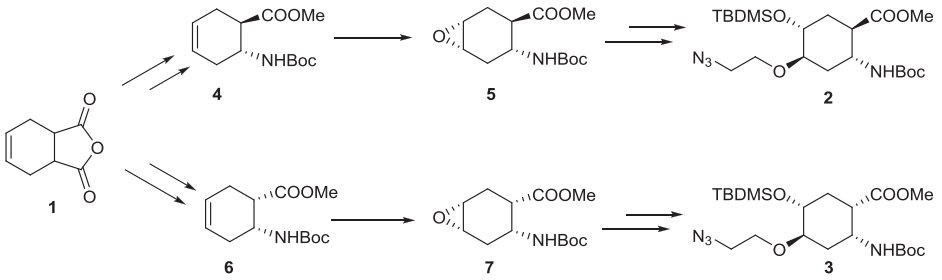
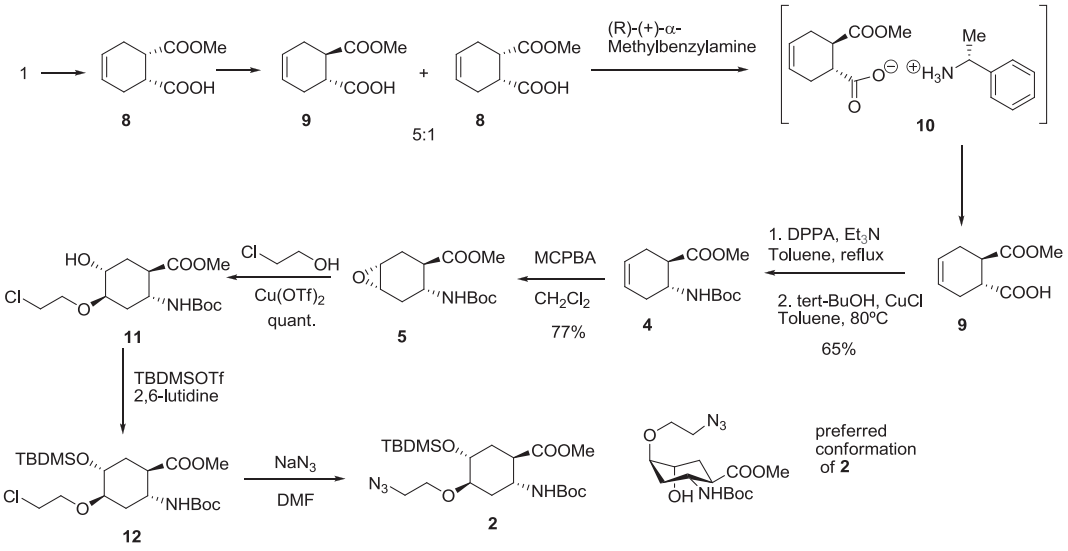


Scheme 1. General strategy for the synthesis of functionalized cyclic β-aminoacids **2** and **3**.

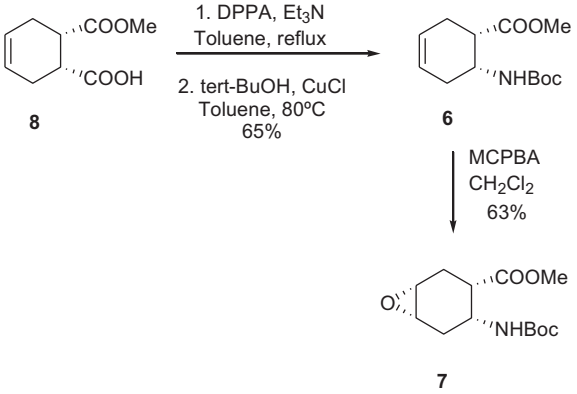


Scheme 2. Stereoselective synthesis of **2**.

potassium *t*-amylate at −15 °C, as described by Yue et al.,[23] to afford a 5.5:1 trans:cis mixture. Finally, the trans-isomer **9** was selectively crystallized (Et_2O/hexane) as its (*R*)-α-methylbenzylamine salt **10**, which improved the trans:cis ratio to 11:1, and the *trans*-hemi-ester **9** was liberated from salt **10** by treatment with HCl (1 N) and extracted into AcOEt. The entire sequence could be performed without any chromatographic purifications and yielded **9** with 80% overall yields from **1**. Curtius rearrangement of **9** and conversion of the resulting isocyanate to a *tert*-butylcarbamate via reaction with *tert*-butyl alcohol and CuCl gave the protected β-amino-cyclohexenecarboxylic acid derivative **4** (65%).[24–27] Remaining traces of the 1,2-cis isomer were chromatographically removed at this stage. MCPBA oxidation of **4** proceeded to afford the (1*R*,2*R*,4*S*,5*R*) epoxide **5**. A single isomer was isolated, featuring the epoxide ring cis to the carbamate moiety, as expected[28] and previously described for the corresponding ethyl ester.[17] No trace of the 4*R*,5*S* isomer could be identified by ^{1}H NMR spectroscopy.

Regioselective alcoholysis of **5** occurred uneventfully, using 20% $Cu(OTf)_2$ in chloroethanol,[29] and afforded **11** in quantitative yield. The position of substituents and the relative configuration of the stereocenters in **11** could be unequivocally established by NMR spectroscopic analysis and are those expected by trans-diaxial opening of a single chair-like conformation of **5**, featuring carbomethoxy and amino groups in a trans-diequatorial disposition. Protection of the hydroxyl group is not necessary at this point, but it was performed (TBDMSOTf, lutidine, 97%) for the sake of obtaining the final compound in a fully orthogonally protected form. Finally, treatment of **12** with NaN_3 afforded the required functionalized (1*R*,2*R*) *trans*-β-aminoacid synthon **2** in quantitative yield (Scheme 2).

For the synthesis of the (1*S*,2*R*) cis isomer **3** (Scheme 3), Curtius rearrangement of hemi-ester **8** under the conditions described above afforded the protected cis amino acid **6**,[24] which was oxidized with MCPBA to give epoxide **4** in 63% yield, as a single isomer. The structure of epoxide **4** could not be fully determined by NMR spectroscopic analysis, but the formation of a single isomer likely results from H-bonding interaction of MCPBA with the carbamate functionality.[28] Thus, the structure of **7** was tentatively attributed, and later confirmed upon analysis of the ring-opening products.



Scheme 3. Synthesis of epoxide **7**.

Alcoholysis of **7** is complicated by the conformational flexibility of the six-membered ring, which can attain two conformations of similar energy, **A** and **B** (Fig. 1). Based on the trans-diaxial requirement of epoxide opening reactions, these conformers are expected to react with opposite regioselectivity: conformer **A** should undergo C5-opening yielding the chloroethyl ether **13** and conformer **B** should react preferentially at C4 affording ether **14** (Fig. 1 and Scheme 4). Molecular mechanics (MM2*) calculations predict that the C5-opening product would exist as an equilibrium mixture of two chair conformations **13-c1** and **13-c2**. On the contrary, the C4-opening compound **14** is expected to adopt mainly conformation **14-c2**, featuring the carbomethoxy group in equatorial position. Although somewhat unexpectedly on the basis of A parameters,[30] a marked conformational bias for equatorial carbalkoxy group over equatorial *N*-carbamate was previously observed in *cis*-2-aminocarbalkoxy-cyclohexanecarboxylic acid esters.[16]

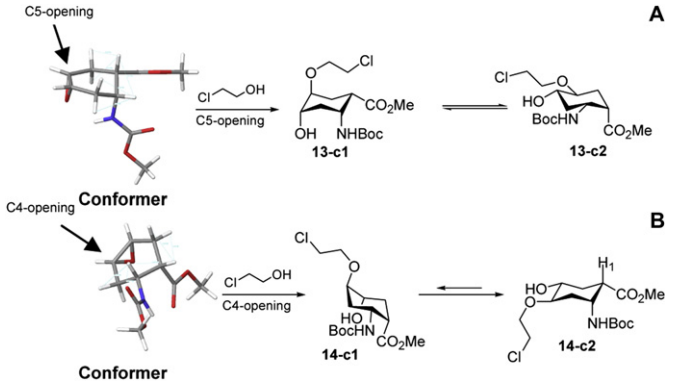
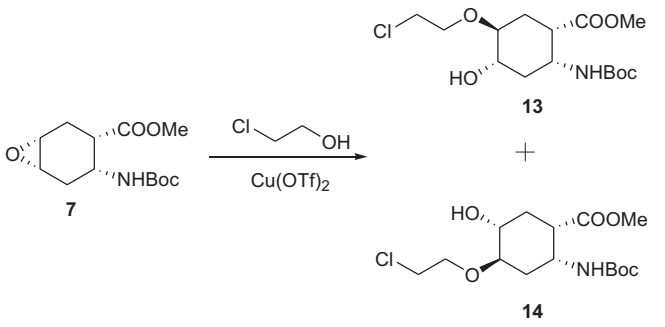


Fig. 1. Conformations **A** and **B** of **7**, as calculated by molecular mechanics (MM2*), their preferred opening pathways and conformational equilibria of the C5- and C4-opening products **13** and **14**.



Scheme 4. Alcoholysis of **7**.

The alcoholysis of epoxides can be catalyzed by a number of Lewis acids and some of these were examined in order to achieve maximum yield and regioselectivity in the 2-chloroethanol opening reaction of **7** (Table 1). We focused our effort on optimizing the C-4 opening process, since it is predicted to afford a product (**14**) with reduced conformational freedom.

No reaction was obtained without a catalyst or using $BF_3 \cdot Et_2O$ as the promoter (entry 1). In contrast, good reactivity was obtained in chloroethanol at room temperature using various metal triflates (entries 2–6), which are known catalysts for alcoholysis of epoxides.[29] The reaction showed little regioselectivity, however the two ether products proved easily separable by flash chromatography and could be fully characterized, based on the different ^{13}C chemical shifts of C4 and C5, which are found, respectively, at 71.1 and 79.8 in **13** and 79.3 and 70.2 in **14**. This set of experiments allowed to select $Cu(OTf)_2$ as the promoter of choice for the synthesis of **14**.

Table 1
Alcoholysis of **7** in chloroethanol[a]

Entry	Catalyst	% Cat	*T* (°C)	**14**/**13** Ratio[b]	**14** (%)[c]
1	$BF_3 \cdot Et_2O$	1 equiv	25	—	No rxn
2	$La(OTf)_3$	10	25	1.2/1	Not isol.
3	$Zn(OTf)_2$	10	25	1/1.3	Not isol.
4	$Cu(OTf)_2$	5	25	1.4/1	55
5	$Cu(OTf)_2$	10	25	1.5/1	60
6	$Cu(OTf)_2$	20	25	2.2/1	65
7	$Cu(OTf)_2$	20	40	2.3/1	74

[a] Reactions were performed in chloroethanol, for 3 h at the temperature indicated.
[b] By ^1H NMR spectroscopy of crude reaction mixtures.
[c] Isolated yield.

The selectivity appears to slightly increase by increasing the amount of catalyst from 5% to 20%. The best results were achieved using 20% $Cu(OTf)_2$ at 40 °C (Table 1, entry 7): under these conditions, the global yield of chloroethyl ethers was almost quantitative, which gave **14** in a satisfactory 74% yields after chromatography. No further selectivity increase was observed with higher catalyst loading.

^1H NMR spectroscopic analysis of the chloroethyl ether products allowed to validate the computational predictions concerning the conformational behavior of these cyclic β-aminoacids. Diagnostic data were obtained from the coupling constants of proton H1, which appeared as a quartet with *J* 4.4 Hz in **13** and as a doublet of triplets with *J* 9.3 Hz and 4.1 Hz in **14**. This is consistent with the prediction that **13** exists as a pair of interconverting chairs, while **14** populates one main chair conformation with the carbomethoxy group in equatorial position.

As for the 1,2-*trans* isomer, the free hydroxyl group of **14** was protected as its silyl ether (Scheme 5, 95% yield) and, finally, chloro-azide exchange in the linker was achieved using excess NaN_3 in DMF at 50 °C, to obtain **3** in quantitative yield. The same sequence on the minor isomer **13** afforded in similar yield the regioisomeric derivative **16** (Scheme 5).

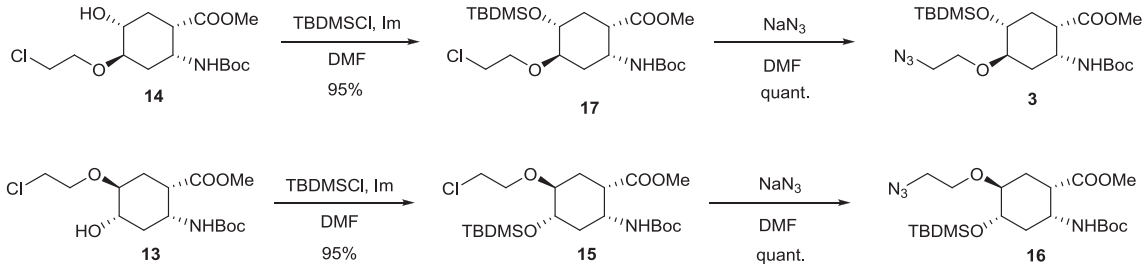
3. Conclusions

In conclusion, in this work we have established a practical synthesis of enantiomerically pure 1,2-*trans* and 1,2-*cis*-2-aminocyclohexanecarboxylic acid (ACHC) derivates **2** and **3** featuring a hydroxyl group and a versatile 2-azidoethyl linker. The regioisomeric 1,2-*cis* compound **16** was also prepared, as a minor isomer of **3**. All compounds were prepared in the 2*R* series using Bölm desymmetrization of tetrahydrophthalic anhydride **1** with quinidine. The enantiomeric 2*S* series can be prepared using quinine in the initial step.[25] We have also shown that both **2** and **3** are conformationally well-defined structures, populating a single (**2**) or a major (**3**) chair conformation. The conformational equilibrium of **3** appears dominated by an apparent bias of the carbomethoxy group to occupy the equatorial position preferentially over the *N*-carbamate group.[16] All the compounds prepared are orthogonally protected and can be used in combination with other ACHC derivatives, as building blocks to construct β-peptides with improved water solubility. The azido group can also be used as a tether to conjugate different residues to the β-peptides like in natural proteins or peptides composed of α-aminoacids.

4. Experimental section

4.1. Material and methods

Solvents were dried by standard procedures: dichloromethane, methanol, *N*,*N*-diisopropylethylamine and triethylamine were



Scheme 5. Synthesis of the 1,2-*cis* functionalized β-aminoacids.

dried with calcium hydride; chloroform and pyridine were dried with activated molecular sieves. Reactions requiring anhydrous conditions were performed under nitrogen. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz with a Bruker AVANCE-400 instrument. Chemical shifts (δ) for the ^{1}H and ^{13}C NMR spectra are expressed in parts per million relative to internal Me_4Si as standard. Signal multiplicities are abbreviated as follows: s, singlet; br. s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were obtained with a Bruker ion-trap Esquire 3000 (ESI ionization) or Autospec Fission spectrometer (FAB ionization) and FT-ICR Mass Spectrometer APEX II & Xmass 4.7 Magnet software (Bruker Daltonics). Thin-layer chromatography (TLC) was carried out on precoated Merck F_{254} silica gel plates. Flash chromatography (FC) was carried out on Macherey–Nagel silica gel 60 (230–400 mesh).

4.2. Synthesis

*4.2.1. Methyl (1R,2R)-2-(N-tert-butoxycarbonylamine)cyclohex-4-enecarboxylate (**4**).* A solution of **9**[23] (600 mg, 3.26 mmol) in dry toluene (6 mL) was treated with Et_3N (550 μL, 2.20 mmol) and DPPA (770 μL, 3.42 mmol). The solution was heated slowly at 80 °C, kept at this temperature until evolution N_2 ceased, and refluxed for 3 h. Then, the solution was cooled at room temperature and *t*-BuOH (1.67 mL, 16.30 mmol) and CuCl (15 mg, 0.13 mmol) were added and the reaction was stirred in reflux overnight. Then, the reaction mixture was cooled and room temperature and washed with $NaHCO_3$ satd (2×50 mL). The aqueous phases were extracted with Et_2O (50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash silica gel column chromathography using as eluent (hexane/AcOEt, 7:1) to obtain **4** (541 mg, 65%) as a transparent oil. $[\alpha]_D^{20}$ −26.6 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.71–5.52 (m, 2H, H_4, H_5), 4.61 (br s, 1H, NH_{Boc}), 4.02(br s, 1H, H_2), 3.68 (s, 1H, COO*Me*), 2.68 (dd, 1H, *J* 14.3, 8.3 Hz, H_1), 2.56–2.40 (m, 2H, H_3, H_6), 2.33–2.23 (m, 1H, $H_{6'}$), 2.00–1.90 (m, 1H, $H_{3'}$), 1.43 (s, 9H, CH_{3Boc}); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.0 (C=O), 155.0 (C=O), 125.0 (C_3 or C_4), 124.2 (C_3 or C_4), 51.9(COO*Me*), 47.25 (C_2), 44.7 (C_1), 31.2 (C_3), 28.3 (CH_{3Boc}), 26.6 (C_6); ESI-MS for $C_{13}H_{21}NO_5$ calcd M^+ 255.1 exptl 278.3 $(M+Na)^+$; HRMS (ESI): $(M+Na)^+$, found 278.13623$C_{13}H_{21}NO_4Na$ requires 278.13628.

*4.2.2. Methyl (1R,2R,4S,5R)-2-(N-tert-butoxycarbonylamine)-4,5-epoxycyclohexanecarboxylate (**5**).* To a solution of **4** (170 mg, 0.67 mmol) in dry CH_2Cl_2 (3 mL) was added MCPBA (160 mg, 0.94 mmol) at 0 °C. Then, the reaction mixture was warmed until room temperature and stirred for 3 h. The reaction was monitored by TLC (hexane/AcOEt, 2:1). The solution was diluted with CH_2Cl_2 (20 mL), washed with $NaHCO_3$ satd (3×20 mL), dried over Na_2SO_4 anhyd and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography using as eluent (hexane/AcOEt, 5:1) to obtain **5** (140 mg, 77%) as a white solid. $[\alpha]_D^{20}$ −35.5 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.11 (d, 1H, *J* 6.6 Hz, NH_{Boc}) 4.03 (br s, 1H, H_2), 3.69 (s, 3H, OCH_3), 3.27 (t, 1H, *J* 3.6 Hz, H_5), 3.18 (t, 1H, *J* 3.1 Hz, H_4), 2.65 (q, 1H, *J* 5.9 Hz, H_1), 2.35 (td, 1H, *J* 15.7, 4.0 Hz, H_{6eq}), 2.26–2.14 (m, 2H, H_{3eq}, H_{6ax}), 1.92 (dd, 1H, *J* 15.7, 5.7 Hz, H_{3ax}), 1.43 (s, 9H, CH_{3Boc}); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.6 (C=O), 154.9 (C=O), 52.0 (CH_3O), 51.7 (C_4), 51.1 (C_5), 45.9 (C_2), 41.2 (C_1), 28.5 (C_3), 28.3 (CH_{3Boc}), 23.8 (C_6); ESI-MS for $C_{13}H_{21}NO_5$ calcd M^+ 271.1 exptl 270.9 M^+ & 294.2 $(M+Na)^+$; HRMS (ESI): $(M+Na)^+$, found 294.13142 $C_{13}H_{21}NO_5Na$ requires 294.13119.

*4.2.3. Methyl (1R,2R,4R,5R)-2-(N-tert-butoxycarbonylamine)-4-(2-chloroethoxy)-5-hydroxycyclohexanecarboxylate (**11**).* To a solution of **5** (130 mg, 0.48 mmol) in 2-chloroethanol (2 mL) was added a catalytic amount of $Cu(OTf)_2$ (40 mg, 0.01 mmol) and the solution was stirred at room temperature under N_2 atmosphere for 3 h. The reaction was monitored by TLC (hexane/AcOEt, 2:1). A solution of NH_4Cl/NH_3 aq (1:1) (30 mL) was added to the reaction mixture. Then, the solution was extracted with AcOEt (2×30 mL). The organic phases were dried over Na_2SO_4 anhyd, and the solvent was eliminated in vacuo to obtain **11** (160 mg, 95%) without further purification as a transparent oil. $[\alpha]_D^{20}$ −16.7 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.52 (br s, 1H, NH_{Boc}) 3.99 (m, 1H, H_2), 3.86–3.76 (m, 2H, CH_2O, H_5), 3.62 (s, 3H, OCH_3), 3.65–3.53 (m, 3H, CH_2O, CH_2Cl), 3.44–3.38 (dt, 1H, H_4), 2.70 (br dt, 1H, *J* 8.8, 4.1 Hz, H_1), 2.24–2.12 (m, 1H, H_6), 1.97–1.66 (m, 3H, 2H_3, $H_{6'}$), 1.36 (s, 9H, CH_{3Boc}); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.6 (C=O), 154.9 (C=O), 78.4 (C_4), 69.3 (CH_2O), 67.4 (C_5), 52.0 (OCH_3), 43.6 (C_1), 43.2 (CH_2Cl), 31.1 (C_3), 30.0 (C_6), 28.3 (CH_{3Boc}); ESI-MS for $C_{15}H_{26}ClNO_6$ calcd M^+ 351.1 exptl 374.2 $(M+Na)^+$; HRMS (ESI): $(M+Na)^+$, found 374.13380$C_{15}H_{26}NO_6ClNa$ requires 374.13409.

*4.2.4. Methyl (1R,2R,4R,5R)-2-(N-tert-butoxycarbonylamine)-4-(2-chloroethoxy)-5-(tert-butyldimethylsilanyloxy)cyclohexane carboxylate (**12**).* To a solution of **11** (43 mg, 0.122 mmol) and 2,6-lutidine (28 μL, 0.245 mmol) in CH_2Cl_2 (300 μL) was added TBDMSOTf (42 μL, 0.183 mmol) and the solution was stirred at room temperature under N_2 atmosphere for 3 h. Then, H_2O (5 mL) was added to the reaction. The reaction mixture was extracted with AcOEt (15 mL). The organic phase was dried over Na_2SO_4 anhyd, and the solvent was eliminated in vacuo. The residue was purified by flash silica gel column chromathography using as eluent (hexane/AcOEt, 11:1) to obtain **12** (58 mg, 97%) as a transparent oil. $[\alpha]_D^{20}$ −8.2 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.47 (br s, 1H, NH_{Boc}), 3.95 (br s, 1H, H_2), 3.92–3.80 (m, 2H, CH_2O, H_5), 3.69 (s, 3H, OCH_3), 3.69–3.59 (m, 3H, CH_2O, CH_2Cl), 3.47–3.42 (m, 1H, H_4), 2.61 (dt, 1H, *J* 11.9, 3.6 Hz, H_1), 2.16–2.11 (m, H, H_6), 2.07 (td, 1H, *J* 13.5, 3.7 Hz, H_3), 1.66 (td, 1H, *J* 14.1, 3.5 Hz, H_6), 1.63–1.55 (m, 1H, H_3), 1.37 (s, 9H, CH_{3Boc}), 0.83 (s, 9H, SiC(CH_3)$_{3\ t\text{-}Bu}$), 0.01 (s, 3H, SiCH_3), 0.00 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.2 (C=O), 154.9 (C=O), 78.2 (C_4), 69.2 (CH_2O), 66.7 (C_5), 51.9 (CH_3O), 45.5 (C_2), 44.1 (C_1), 43.2 (CH_2Cl), 31.3 (C_6 or C_3), 30.9 (C_6 or C_3), 28.4 (CH_{3Boc}), 25.7 (SiC(CH_3)$_3$), −4.9 (SiCH_3), −5.0 (SiCH_3); ESI-MS for $C_{21}H_{40}ClNO_6Si$

calcd M^+ 465.2 exptl 488.4 $(M+Na)^+$; HRMS (ESI): $(M+Na)^+$, found 488.22031 $C_{21}H_{40}NO_6ClSiNa$ requires 294.22056.

*4.2.5. Methyl (1R,2R,4R,5R)-4-(2-aminoethoxy)-2-(N-tert-butoxycarbonylamine)-5-(tert-butyldimethylsilanyloxy) cyclohexancarboxylate (**2**).* To a solution of **12** (34 mg, 0.073 mmol) in DMF (1 mL) were added NaN_3 (38 mg, 0.58 mmol) and a catalytic amount of I_2, the reaction was stirred for 72 h at 50 °C. Then, the solution was diluted in CH_2Cl_2 (10 mL), washed with water (3×10 mL) and dried over Na_2SO_4 anhyd. The residue was purified by flash chromatography using as eluent (hexane/AcOEt, 8:1) to yield **2** (35 mg, quant.) as a transparent oil. $[\alpha]_D^{20}$ −11.4 (*c* 1.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.46 (br s, 1H, NH), 4.00–3.88 (m, 1H, H_2), 3.88 (dd, 1H, *J* 6.0, 3.3 Hz, H_5), 3.88–3.78 (m, 1H, CH_2O), 3.67 (s, 3H, OCH_3), 3.60–3.51 (m, 1H, CH_2O), 3.48–3.38 (m, 2H, H_4, CH_2N_3), 3.33–3.23 (m, 1H, CH_2N_3), 2.60 (dt, 1H, *J* 12.2, 3.5 Hz, H_1), 2.17–2.05 (m, 2H, H_3, H_6), 1.76 (td, 1H, *J* 13.4, 3.3 Hz, H_6), 1.67–1.56 (m, 1H, H_3), 1.42 (s, 9H, CH_{3Boc}), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.06 & 0.05 (2s, 6H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.2 (C=O), 154.9 (C=O), 78.2 (C_4), 68.2 (CH_2O), 66.8 (C_5), 51.9 (CH_3O), 50.9 (CH_2N_3), 46.5 (C_2), 44.1 (C_1), 30.9 (C_6, C_3), 28.4 (CH_{3Boc}), 25.8 ($SiC(CH_3)_3$), −4.8 ($SiCH_3$), −5.0 ($SiCH_3$); ESI-MS for $C_{21}H_{40}N_4O_6Si$ calcd M^+ 472.3 exptl 495.4 $(M+Na)^+$; HRMS (ESI): $(M+Na)^+$, found 495.26080$C_{21}H_{40}N_4O_6SiNa$ requires 495.26093.

*4.2.6. Methyl (1S,2R,4S,5R)-2-(N-tert-butoxycarbonylamine)-4,5-epoxycyclohexanecarboxylate (**7**).* To a solution of **6** (400 mg, 1.57 mmol) in dry CH_2Cl_2 (4 mL) was added MCPBA (377 mg, 2.20 mmol) and the solution was stirred at room temperature for 3 h. The reaction was monitored by TLC (hexane/AcOEt, 2:1). Then, the solution was diluted with CH_2Cl_2 (40 mL), washed with $NaHCO_3$ satd solution (3×45 mL), dried over Na_2SO_4 anhyd and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography using as eluent (hexane/AcOEt, 4:1) to obtain **7** (265 mg, 63%) as a transparent oil. $[\alpha]_D^{20}$ +25.9 (*c* 0.51, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.53 (d, 1H, *J* 10.1 Hz, NH_{Boc}) 4.07 (dtd, 1H, *J* 9.9, 6.6, 3.3 Hz, H_2), 3.72 (s, 3H, OCH_3), 3.23–3.19 (m, 2H, H_4, H_5), 2.65 (dd, 1H, *J* 15.6, 7.6 Hz, H_6), 2.53–2.48 (m, 1H, H_1), 2.23–2.19 (m, 2H, $2H_3$), 2.11 (ddd, 1H, *J* 15.6, 6.1 & 3.2 Hz, H_6), 1.44 (s, 9H, CH_{3Boc}); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 52.5 (CH_3O), 52.3 (C_4 o C_5), 51.6 (C_4 o C_5), 46.0 (C_2), 41.0 (C_1), 30.4, 29.7 (C_3), 29.0 (CH_{3Boc}), 25.2 (C_6); ESI-MS for $C_{13}H_{21}NO_5$ calcd M^+ 271.1 exptl 270.9 M^+ & 271.9 $(M+H)^+$; HRMS (ESI): $(M+Na)^+$, found 294.13148$C_{13}H_{21}NO_5Na$ requires 294.13119.

*4.2.7. Methyl (1S,2R,4S,SR)-2-(N-tert-butoxycarbonylamino)-4-(2-chloroethoxy)-5-hydroxycyclohexanecarboxylate (**13**) and Methyl (1S,2R,4R,5R)-2-(N-tert-butoxycarbonylamine)-4-(2-chloroethoxy)-5-hydroxycyclohexanecarboxylate (**14**).* To a solution of **7** (24 mg, 0.088 mmol) in 2-chloroethanol (300 μL) was added a catalytic amount of $Cu(OTf)_2$ (6.5 mg, 0.01 mmol) and the solution was stirred at room temperature under N_2 atmosphere for 3 h. The reaction was monitored by TLC (hexane/AcOEt, 2:1). A solution of NH_4Cl/NH_3 aq (1:1) (8 mL) was added to the reaction mixture. Then, the solution was extracted with AcOEt (2×20 mL). The organic phases were dried over Na_2SO_4 anhyd, and the solvent was eliminated in vacuo. The final product was purified by silica gel column chromatography using as eluent (hexane/AcOEt, 2:1) to obtain **13** (9 mg, 30%) and **14** (20 mg, 65%) as a transparent oil.

Compound **13**: $[\alpha]_D^{20}$ +36.2 (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.58 (br s, 1H, NH_{Boc}), 4.03–3.90 (br s, 1H, H_2), 3.90 (dd, 1H, *J* 9.6, 4.4 Hz, CH_2O), 3.75 (s, 3H, OCH_3), 3.74–3.63 (m, 4H, CH_2O, CH_2Cl, H_4), 3.33–3.26 (m, 1H, H_5), 3.00 (q, 1H, *J* 4.4 Hz, H_1), 2.55(br s, 1H, OH), 2.41 (td, 1H, *J* 13.9, 4.1 Hz, H_6), 2.14 (dtd, 1H, *J* 12.9, 4.4, 1.1 Hz, H_3), 1.83 (ddd, 1H, *J* 13.0, 10.6, 9.8 Hz, H_3), 1.58 (ddd, 1H, *J* 14.0, 10.8, 4.6 Hz, H_6), 1.46 (s, 9H, CH_{3Boc}); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.0 (C=O), 79.8 (C_5), 71.1 (C_4), 69.5 (CH_2O), 52.0 (OCH_3), 47.3 (C_2), 43.4 (CH_2Cl), 42.7 (C_1), 34.2 (C_3), 28.3 (C_6), 28.3 (CH_{3Boc}); ESI-MS for $C_{15}H_{26}ClNO_6$ calcd M^+ 351.1 exptl 374.2 $(M+Na)^+$; HRMS (ESI): $(M+Na)^+$, found 374.13385 $C_{15}H_{26}NO_6ClNa$ requires 374.13409.

Compound **14**: $[\alpha]_D^{20}$ −3.2 (*c* 1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.90 (br s, 1H, NH_{Boc}) 4.23 (br s, 1H, H_2), 3.88 (td, 1H, *J* 7.7, 3.3 Hz, CH_2O), 3.69 (s, 3H, OCH_3), 3.69–3.60 (m, 3H, CH_2O, CH_2Cl, H_5), 3.39 (dt, 1H, *J* 9.0, 3.8 Hz, H_4), 2.76 (dt, 1H, *J* 9.3, 4.1 Hz, H_1), 2.29 (ddd, 1H, *J* 13.2, 5.7, 3.9 Hz, H_3), 2.15 (td, 1H, *J* 14.2, 4.3 Hz, H_6), 1.85 (td, 1H, *J* 14.2, 9.3 Hz, H_6), 1.55 (ddd, 1H, *J* 13.1, 9.1, 3.7 Hz, H_3), 1.43 (s, 9H, CH_{3Boc}); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.0 (C=O), 79.3 (C_4), 70.2 (C_5), 69.4 (CH_2O), 52.0 (OCH_3), 46.7 (C_2), 43.4 (CH_2Cl), 42.8 (C_1), 29.7 (C_3), 29.0 (C_6), 28.3 (CH_{3Boc}); ESI-MS for $C_{15}H_{26}ClNO_6$ calcd M^+ 351.1 exptl 374.2 $(M+Na)^+$; HRMS (ESI): $(M+Na)^+$, found 374.13377 $C_{15}H_{26}NO_6ClNa$ requires 374.13409.

*4.2.8. Methyl (1S,2R,4S,5S)-2-(N-tert-butoxycarbonylamine)-4-(2-chloroethoxy)-5-(tert-butyldimethylsilanyloxy)cyclohexane carboxylate (**15**).* To a solution of **13** (130 mg, 0.37 mmol) and imidazol (38 mg, 0.56 mmol) in DMF (1 mL) was added TBDMS-Cl (83 mg, 0.56 mmol) and the reaction was for 6 h at room temperature. Then, the solution was diluted in CH_2Cl_2 (15 mL), washed with water (3×10 mL) and dried over Na_2SO_4 anhyd. The residue was purified by flash chromatography using as eluent (hexane/AcOEt, 9:1) to yield **15** (153 mg, 89%) as a transparent oil. $[\alpha]_D^{20}$ +28.1 (*c* 0.65, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.03 (d, 1H, *J* 9.4 Hz, NH_{Boc}), 4.26 (dd, 1H, *J* 8.6, 3.2 Hz, H_2), 3.94–3.89 (m, 1H, H_4), 3.78–3.71 (m, 1H, CH_2O), 3.69–3.63 (m, 1H, CH_2O), 3.66 (s, 3H, OCH_3), 3.57 (t, 2H, *J* 5.5 Hz, CH_2Cl), 3.46–3.42 (m, 1H, H_5), 2.86 (td, 1H, *J* 12.4, 3.5 Hz, H_1), 2.14 (ddd, 1H, *J* 14.4, 12.4, 2.1 Hz, H_6), 2.00 (td, 1H, *J* 14.4, 3.6 Hz, H_3), 1.79 (td, 1H, *J* 14.4, 3.1 Hz, H_6), 1.71 (td, 1H, *J* 14.3, 3.6 Hz, H_3), 1.38 (s, 9H, CH_{3Boc}), 0.92 (s, 9H, $SiC(CH_3)_3$), 0.10 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.9 (C=O), 155.0 (C=O), 77.4 (C_5), 69.4 (CH_2O), 68.7 (C_4), 51.8 (CH_3O), 46.7 (C_2), 43.2 (CH_2Cl), 40.6 (C_1), 32.6 (C_3), 28.3 (CH_{3Boc}), 25.7 ($SiC(CH_3)_3$), 17.8 (C_6), −5.0 ($SiCH_3$), −5.2 ($SiCH_3$); ESI-MS for $C_{21}H_{40}ClNO_6Si$ calcd M^+ 465.2 exptl 488.4 $(M+Na)^+$ & 504.3 $(M+K)^+$; HRMS (ESI): $(M+Na)^+$, found 488.22088 $C_{21}H_{40}NO_6ClSiNa$ requires 488.22056.

*4.2.9. Methyl (1S,2R,4R,5R)-2-(N-tert-butoxycarbonylamine)-4-(2-chloroethoxy)-5-(tert-butyldimethylsilanyloxy)cyclohexane carboxylate (**17**).* To a solution of **14** (360 mg, 1.03 mmol) and imidazol (105 mg, 1.54 mmol) in DMF (3 mL) was added TBDMS-Cl (231 mg, 1.54 mmol) and the reaction was for 6 h at room temperature. Then, the solution was diluted in CH_2Cl_2 (50 mL), washed with water (3×25 mL) and dried over Na_2SO_4 anhyd. The residue was purified by flash chromatography using as eluent (hexane/AcOEt, 9:1) to yield **17** (397 mg, 86%) as a transparent oil. $[\alpha]_D^{20}$ −2.6 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.46 (br s, 1H, NH_{Boc}), 4.11 (br s, 1H, H_2), 3.85 (td, 1H, *J* 10.7, 5.6 Hz, CH_2O), 3.75 (dd, 1H, *J* 8.8, 4.3 Hz, H_5), 3.71–3.65 (m, 1H, CH_2O), 3.69 (s, 3H, OCH_3), 3.61 (t, 2H, *J* 5.4 Hz, CH_2Cl), 3.44–3.40 (m, 1H, H_4), 2.68 (q, 1H, *J* 5.1 Hz, H_1), 2.31 (ddd, 1H, *J* 13.4, 10.0, 3.8.1 Hz, H_3), 2.13–2.05 (m, 2H, $2H_6$), 1.70 (td, 1H, *J* 13.4, 4.4 Hz, H_3), 1.45 (s, 9H, CH_{3Boc}), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.75 (s, 3H, $SiCH_3$), 0.65 (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.0 (C=O), 155.1 (C=O), 79.2 (C_4), 69.6 (CH_2O), 68.8 (C_5), 51.5 (CH_3O), 44.8 (C_2), 43.0 (CH_2Cl), 41.4 (C_1), 31.0 (C_6), 29.7 (C_3), 29.3 (CH_{3Boc}), 25.8 ($SiC(CH_3)_3$), −4.8 ($SiCH_3$), −5.1 ($SiCH_3$); ESI-MS for $C_{21}H_{48}ClNO_6Si$ calcd M^+ 465.2 exptl 488.4 $(M+Na)^+$; HRMS (ESI): $(M+Na)^+$, found 488.22001 $C_{21}H_{40}NO_6ClSiNa$ requires 294.22056.

*4.2.10. Methyl (1S,2R,4S,5S)-4-(2-aminoethoxy)-2-(N-tert-butoxycarbonylamino)-5-(tert-butyldimethylsilanyloxy) cyclohexancarboxylate (**16**).* To a solution of **15** (225 mg, 0.49 mmol) in DMF (5 mL) were added NaN_3 (452 mg, 6.90 mmol) and a catalytic amount of I_2,

the reaction was stirred for 48 h at 50 °C. Then, the solution was diluted in CH_2Cl_2 (50 mL), washed with water (3×50 mL) and dried over Na_2SO_4 anhyd. The solvent was evaporated to yield **16** (231 mg, quant.) without further purification as a transparent oil. $[\alpha]_D^{20}$ +13.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.06 (d, 1H, *J* 9.4 Hz, NH_{Boc}), 4.31 (td, 1H, *J* 12.4, 3.2 Hz, H_2), 3.98–3.94 (m, 1H, H_5), 3.73 (ddd, 1H, *J* 9.8, 5.6, 3.2 Hz, CH_2O), 3.69 (s, 3H, OCH_3), 3.62 (ddd, 1H, *J* 10.1, 5.7, 4.4 Hz, CH_2O), 3.50–3.47 (m, 1H, H_4), 3.35 (ddd, 1H, *J* 5.7, 4.2, 1.6 Hz, CH_2N_3), 2.87 (td, 1H, *J* 12.5, 3.5 Hz, H_1), 2.18 (ddd, 1H, *J* 14.9, 12.6, 2.2 Hz, H_6), 2.04 (ddd, 1H, *J* 14.9, 4.0, 3.1 Hz, H_3), 1.85 (td, 1H, *J* 14.9, 3.7 Hz, H_6), 1.74 (td, 1H, *J* 14.0, 3.6 Hz, H_3), 1.41 (s, 9H, CH_{3Boc}), 0.96 (s, 9H, SiC(CH_3)$_3$), 0.14 (s, 3H, SiCH_3), 0.13 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.9 (C=O), 155.0 (C=O), 77.6 (C_4), 68.7 (C_5), 68.2 (CH_2O), 51.8 (CH_3O), 50.9 (CH_2N_3), 46.7 (C_2), 40.5 (C_1), 32.5 (C_3), 28.3 (CH_{3Boc}), 25.7 (SiC(CH_3)$_3$), 17.8 (C_6), −5.0 ($SiCH_3$), −5.1 ($SiCH_3$); ESI-MS for $C_{21}H_{40}N_4O_6Si$ calcd M^+ 472.3 exptl 495.4 $(M+Na)^+$; HRMS (ESI): $(M+Na)^+$, found 495.26058 $C_{21}H_{40}N_4O_6SiNa$ requires 495.26093.

*4.2.11. Methyl (1S,2R,4R,5R)-4-(2-aminoethoxy)-2-(N-tert-butoxycarbonylamine)-5-(tert-butyldimethylsilanyloxy) cyclohexancarboxylate (**3**).* To a solution of **17** (400 mg, 0.862 mmol) in DMF (9 mL) were added NaN_3 (448 mg, 6.90 mmol) and a catalytic amount of I_2, the reaction was stirred for 48 h at 50 °C. Then, the solution was diluted in CH_2Cl_2 (50 mL), washed with water (3×50 mL) and dried over Na_2SO_4 anhyd. The solvent was evaporated to yield **3** (410 mg, quant.) without further purification as a transparent oil. $[\alpha]_D^{20}$ −10.5 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.52 (br s, 1H, NH_{Boc}), 4.10 (br s, 1H, H_2), 3.87–3.70 (m, 2H, H_5, CH_2O), 3.70 (s, 3H, OCH_3), 3.62 (ddd, 1H, *J* 12.6, 7.1, 3.3 Hz, CH_2O), 3.46–3.40 (m, 2H, H_4, CH_2N_3), 3.36–3.30 (m, 1H, CH_2N_3), 2.70 (q, 1H, *J* 4.8 Hz, H_1), 2.31 (ddd, 1H, *J* 13.5, 10.5, 3.0 Hz, H_3), 2.12 (dd, 2H, *J* 5.1, 4.3 Hz, $2H_6$), 1.76 (td, 1H, *J* 9.3, 4.5 Hz, H_3), 1.46 (s, 9H, CH_{3Boc}), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.08 (s, 3H, SiCH_3) 0.07 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.0 (C=O), 155.2 (C=O), 79.0 (C_4), 68.7 (C_5), 68.1 (CH_2O), 51.4 (CH_3O), 51.0 (CH_2N_3), 44.8 (C_2), 41.3 (C_1), 31.0 (C_6), 28.8 (C_3), 28.4 (CH_{3Boc}), 25.8 (SiC(CH_3)$_3$), −4.8 (SiCH_3), −5.1 (SiCH_3); ESI-MS for $C_{21}H_{40}N_4O_6Si$ calcd M^+ 472.3 exptl 495.4 $(M+Na)^+$; HRMS (ESI): $(M+Na)^+$, found 495.26055 $C_{21}H_{40}N_4O_6SiNa$ requires 495.26055.

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References and notes

1. *Enantioselective Synthesis of β-Aminoacids*; Juaristi, E., Soloshonok, V. A., Eds.; Wiley-Interscience: New York, NY, 2005.
2. Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181–2204.
3. Miller, J. A.; Nguyen, S. T. *Mini-Rev. Org. Chem.* **2005**, *2*, 39–45.
4. Ortuno, R. M.; Moglioni, A. G.; Moltrasio, G. Y. *Curr. Org. Chem.* **2005**, *9*, 237–259.
5. Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833–2891.
6. Frackenpohl, J.; Arvidsson, P. I.; Schreiber, J. V.; Seebach, D. *ChemBioChem* **2001**, *2*, 445–455.
7. Weigand, H.; Wirz, B.; Schweitzer, A.; Camenisch, G. P.; Rodriguez-Perez, M. I.; Gross, R.; Woessner, R.; Voges, R.; Arvidsson, P. I.; Franckenpohl, J.; Seebach, D. *Biopharm. Drug Dispos.* **2002**, *23*, 251–262.
8. Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180.
9. Kirshenbaum, K.; Zuckermann, R. N.; Dill, K. A. *Curr. Opin. Struct. Biol.* **1999**, *9*, 530–535.
10. Stigers, K. D.; Soth, M. L.; Nowick, J. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 714–723.
11. Barron, A. E.; Zuckermann, R. N. *Curr. Opin. Chem. Biol.* **1999**, *3*, 681–687.
12. Appella, D. H.; Barchi, J. J.; Durell, S.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 2309–2310.
13. Abele, S.; Guichard, G.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2141–2156.
14. Gung, B. W.; Zou, D.; Stalcup, A. M.; Cottrell, C. E. *J. Org. Chem.* **1999**, *64*, 2176–2177.
15. Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071–13072.
16. Timpano, G.; Tabarani, G.; Anderluh, M.; Invernizzi, D.; Vasile, F.; Potenza, D.; Nieto, P. M.; Rojo, J.; Fieschi, F.; Bernardi, A. *ChemBioChem* **2008**, *9*, 1921–1930.
17. Kiss, L.; Forró, E.; Fülöp, F. *Tetrahedron Lett.* **2006**, *47*, 2855–2858.
18. (a) Fulop, F.; Palko, M.; Forro, E.; Dervarics, M.; Martinek, T. A.; Sillanpaa, R. *Eur. J. Org. Chem.* **2005**, *15*, 3214–3220; (b) Kiss, L.; Forró, E.; Sillanpää, R.; Fülöp, F. *J. Org. Chem.* **2007**, *72*, 8786–8790; (c) Kiss, L.; Forró, E.; Martinek, T. A.; Bernáth, G.; De Kimpe, N.; Fülöp, F. *Tetrahedron* **2008**, *64*, 5036–5043; Kiss, L.; Fülöp, F. *Synlett* **2010**, 1302–1314.
19. (a) Sattin, S.; Daghetti, A.; Thépaut, M.; Berzi, A.; Sánchez-Navarro, M.; Tabarani, G.; Rojo, J.; Fieschi, F.; Clerici, M.; Bernardi, A. *ACS Chem. Biol.* **2010**, *3*, 301–312; (b) Luczkowiak, J.; Sattin, S.; Sutkevičiūtė, I.; Reina, J. J.; Sánchez-Navarro, M.; Thépaut, M.; Martínez-Prats, L.; Daghetti, A.; Fieschi, F.; Delgado, R.; Bernardi, A.; Rojo, J. *Bioconjugate Chem.* **2011**, doi.org/10.1021/bc2000403.
20. Garber, K. C. A.; Wangkanont, K.; Carlson, E. E.; Kiessling, L. L. *Chem. Commun.* **2010**, 6747–6749.
21. Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *18*, 1128–1137.
22. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2113–2116.
23. Yue, T.-Y.; McLeod, D. D.; Albertson, K. B.; Beck, S. R.; Deerberg, J.; Fortunak, J. M.; Nugent, W. A.; Radesca, L. A.; Tang, L.; Xiang, C. D. *Org. Process Res. Dev.* **2006**, *10*, 262–271.
24. Kapferer, P.; Vasella, A. *Helv. Chim. Acta* **2004**, *87*, 2764–2789.
25. Bölm, C.; Gerlach, A.; Dinter, C. L. *Synlett* **1999**, 195–196.
26. Bernardi, A.; Arosio, D.; Dellavecchia, D.; Micheli, F. *Tetrahedron: Asymmetry* **1999**, *10*, 3403–3407.
27. Jacobi, P. A.; Murphree, S.; Rupprecht, F.; Zheng, W. *J. Org. Chem.* **1996**, *61*, 2413–2427.
28. (a) O'Brien, P.; Childs, A. C.; Ensor, G. J.; Hill, C. L.; Kirby, J. P.; Dearden, M. J.; Oxenford, S. J.; Rosser, C. M. *Org. Lett.* **2003**, 4955–4957 (and references cited therein).
29. Bernardi, A.; Arosio, D.; Manzoni, L.; Micheli, F.; Pasquarello, A.; Seneci, P. *J. Org. Chem.* **2001**, *66*, 6209–6216.
30. Hirsch, J. A. *Topics in Stereochemistry* **1967**, *1*, 199–219.