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Efficient Synthesis of Hydroxy-Substituted Cispentacin Derivatives

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

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Starting from *N*-protected *cis*- and *trans*-2-aminocyclopent-3-enecarboxylic acid derivatives, isomers of 2-amino-3-hydroxycyclopentanecarboxylic acid (**8** and **12**) were prepared via oxazoline intermediates, whereas the stereoisomeric 2-amino-3,4-dihydroxycyclopentanecarboxylic acids **14** and **17** were synthesized by OsO_4-catalyzed oxidation. The enantiomers of **8** and **14** were also prepared by the same pathway. The structures, stereochemistry and relative configurations of the synthesized compounds were proved by NMR spectroscopy.

Introduction

The importance of alicyclic β-amino acids,[1,2] derived from β-lactams,[3,4] has recently increased because of their occurrence in many pharmacologically important compounds.[5] They can also be introduced into peptides to increase and modify their biological activity.[6] These compounds are found in a large number of natural products, some of which, for example, cispentacin [(1*R*,2*S*)-2-aminocyclopentanecarboxylic acid], exhibit antifungal activity.[7–9] The 4-methylene analogue of cispentacin[10–12] (Icofungipen, PLD-118) is a representative of a novel class of antifungals that are active in vitro against *Candida* species.[13] This β-amino acid actively accumulates in yeast, competitively inhibiting isoleucyl-*t*RNA synthetase and consequently disrupting protein biosynthesis.[14,15]

Hydroxy-functionalized β-amino acids play an important role in medicinal chemistry because they also occur in many important and essential products such as Paclitaxel (Taxol) and Docetaxel (Taxotere), which have chemotherapeutic effects.[16–18] Although of less biological importance than their open-chain analogues, some cyclic hydroxylated β-amino acid derivatives have antibiotic (oryzoxymycin)[19–22] or antifungal activities and are building blocks for pharmaceutically important natural substances.[23]

In our earlier work we described several methods for the synthesis of hydroxy-substituted cyclohexane β-amino acids. The introduction of a hydroxy group into the cyclohexane ring was accomplished stereoselectively starting from *cis*- and *trans*-2-aminocyclohexenecarboxylic acids by iodolactonization or via the corresponding oxazine derivatives.[24,25] Another method involves the hydroxylation of the 2-aminocyclohexenecarboxylic acid by functionalization of the olefinic bond by epoxidation.[26–28]

Only a few syntheses of hydroxylated 2-aminocyclopentanecarboxylic acid derivatives have been reported.[29–32] For example, 2-amino-4-hydroxycyclopentanecarboxylic acid was synthesized from the 4-methylene analogue of cispentacin. After esterification and protection, ozonolysis of the olefinic bond, reduction of the carbonyl group, hydrolysis and deprotection resulted in a diastereomeric (3:1) mixture of the 4-hydroxylated amino acid.[10,31] The all-*cis*-2-amino-4-hydroxycyclopentanecarboxylic acid was accessible by a Curtius reaction of the half acid derived from the *meso*-diester of the appropriate 4-oxocyclopentane and subsequent removal of the oxo group by Clemensen reduction.[30] (1*R*,2*S*,5*S*)-5-Amino-2-hydroxycyclopentanecarboxylic acid can be obtained by lithium amide conjugate addition to ε-oxo α,β-unsaturated esters and subsequent intramolecular cyclization.[29] The polyhydroxylated *trans*-2-aminocyclopentanecarboxylic acid was formed from a D-glucose derivative via a bicyclic sugar nitrolactone.[32]

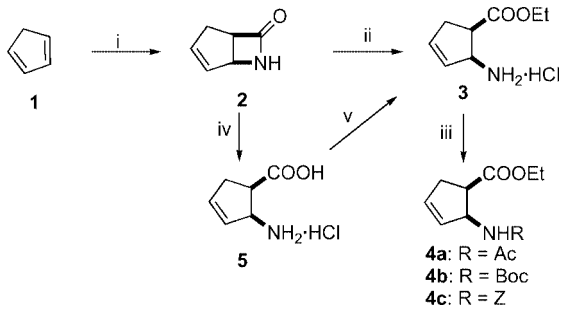
The aim of this work was to functionalize the olefinic bond of *cis*-2-amino-3-cyclopentenecarboxylic acid and to synthesize and structurally analyze new mono- or dihydroxy-substituted derivatives.

Results and Discussion

Diastereomerically pure β-lactam **2** was prepared by 1,2-cycloaddition of chlorosulfonyl isocyanate (CSI) in Et_2O at –10 °C by a modification of a literature procedure.[33] Ring-opening of the β-lactam with ethanolic HCl resulted in the amino ester hydrochloride **3**, which was protected with AcCl, di-*tert*-butyl dicarbonate or benzyl chloroformate to give *N*-acylated esters **4a**–**c** (Scheme 1). An alternative syn-

[a] Institute of Pharmaceutical Chemistry, University of Szeged, 6720 Szeged, Eötvös utca 6, Hungary
Fax: +36-62-545705
E-mail: fulop@pharm.u-szeged.hu
[b] Stereochemistry Research Group of the Hungarian Academy of Sciences, University of Szeged, 6720 Szeged, Eötvös utca 6, Hungary

thesis of **3** comprised hydrolysis of β-lactam **2** with concentrated aqueous HCl at room temperature to amino acid hydrochloride **5**, which was esterified in the presence of EtOH and $SOCl_2$ to give amino ester hydrochloride **3**, which was then acylated by the above methods.



Scheme 1. Reagents and conditions: (i) CSI, Et_2O, 3 h, –10 °C, Na_2SO_3, 61%; (ii) HCl/EtOH, room temp., 1 h, 64%; (iii) R = Ac: Et_3N, AcCl, $CHCl_3$, 2 h, room temp., 73%; R = Boc: Et_3N, Boc_2O, toluene, 2 h, room temp., 69%; R = Z: Et_3N, ZCl, THF, 16 h, room temp., 65%; (iv) concd. HCl, 74%; (v) $SOCl_2$, EtOH, 30 min, 0 °C; 3 h room temp.; 1 h, Δ*T*, 86%.

The selective iodolactonization of *cis*- and *trans*-2-amino-4-cyclohexenecarboxylic acids and *cis*-2-amino-3-cyclohexenecarboxylic acid has previously been reported.[24,25] The iodolactonization of *cis*-2-*tert*-butoxycarbonylaminocyclopent-3-enecarboxylic acid with I_2/KI/$NaHCO_3$ was attempted, but not even traces of the iodolactone product were observed. The starting compound remained unchanged, most probably because of the unstable lactone ring.

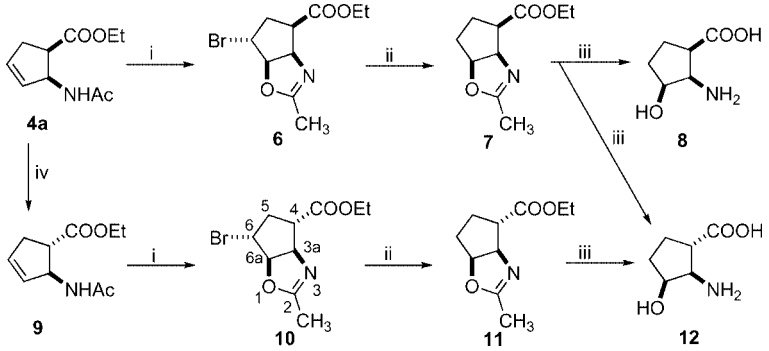
Another possible way to introduce a hydroxy group is the epoxidation of the double bond and then opening of the oxirane ring.[28] Epoxidation of ethyl *cis*-2-acetylamino- (**4a**) and ethyl *cis*-2-benzyloxycarbonylaminocyclopent-3-enecarboxylate (**4c**) in the presence of *m*-chloroperbenzoic acid in CH_2Cl_2 gave the corresponding *cis*-epoxides.[28] In the presence of $NaBH_4$ in EtOH, the oxirane ring remained unchanged.

When *N*-acetyl derivative **4a** was treated with *N*-bromosuccinimide (NBS), bicyclic bromooxazoline derivative **6** was obtained regio- and diastereoselectively (Scheme 2). Not even traces of other regio- or diastereomers were observed in the crude product, according to Markovnikov's rule.[34] Bromooxazoline **6** was then converted into oxazoline **7** by reduction of the bromo group with Bu_3SnH under argon. When **7** was heated to reflux in a 20% aqueous solution of HCl, partial *cis* → *trans* isomerization took place, and ion-exchange chromatography followed by fractional crystallization resulted in (1*S**,2*R**,3*S**)-2-amino-3-hydroxycyclopentanecarboxylic acid (**12**). From the mother liquor the all-*cis*-2-amino-3-hydroxycyclopentanecarboxylic acid (**8**) was also isolated by crystallization (Scheme 2).

The isomerization of **4a** with NaOEt gave the *trans*-*N*-acetyl amino ester **9**. It is known from the literature that such reactions are generally not quantitative and the yields are therefore low.[28] Hydrolysis of **7** followed by isomerization resulted in the corresponding (1*S**,2*R**,3*S**)-2-amino-3-hydroxycyclopentanecarboxylic acid (**12**).

Compounds **6**, **7**, **10** and **11** were characterized by NMR measurements. The values of ^3J(3a-H,6a-H) were in the range of 7.2–7.8 Hz, and large NOE signals were observed between 3a-H and 6a-H, which supports the expected *cis* ring anellation. The fact that no coupling was observed between 6-H and 6a-H for **6** and **10** suggests a *trans*-diequatorial orientation. Consequently, the 6-bromo group should be *trans* relative to the oxazoline ring. In **6** and **7**, ^3J(3a-H,4-H) = 7.2 Hz, and the large NOE signal between 3a-H and 4-H indicates a *cis* (synperiplanar) orientation for 3a-H and 4-H, and consequently a *cis* orientation for the C-4 substituent relative to the oxazoline ring. For **10** and **11**, no coupling was observed between 4-H and 3a-H, which indicates that 4-H and 3a-H are perpendicular to each other. This, together with the small NOE signal between 4-H and 3a-H, suggests a *trans*-diequatorial orientation for the hydrogen atoms and a *trans*-diaxial orientation for the C-3a and C-4 substituents.

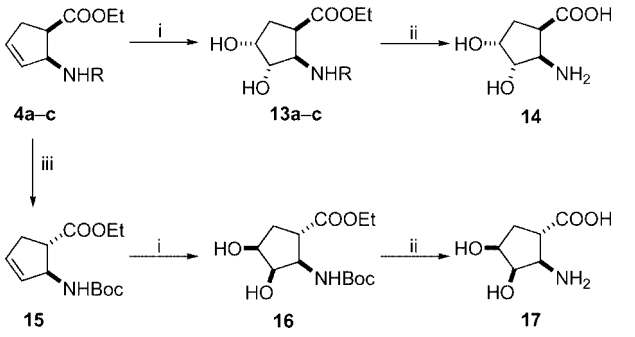
For **12**, the small NOE signal between 1-H and 2-H and the value of ^3J(1-H,2-H) = 9.5 Hz suggest a *trans*-diaxial orientation. Thus, the C-1 and C-2 substituents are *trans*. ^3J(2-H,3-H) = 5.0 Hz indicates an equatorial position for 3-H, which, together with the large NOE between 2-H and 3-H, points to *cis*-oriented C-2 and C-3 substituents. The large NOE signal between 1-H and 2-H and the value ^3J(1-H,2-H) = 6.5 Hz for **8** suggest a *cis*-oriented C-1 carboxy group relative to the C-2 amino group. This is sup-



Scheme 2. Reagents and conditions: (i) NBS, CH_2Cl_2, 3 h, room temp., 71–86%; (ii) Bu_3SnH, CH_2Cl_2, Ar, 20 h, Δ*T*, 63–65%; (iii) 20% HCl/H_2O, 24 h, Δ*T*, 22–67%; (iv) NaOEt, EtOH, 24 h, room temp., 37%.

ported by the fact that an NOE signal was observed between 1-H and 3-H in **8**, whereas no signal was observed between these hydrogen atoms in **12**.

The osmium-catalyzed dihydroxylation of olefins is one of the most efficient methods for the preparation of vicinal diols.[35,36] Ethyl 2-benzoylaminocyclopent-3-enecarboxylate has been successfully dihydroxylated with OsO_4 and 4-methylmorpholine *N*-oxide (NMO).[36] The facile dihydroxylation of olefins **4a**–**c** by oxidation with catalytic OsO_4 and NMO as the stoichiometric co-oxidant afforded the desired products **13a**–**c** as single diastereomers in good yields (Scheme 3). Not even traces of other diastereomers were observed in the crude product, as determined by ^{1}H NMR spectroscopy. The ester functions of **13a**–**c** were then hydrolyzed and the amino group then deprotected to furnish the desired (1*R**,2*R**,3*S**,4*R**)-2-amino-3,4-dihydroxycyclopentanecarboxylic acid (**14**).



Scheme 3. Reagents and conditions: (i) 2.0 wt.-% solution of OsO_4 in *t*BuOH, NMO, acetone, 4 h, room temp.; R = Ac: 47%; R = Boc: 56%; R = Z: 58%; (ii) R = Ac: 20% HCl/H_2O, Δ*T*, 48 h; R = Boc: 10% HCl/H_2O, 24 h, room temp.; R = Z: 5% Pd/C, H_2, EtOH, 12 h, room temp.; 20% HCl/H_2O, Δ*T*, 24 h, 35–37%; (iii) NaOEt, EtOH, 24 h, room temp., 51%.

The isomerization of **4b** with NaOEt resulted in *trans*-*N*-Boc amino ester **15**. By a transformation similar to that of the *cis* isomer **4a**, *trans*-*N*-Boc amino ester **15** reacted via the dihydroxy ester intermediate **16** to yield the corresponding (1*S**,2*R**,3*R**,4*R**)-2-amino-3,4-dihydroxycyclopentanecarboxylic acid (**17**) (Scheme 3).

For **13c** the value ^3J(1-H,2-H) = 8.1 Hz and the very large NOE signal between 1-H and 2-H indicate a *cis* (synperiplanar) orientation of the C-1 and C-2 substituents. The 3-H and 4-H atoms and consequently the C-3 and C-4 hydroxy groups should also be *cis* relative to each other because of the large NOE signal between 3-H and 4-H and the value ^3J(3-H,4-H) = 3.5 Hz. Moreover, the hydroxy groups are located on opposite sides of the cyclopentane ring to the C-1 and C-2 substituents; this can be concluded from the small NOE signal between 2-H and 3-H, the large signal between 3-H and the NH group, and the absence of an NOE signal between 3-H and 1-H or between 4-H and 1-H. The same pattern was detected for **13a**,**b**.

The double bonds in **4a**–**c** undergo oxidation on the sterically less hindered side of the ring. The diastereoselectivity of the dihydroxylation of **15** is not likely to be determined by simple steric repulsion because both the ester and the protected amino group are in equatorial positions. In this case, the hydroxy groups have the same steric orientation as the protected amino group in the final product. This can be rationalized by the probability of an electrostatically advantageous interaction in the intermediate complex of OsO_4 and **15** between the partially positive amide hydrogen atom and the partially negative oxygen atom attacking the sp^2 carbon atom vicinal to the protected amine substituent. This interaction is possible only if OsO_4 is in juxtaposition with the NHBoc moiety.

In the ring closures of the 1,2-disubstituted 1,2- and 1,3-difunctionalized cycloalkanes, striking differences were observed in the cyclization reaction: although the *cis* isomers reacted readily, their *trans* counterparts did not undergo ring closure in most cases.[37,38]

On this basis, we also attempted to prove the relative configurations of **14** and **17** chemically. Compound **14** was esterified with CH_2N_2 and then allowed to react in MeOH with 1 equiv. of *p*-nitrobenzaldehyde. A well-defined product was obtained. ^{1}H NMR spectroscopy indicated that in $CDCl_3$ this compound exists solely as the open Schiff base form.[38] A well-defined signal was observed at δ = 8.4 ppm (s, 1 H, N=CH). No peaks were detected in the interval δ = 5–6 ppm (ring closure product: s, 1 H, NCHO), which underlines the *trans* orientation of the 2-NH_2 and 3-OH substituents. In contrast, for the similar transformation of **17**, both the open Schiff base form and the ring-closure product were observed in the ^{1}H NMR spectra, which points to a *cis* orientation of the 2-NH_2 and 3-OH substituents.

For **15**, the value ^3J(1-H,2-H) = 8.6 Hz and the small NOE signal between 1-H and 2-H suggest a *trans* orientation for 1-H and 2-H. Consequently, the C-1 and C-2 substituents are *trans*. Compound **9** exhibits the same coupling pattern and stereochemistry. For **16** and **17**, the values ^3J(1-H,2-H) = 6–7 Hz and the small NOE signals between 1-H and 2-H point to a *trans* orientation for 1-H and 2-H. Consequently, the carboxy and amino groups should again be *trans*. The relative orientation of the hydroxy groups is *cis* because of the large NOE and the small coupling constant between 3-H and 4-H, and they are located on the same side of the cyclopentane ring as the C-2 substituent. This is proved by the large NOE between 2-H and 3-H. Moreover, in **16**, which was dissolved in [D_6]DMSO for the NMR experiments, NOE signals were observed between the NH and OH groups. The positions of the hydroxy groups are supported by the fact that no NOE signal was detected between 1-H and 3-H or between 1-H and 4-H, whereas a small NOE was found between 2-H and 4-H.

All the above reactions were also performed starting from the enantiomeric (1*R*,2*S*)-2-aminocyclopent-3-enecarboxylic acid hydrochloride [(+)-**5**]. Compound (+)-**5** was prepared by Lipolase (lipase B from *Candida antarctica*) catalyzed enantioselective ring cleavage of *rac*-6-azabicyclo[3.2.0]hept-3-en-7-one (**2**) in iPr_2O at 70 °C.[39] This enantiopure amino acid was transformed with $SOCl_2$ into ethyl (1*R*,2*S*)-2-aminocyclopent-3-enecarboxylate hydrochloride [(+)-**3**]. The 3-hydroxy- and 3,4-dihydroxyamino

acid derivatives (+)-**8** and (–)-**14**, respectively, were synthesized similarly to the corresponding *rac* compounds (Schemes 2 and 3).

Conclusion

Effective and stereoselective routes to mono- and dihydroxylated *cis*- and *trans*-2-aminocaclopentanecarboxylic acid has been developed via oxazoline intermediates and OsO_4-catalyzed oxidation, respectively. Ongoing work uses these amino acids to create foldameric structures.

Experimental Section

General Procedures: ^{1}H NMR spectra were recorded at 400.13 MHz and ^{13}C NMR spectra at 100.62 MHz in D_2O or in [D_6]DMSO at ambient temperature with a Bruker AM 400 spectrometer. Some spectra were recorded with a Bruker AV 600 spectrometer at 600.20 and 150.94 MHz for the ^{1}H and ^{13}C NMR spectra, 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. The *ee* for (1*R*,2*S*)-2-aminocyclopent-3-enecarboxylic acid hydrochloride [(+)-**5**] (>99%) was determined by gas chromatography on a Chromopak Chiralsil-Dex CB column (25 m) after double derivatization with (i) CH_2N_2 and (ii) Ac_2O in the presence of 4-dimethylaminopyridine and pyridine [120 °C for 5 min → 190 °C (rate of temperature rise 10 °C/min, 140 kPa), retention time: 11.51 min], whereas the *ee* for the corresponding ethyl (1*R*,2*S*)-2-aminocyclopent-3-enecarboxylate hydrochloride [(+)-**3**] (>99%) was determined under the same conditions, but the sample was derivatized only with Ac_2O (retention time: 12.28 min). As the *ee* of ethyl (1*R*,2*S*)-2-aminocyclopent-3-enecarboxylate hydrochloride [(+)-**3**] is >99% and not even traces of other diastereomers were detected in the prepared compounds by ^{1}H NMR spectroscopy, the *ee* values for the products are undoubtedly >99%.

***cis*-6-Azabicyclo[3.2.0]hept-3-en-7-one (2):** A solution of CSI (10.5 g, 74.19 mmol) in dry Et_2O (50 mL) was added dropwise to a solution of freshly distilled 1,3-cyclopentadiene (7.00 g, 105.90 mmol) dissolved in dry Et_2O (100 mL) at –10 °C. After the addition was completed, the resulting colourless solution was stirred for 40 min. The reaction mixture was then poured into a stirred solution of Na_2SO_3 (7.6 g, 60.8 mmol) in water (100 mL) and the pH was adjusted to 8–9 with 15% KOH. After stirring at 0 °C for 3 h, the organic layer was separated and the aqueous layer washed with Et_2O (2 × 250 mL) and then with EtOAc (2 × 250 mL). The combined organic layers were dried with Na_2SO_4, and the solution was concentrated to dryness under reduced pressure. The residue was purified by column chromatography (*n*-hexane/EtOAc, 1:3) to afford white crystals (7.04 g, 61%), m.p. 30–32 °C (ref.[33] oil). ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): δ = 2.42–2.49 (m, 1 H, 2-H), 2.69–2.76 (m, 1 H, 2-H), 3.82–3.84 (m, 1 H, 1-H), 4.50–4.51 (m, 1 H, 5-H), 5.93–5.95 (m, 1 H, 4-H), 6.01–6.03 (m, 1 H, 4-H), 6.01–6.03 (m, 1 H, 3-H), 6.48 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 30 °C): δ = 31.5, 54.0, 59.9, 131.3 137.7, 173.0 ppm. C_6H_7NO (109.13): calcd. C 66.04, H 6.47, N 12.84; found C 66.22, H 6.55, N 12.61.

Ethyl *cis*-2-Aminocyclopent-3-enecarboxylate Hydrochloride (3): A solution of β-lactam **2** (5 g, 45.82 mmol) in EtOH containing 22% HCl (50 mL) was stirred at room temperature for 1 h. After removal of the solvent, amino ester hydrochloride **3** was obtained, which was recrystallized from EtOH/Et_2O. Colourless crystals (5.62 g, 64%), m.p. 190–193 °C (ref.[28] 198–200 °C). ^{1}H NMR (400 MHz, [D_6]DMSO, 30 °C): δ = 1.24 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 2.60 (dd, J = 8.8, 16.8 Hz, 1 H, 5-H$_{eq}$), 2.76 (dddd, J = 2.0, 4.5, 8.1, 16.8 Hz, 1 H, 5-H$_{ax}$), 3.42 (ddd, J = 7.7, 8.1, 8.8 Hz, 1 H, 1-H), 4.09–4.18 (m, 2 H, CH$_3$CH_2), 4.28 (d, J = 7.7 Hz, 1 H, 2-H), 5.78–5.82 (m, 1 H, 3-H), 6.12–6.17 (m, 1 H, 4-H), 8.19 (s, 3 H, NH_2) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 30 °C): δ = 14.8, 34.9, 44.6, 56.1, 61.7, 128.2, 137.7, 171.8 ppm. $C_8H_{14}ClNO_2$ (191.70): calcd. C 50.08, H 7.30, Cl 18.52, N 7.30; found C 50.12, H 7.45, N 7.19.

Ethyl *cis*-2-Aminocyclopent-3-enecarboxylate Hydrochloride (3): Thionyl chloride (4.42 g, 37.15 mmol) was added dropwise with stirring to dry EtOH (31 mL) at –15 °C. Compound **5** (5.55 g, 30.92 mmol) was added in one portion to this mixture, which was then stirred at 0 °C for 30 min. After stirring at room temperature for 3 h, the mixture was refluxed for a further 1 h and then concentrated. The residue was recrystallized from EtOH/Et_2O to give colourless crystals. Yield (5.59 g, 86%); m.p. 190–193 °C (ref.[28] 198–200 °C). ^{1}H NMR (400 MHz, [D_6]DMSO, 30 °C): δ = 1.24 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 2.60 (dd, J = 8.8, 16.8 Hz, 1 H, 5-H^{eq}), 2.76 (dddd, J = 2.0, 4.5, 8.1, 16.8 Hz, 1 H, 5-H^{ax}), 3.42 (ddd, J = 7.7, 8.1, 8.8 Hz, 1 H, 1-H), 4.09–4.18 (m, 2 H, CH$_3$CH_2), 4.28 (d, J = 7.7 Hz, 1 H, 2-H), 5.78–5.82 (m, 1 H, 3-H), 6.12–6.17 (m, 1 H, 4-H), 8.19 (s, 3 H, NH_2) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 30 °C): δ = 14.8, 34.9, 44.6, 56.1, 61.7, 128.2, 137.7, 171.8 ppm. $C_8H_{14}ClNO_2$ (191.70): calcd. C 50.08, H 7.30, Cl 18.52, N 7.30; found C 50.12, H 7.45, N 7.19.

Ethyl *cis*-2-Acetylaminocyclopent-3-enecarboxylate (4a): Et_3N (4.05 g, 40 mmol) and AcCl (1.88 g, 24 mmol) were added to a suspension of **3**·HCl (3.83 g, 20 mmol) in $CHCl_3$ (50 mL), and the mixture was stirred at room temperature for 2 h and then washed with water (2 × 20 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 30 mL). The combined organic phases were dried (Na_2SO_4) and the solvents evaporated. The residue was purified by column chromatography (*n*-hexane/EtOAc, 1:3) to afford white crystals (2.88 g, 73%), m.p. 84–86 °C. ^{1}H NMR (400 MHz, [D_6]-DMSO, 30 °C): δ = 1.14 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 1.74 (s, 3 H, COCH$_3$), 2.41 (dd, J = 8.7, 16.7 Hz, 1 H, 5-H$_{eq}$), 2.73 (dddd, J = 2.3, 4.9, 7.2, 16.7 Hz, 1 H, 5-H$_{ax}$), 3.27 (ddd, J = 7.2, 8.6, 8.7 Hz, 1 H, 1-H), 3.93–4.05 (m, 2 H, CH$_3$CH_2), 5.17 (dd, J = 8.6, 9.2 Hz, 1 H, 2-H), 5.51–5.54 (m, 1 H, 3-H), 5.90–5.94 (m, 1 H, 4-H), 7.75 (d, J = 9.2 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 30 °C): δ = 14.0, 22.2, 33.3, 45.8, 55.0, 59.7, 129.5, 132.8, 168.7, 172.3 ppm. $C_{10}H_{15}NO_3$ (197.24): calcd. C 60.90, H 7.67, N 7.10; found C 60.67, H 8.05, N 7.47.

Ethyl *cis*-2-*tert*-Butoxycarbonylaminocyclopent-3-enecarboxylate (4b): Et_3N (4.05 g, 40 mmol) and di-*tert*-butyl dicarbonate (5.24 g, 24 mmol) were added to a suspension of **3**·HCl (3.83 g, 20 mmol) in toluene (50 mL) at 0 °C. Stirring was continued at room temperature for 2 h, after which the organic layer was washed with H_2O (2 × 20 mL) and the aqueous layer extracted with EtOAc. The combined organic phases were dried (Na_2SO_4) and the solvents evaporated. The residue was recrystallized from *n*-hexane to give a white solid (3.52 g, 69%), m.p. 97–99 °C (ref.[28] 89–91 °C). ^{1}H NMR (600 MHz, [D_6]DMSO, 25 °C): δ = 1.17 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 1.35 (s, 9 H, *t*Bu), 2.32 (dd, J = 8.5, 16.5 Hz, 1 H, 5-H$_{eq}$), 2.72 (dddd, J = 2.5, 4.5, 7.4, 16.5 Hz, 1 H, 5-H$_{ax}$), 3.21 (ddd, J = 7.4, 8.5, 8.6 Hz, 1 H, 1-H), 3.97–4.04 (m, 2 H, CH$_3$CH_2), 4.85 (dd, J = 8.6, 9.4 Hz, 1 H, 2-H), 5.51–5.54 (m, 1 H, 3-H), 5.86 (dd,

J = 2.1, 5.1 Hz, 1 H, 4-H), 6.70 (d, J = 9.4 Hz, 1 H, NH) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO, 25 °C): δ = 14.0, 28.2, 33.0, 46.2, 56.9, 59.7, 77.6, 129.3, 132.7, 154.6, 171.8 ppm. $C_{13}H_{21}NO_4$ (255.32): calcd. C 61.16, H 8.29, N 5.49; found C 61.18, H 8.63, N 5.83.

Ethyl *cis*-2-Benzyloxycarbonylaminocyclopent-3-enecarboxylate (4c): Benzyl chloroformate (5.12 g, 30 mmol) was added to a solution of **3**·HCl (3.83 g, 20 mmol) and Et_3N (4.05 g, 40 mmol) in THF (160 mL) at 0 °C. After stirring at room temperature for 16 h, the mixture was taken up in EtOAc (300 mL), washed with H_2O, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was recrystallized from *n*-hexane to give a white solid (4.2 g, 65%), m.p. 55–57 °C (ref.[28] 60–65 °C). ^{1}H NMR (400 MHz, [D$_6$]-DMSO, 30 °C): δ = 1.08 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 2.36 (dd, J = 8.6, 16.7 Hz, 1 H, 5-H$_{eq}$), 2.74 (dddd, J = 2.3, 4.8, 8.2, 16.7 Hz, 1 H, 5-H$_{ax}$), 3.28 (ddd, J = 8.2, 8.6, 9.0 Hz, 1 H, 1-H), 3.95 (q, J = 7.1 Hz, 2 H, CH$_3$CH_2), 4.89–5.00 (m, 3 H, 2-H, OCH_2Ph), 5.53–5.57 (m, 1 H, 3-H), 5.89 (d, J = 4 Hz, 1 H, 4-H), 7.26 (d, J = 9.5 Hz, 1 H, NH), 7.28–7.39 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO, 30 °C): δ = 14.8, 33.9, 47.1, 58.4, 60.6, 66.0, 128.6, 129.1, 130.1, 133.9, 138.0, 156.2, 172.5 ppm. $C_{16}H_{19}NO_4$ (289.33): calcd. C 66.42, H 6.62, N 4.84; found C 66.54, H 6.92, N 5.11.

***cis*-2-Aminocyclopent-3-enecarboxylic Acid Hydrochloride (5):** A solution of β-lactam **2** (5 g, 45.82 mmol) in concentrated HCl (50 mL) was stirred at room temperature for 1 h. After removal of the solvent, the resulting amino acid hydrochloride **5** was recrystallized from EtOH/Et_2O to give a white crystalline solid (5.55 g, 74%), m.p. 185–188 °C (ref.[28] 178–180 °C). ^{1}H NMR (400 MHz, D_2O, 30 °C): δ = 2.58–2.64 (m, 2 H, 5-H), 3.26 (q, J = 8.2 Hz, 1 H, 1-H), 4.24 (d, J = 7.6 Hz, 1 H, 2-H), 5.79–5.83 (m, 1 H, 3-H), 6.18 (d, J = 4.4 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, D_2O, 30 °C): δ = 34.9, 47.8, 57.0, 128.5, 137.7, 180.1 ppm. $C_6H_{10}ClNO_2$ (163.6): calcd. C 44.05, H 6.16, Cl 21.67, N 8.56; found C 43.85, H 6.32, N 8.45.

Ethyl *trans*-2-Acetylaminocyclopent-3-enecarboxylate (9): Freshly prepared NaOEt (1.46 g, 21.54 mmol) was added to a solution of ethyl *cis*-2-acetylaminocyclopent-3-enecarboxylate (**4a**; 5.5 g, 21.54 mmol) in anhydrous EtOH (40 mL), and the mixture was stirred at room temperature for 24 h. It was then concentrated under reduced pressure and taken up in EtOAc, washed with H_2O (2 × 20 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexane/EtOAc, 1:3) to afford white crystals (2.05 g, 37%), m.p. 56–58 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 30 °C): δ = 1.18 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 1.79 (s, 3 H, COCH$_3$), 2.43 (dddd, J = 2.0, 4.2, 5.8, 15.8 Hz, 1 H, 5-H$_{eq}$), 2.66–2.79 (m, 2 H, 1-H, 5-H$_{ax}$), 4.07 (q, J = 7.1 Hz, 2 H, CH$_3$CH_2), 4.97–5.03 (m, 1 H, 2-H), 5.54–5.58 (m, 1 H, 3-H), 5.80–5.84 (m, 1 H, 4-H), 8.06 (d, J = 7.4 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 30 °C): δ = 14.9, 23.4, 36.3, 50.0, 59.5, 61.0, 131.9, 131.9, 169.5, 175.0 ppm. $C_{10}H_{15}NO_3$ (197.24): calcd. C 60.90, H 7.67, N 7.10; found C 60.78, H 7.56, N 7.02.

General Procedure for the Synthesis of Bromooxazolines 6 and 10: A solution of *N*-acetylamino ester **4a** or **9** (2 g, 10.14 mmol) in CH_2Cl_2 (80 mL) was treated with 1.1 equiv. of NBS, and the reaction mixture was stirred at room temperature for 3 h. When the reaction was complete (monitored by TLC), the mixture was treated with aqueous NaOH solution (10%, 3 × 20 mL). The aqueous solution was next extracted with CH_2Cl_2 (3 × 40 mL), the combined organic layers were dried (Na_2SO_4) and the solvents evaporated. The residue was purified by column chromatography (CH_2Cl_2/EtOAc, 10:1) to give a yellow oil.

Ethyl (3a*R,4*R**,6*R**,6a*R**)-6-Bromo-2-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopentaoxazole-4-carboxylate (6):** Yield: 2.41 g, 86%. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 30 °C): δ = 1.21 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 1.87 (s, 3 H, CH$_3$), 2.07 (dd, J = 5.8, 14.9 Hz, 1 H, 5-H$_{eq}$), 2.17 (ddd, J = 4.8, 12.5, 14.9 Hz, 1 H, 5-H$_{ax}$), 3.40 (ddd, J = 6.2, 7.2, 12.5 Hz, 1 H, 4-H), 4.04–4.15 (m, 2 H, CH$_3$CH_2), 4.55 (d, J = 4.8 Hz, 1 H, 6-H), 4.88 (dd, J = 7.2, 7.3 Hz, 1 H, 3-H), 5.05 (d, J = 7.3 Hz, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 30 °C): δ = 13.9, 15.0, 34.7, 48.2, 53.5, 60.9, 72.4, 89.4, 164.6, 170.9 ppm. $C_{10}H_{14}BrNO_3$ (276.13): calcd. C 43.50, H 5.11, N 5.07; found C 43.39, H 5.13, N 5.20.

Ethyl (3a*R,4*S**,6*R**,6a*R**)-6-Bromo-2-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopentaoxazole-4-carboxylate (10):** Yield: 1.99 g, 71%. ^{1}H NMR (600 MHz, [D$_6$]DMSO, 25 °C): δ = 1.21 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 1.89 (s, 3 H, CH$_3$), 2.19–2.27 (m, 1 H, 5-H$_{eq}$), 2.40 (ddd, J = 4.6, 5.0, 14.5 Hz, 1 H, 5-H$_{ax}$), 2.78 (ddd, J = 2.8, 5.1, 7.8 Hz, 1 H, 4-H), 4.12–4.22 (m, 2 H, CH$_3$CH_2), 4.35 (d, J = 4.8 Hz, 1 H, 6-H), 4.81 (d, J = 7.8 Hz, 1 H, 3a-H), 5.01 (d, J = 7.8 Hz, 1 H, 6a-H) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO, 25 °C): δ = 13.3, 13.9, 35.8, 49.7, 52.1, 60.5, 72.4, 88.9, 162.8, 171.9 ppm. $C_{10}H_{14}BrNO_3$ (276.13): calcd. C 43.50, H 5.11, N 5.07; found C 43.42, H 5.17, N 4.95.

General Procedure for the Dehalogenation of Bromooxazolines 6 and 10 to 7 and 11: Bu_3SnH (4.07 g, 14 mmol) was added to a solution of the bromooxazoline (1.93 g, 7 mmol) in CH_2Cl_2 (120 mL) under Ar, and the reaction mixture was stirred at 40 °C for 20 h. The solvent was then evaporated and the residue purified by column chromatography on silica gel (*n*-hexane/EtOAc, 9:1) to afford the oxazoline as an oil.

Ethyl (3a*R,4*R**,6a*S**)-2-Methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopentaoxazole-4-carboxylate (7):** Yield: 0.89 g, 65%. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 30 °C): δ = 1.19 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 1.54–1.69 (m, 3 H, 5-H$_{ax}$, 5-H$_{eq}$, 6-H), 1.81–1.86 (m, 4 H, 6-H, CH$_3$), 2.88 (ddd, J = 6.2, 7.2, 12.5 Hz, 1 H, 4-H), 3.99–4.12 (m, 2 H, CH$_3$CH_2), 4.60 (dd, J = 7.2, 7.3 Hz, 1 H, 3a-H), 4.89 (dd, J = 4.8, 7.3 Hz, 1 H, 6a-H) ppm. ^{13}C NMR (100 MHz, [D$_6$] DMSO, 30 °C): δ = 14.1, 15.0, 24.4, 33.4, 50.1, 60.4, 73.4, 84.2, 165.6, 171.8 ppm. $C_{10}H_{15}NO_3$ (197.24): calcd. C 60.90, H 7.67, N 7.10; found C 60.97, H 7.38, N 7.35.

Ethyl (3a*R,4*S**,6a*S**)-2-Methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopentaoxazole-4-carboxylate (11):** Yield: 0.87 g, 63%. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 30 °C): δ = 1.19 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 1.65–1.87 (m, 4 H, 5-H, 6-H), 1.86 (s, 1 H, CH$_3$), 2.73 (d, J = 7.1 Hz, 1 H, 4-H), 4.07 (q, J = 7.1 Hz, 2 H, CH$_3$CH_2), 4.56 (d, J = 7.7 Hz, 1 H, 3a-H), 4.92 (dd, J = 5.8, 7.7 Hz, 1 H, 6a-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 30 °C): δ = 14.2, 14.9, 26.5, 33.4, 51.5, 61.1, 74.9, 84.4, 164.6, 173.6 ppm. $C_{10}H_{15}NO_3$ (197.24): calcd. C 60.90, H 7.67, N 7.10; found C 60.51, H 7.49, N 7.42.

Synthesis of Stereoisomeric 2-Amino-3-hydroxycyclopentanecarboxylic Acids 8 and 12: A solution of oxazoline derivative **7** (0.6 g, 3.04 mmol) was dissolved in aqueous HCl (20%, 20 mL) and heated at reflux for 24 h. The solvent was then evaporated to afford the crude amino acid hydrochloride. The free amino acid base was liberated by ion-exchange chromatography with Dowex 50. After concentration, the residue was dissolved in water (5 mL) and diluted with acetone (25 mL). After filtration, the solution was left to stand in a refrigerator for 1 h, which resulted in crystalline (1*S**,2*R**,3*S**)-2-amino-3-hydroxycyclopentanecarboxylic acid (**12**) as the main product. From the mother liquor, all-*cis*-2-amino-3-hydroxycyclopentanecarboxylic acid (**8**) was isolated as a diastereomerically enriched (9:1) mixture, which was separated from

12 by crystallization (water/acetone). Compound **12** was synthesized in the same way starting from **11** (0.6 g, 3.04 mmol).

(1*R,2*R**,3*S**)-2-Amino-3-hydroxycyclopentanecarboxylic Acid (8):** Compound **8** was prepared as a white crystalline solid (0.11 g, 25%), m.p. 250–255 °C (dec.). ^{1}H NMR (600 MHz, D_2O, 25 °C): δ = 1.63–1.70 (m, 1 H, 4-H), 1.89–2.07 (m, 3 H, 4-H, 5-H_{ax}, 5-H_{eq}), 2.92 (ddd, J = 6.5, 7.0, 8.7 Hz, 1 H, 1-H), 3.60 (dd, J = 5.4, 6.5 Hz, 1 H, 2-H), 4.31 (ddd, J = 5.4, 5.9, 6.7 Hz, 1 H, 3-H) ppm. ^{13}C NMR (150 MHz, D_2O, 25 °C): δ = 25.3, 30.0, 44.9, 55.0, 71.1, 180.4 ppm. $C_6H_{11}NO_3$ (145.16): calcd. C 49.65, H 7.64, N 9.65; found C 49.41, H 7.43, N 9.58.

(1*S,2*R**,3*S**)-2-Amino-3-hydroxycyclopentanecarboxylic Acid (12):** Compound **12** was prepared as a white crystalline solid (0.097 g, 22% from **7**; 0.20 g, 45% from **11**), m.p. 262–266 °C (dec.). ^{1}H NMR (400 MHz, D_2O, 30 °C): δ = 1.65–1.78 (m, 2 H, 4-H, 5-H), 2.01–2.10 (m, 1 H, 4-H), 2.15–2.25 (m, 1 H, 5-H), 2.80 (q, J = 9.2 Hz, 1 H, 1-H), 3.61 (dd, J = 5.1, 9.3 Hz, 1 H, 2-H), 4.33 (ddd, J = 2.6, 4.9, 5.1 Hz, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, D_2O, 30 °C): δ = 25.9, 31.5, 48.3, 57.6, 71.3, 181.4 ppm. $C_6H_{11}NO_3$ (145.16): calcd. C 49.65, H 7.64, N 9.65; found C 49.41, H 7.43, N 9.58.

Ethyl *trans*-2-*tert*-Butoxycarbonylaminocyclopent-3-enecarboxylate (15): Freshly prepared NaOEt (0.79 g, 11.75 mmol) was added to a solution of ethyl *cis*-2-*tert*-butoxycarbonylaminocyclopent-3-enecarboxylate (**4b**) (3 g, 11.75 mmol) in anhydrous EtOH (35 mL), and the mixture was stirred at room temperature for 24 h. It was then concentrated under reduced pressure, taken up in EtOAc and washed with H_2O (2 × 20 mL). The combined organic phases were dried (Na_2SO_4) and the solvents evaporated. The residue was recrystallized from *n*-hexane to give a white solid (1.53 g, 51%), m.p. 65–67 °C. ^{1}H NMR (400 MHz, [D_6]DMSO, 30 °C): δ = 1.18 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 1.38 (s, 9 H, *t*Bu), 2.40 (dd, J = 6.9, 16.0 Hz, 1 H, 5-H_{eq}), 2.65 (dd, J = 9.6, 16.0 Hz, 1 H, 5-H_{ax}), 2.81 (ddd, J = 6.9, 8.6, 9.6 Hz, 1 H, 1-H), 4.08 (q, J = 7.1 Hz, 2 H, CH$_3$CH_2), 4.72–4.76 (m, 1 H, 2-H), 5.52–5.55 (m, 1 H, 3-H), 5.75–5.77 (m, 1 H, 4-H), 7.08 (d, J = 8.0 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 30 °C): δ = 14.9, 29.1, 36.0, 50.1, 60.9, 61.2, 78.1, 131.4, 132.1, 156.2, 174.7 ppm. $C_{13}H_{21}NO_4$ (255.32): calcd. C 61.16, H 8.29, N 5.49; found C 60.99, H 8.21, N 5.37.

General Procedure for the Dihydroxylation of *N*-Acylamino Esters 4a–c and 15: OsO_4 (3.2 mL, 0.25 mmol; a 2.0 wt.-% solution in *t*BuOH) was added to a stirred solution of *N*-methylmorpholine *N*-oxide (1.73 g, 14.81 mmol) and **4a–c** or **15** (5 mmol) in acetone (35 mL), and the mixture was stirred for 4 h. When the reaction was complete (monitored by TLC), the mixture was treated with aqueous Na_2SO_3 (20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed by evaporation under reduced pressure to afford **13a–c** and **16**, which were recrystallized from EtOAc.

Ethyl (1*R,2*R**,3*S**,4*R**)-2-Acetylamino-3,4-dihydroxycyclopentanecarboxylate (13a):** Compound **13a** was prepared as a white crystalline solid (0.54 g, 47%), m.p. 160–162 °C. ^{1}H NMR (400 MHz, [D_6]DMSO, 30 °C): δ = 1.14 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 1.69 (ddd, J = 2.3, 9.2, 13.7 Hz, 1 H, 5-H_{ax}), 1.77 (s, 3 H, COCH$_3$), 2.09 (ddd, J = 6.1, 7.0, 13.7 Hz, 1 H, 5-H_{eq}), 3.11 (ddd, J = 7.0, 8.9, 9.2 Hz, 1 H, 1-H), 3.73–3.78 (m, 1 H, 3-H), 3.91–4.07 (m, 3 H, 4-H, CH$_3$CH_2), 4.24 (ddd, J = 7.8, 8.4, 8.9 Hz, 1 H, 2-H), 4.57 (d, J = 3.9 Hz, 1 H, OH), 4.63 (d, J = 6.4 Hz, 1 H, O*H*), 7.80 (d, J = 8.4 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 30 °C): δ = 14.9, 23.3, 33.4, 43.5, 56.0, 60.6, 70.4, 76.6, 170.1, 174.2 ppm. $C_{10}H_{17}NO_5$ (231.25): calcd. C 51.94, H 7.41, N 6.06; found C 52.15, H 7.71, N 6.42.

Ethyl (1*R,2*R**,3*S**,4*R**)-2-*tert*-Butoxycarbonylamino-3,4-dihydroxycyclopentanecarboxylate (13b):** Compound **13b** was prepared as a white crystalline solid (0.81 g, 56%), m.p. 122–124 °C. ^{1}H NMR (400 MHz, [D_6]DMSO, 30 °C): δ = 1.16 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 1.37 (s, 9 H, *t*Bu), 1.64 (ddd, J = 2.3, 8.7, 14.0 Hz, 1 H, 5-H_{ax}), 2.07 (ddd, J = 6.1, 7.0, 14.0 Hz, 1 H, 5-H_{eq}), 3.11 (ddd, J = 7.0, 8.7, 9.0 Hz, 1 H, 1-H), 3.72–3.77 (m, 1 H, 3-H), 3.89–4.06 (m, 4 H, 2-H, 4-H, CH$_3$CH_2), 4.51 (d, J = 3.5 Hz, 1 H, OH), 4.60 (d, J = 6.2 Hz, 1 H, OH), 6.72 (d, J = 8.4 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 30 °C): δ = 14.9, 29.1, 33.3, 43.9, 57.8, 60.6, 70.5, 76.7, 78.4, 156.2, 174.0 ppm. $C_{13}H_{28}NO_6$ (289.33): calcd. C 53.97, H 8.01, N 4.84; found C 54.21, H 8.35, N 5.20.

Ethyl (1*R,2*R**,3*S**,4*R**)-2-Benzyloxycarbonylamino-3,4-dihydroxycyclopentanecarboxylate (13c):** Compound **13c** was prepared as a white crystalline solid (0.93 g, 58%), m.p. 118–121 °C. ^{1}H NMR (400 MHz, [D_6]DMSO, 30 °C): δ = 1.08 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 1.66 (ddd, J = 2.3, 9.2, 13.6 Hz, 1 H, 5-H_{ax}), 2.10 (ddd, J = 6.0, 7.3, 13.6 Hz, 1 H, 5-H_{eq}), 3.14 (ddd, J = 7.3, 8.9, 9.2 Hz, 1 H, 1-H), 3.72–3.78 (m, 1 H, 3-H), 3.90–3.99 (m, 3 H, 4-H, CH$_3$CH_2), 4.06 (ddd, J = 7.7, 8.8, 8.9 Hz, 1 H, 2-H), 4.56 (d, J = 3.9 Hz, 1 H, OH), 4.67 (d, J = 6.1 Hz, 1 H, OH), 5.01 (d, J = 2.2 Hz, 2 H, OCH_2Ph), 7.27 (d, J = 8.8 Hz, 1 H, NH), 7.30–7.39 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 30 °C): δ = 14.8, 33.2, 43.8, 58.1, 60.6, 66.1, 70.4, 76.6, 128.6, 129.2, 138.0, 156.9, 173.8 ppm. $C_{16}H_{21}NO_6$ (323.35): calcd. C 59.23, H 6.55, N 4.33; found C 59.01, H 6.39, N 4.52.

Ethyl (1*S,2*R**,3*R**,4*R**)-2-*tert*-Butoxycarbonylamino-3,4-dihydroxycyclopentanecarboxylate (16):** Compound **16** was prepared as a white crystalline solid (0.78 g, 54%), m.p. 150–153 °C. ^{1}H NMR (600 MHz, [D_6]DMSO, 25 °C): δ = 1.16 (t, J = 7.1 Hz, 3 H, CH_3CH$_2$), 1.37 (s, 9 H, *t*Bu), 1.77–1.88 (m, 2 H, 5-H), 2.74–2.79 (m, 1 H, 1-H), 3.72–3.76 (m, 1 H, 3-H), 3.89 (ddd, J = 4.7, 8.4, 8.7 Hz, 1 H, 2-H), 3.93–3.97 (m, 1 H, 4-H), 4.03 (q, J = 7.1 Hz, 2 H, CH$_3$CH_2), 4.68 (d, J = 6.0 Hz, 1 H, OH), 4.83 (d, J = 4.2 Hz, 1 H, OH), 6.28 (d, J = 8.7 Hz, 1 H, NH) ppm. ^{13}C NMR (150 MHz, [D_6]DMSO, 25 °C): δ = 14.0, 28.1, 33.4, 46.0, 55.5, 59.9, 71.0, 72.7, 77.8, 154.9, 174.7 ppm. $C_{13}H_{28}NO_6$ (289.33): calcd. C 53.97, H 8.01, N 4.84; found C 54.08, H 7.79, N 5.03.

General Synthesis of the Stereoisomeric 2-Amino-3,4-dihydroxycyclopentanecarboxylic Acids 14 and 17: A solution of dihydroxy ester **13b** or **16** (2.3 mmol) was dissolved in aqueous HCl (20%, 20 mL), and the mixture was stirred at room temperature for 24 h. In the case of **13a**, the mixture was refluxed for 48 h. The solvent was then evaporated to afford the crude amino ester hydrochloride. The free amino acid base was liberated by ion-exchange chromatography with Dowex 50. An exception was for **13c**: the protected dihydroxy amino acid was first stirred with 10% Pd/C (80 mg) in EtOH (30 mL) under H_2 for 2 h. The catalyst was then filtered off, and the filtrate was concentrated under reduced pressure and subsequently treated with aqueous HCl by the above method.

(1*R,2*R**,3*S**,4*R**)-2-Amino-3,4-dihydroxycyclopentanecarboxylic Acid (14):** Compound **14** was prepared as a white crystalline solid (0.13 g, 35%), m.p. 230–232 °C. ^{1}H NMR (400 MHz, D_2O, 30 °C): δ = 2.14 (ddd, J = 2.3, 9.3, 14.8 Hz, 1 H, 5-H_{ax}), 2.23 (ddd, J = 5.9, 6.8, 14.8 Hz, 1 H, 5-H_{eq}), 3.11 (ddd, J = 6.8, 8.9, 9.3 Hz, 1 H, 1-H), 3.60 (dd, J = 8.4, 8.9 Hz, 1 H, 2-H), 4.15–4.23 (m, 2 H, 3-H, 4-H) ppm. ^{13}C NMR (100 MHz, D_2O, 30 °C): δ = 35.2, 41.0, 55.5, 69.9, 75.5, 180.6 ppm. $C_6H_{11}NO_4$ (161.16): calcd. C 44.72, H 6.88, N 8.69; found C 44.89, H 8.25, N 9.01.

(1*S,2*R**,3*R**,4*S**)-2-Amino-3,4-dihydroxycyclopentanecarboxylic Acid (17):** Compound **17** was prepared as a white crystalline solid (0.12 g, 37%), m.p. 175–179 °C. ^{1}H NMR (400 MHz, D_2O, 30 °C): δ = 2.06–2.23 (m, 2 H, 5-H), 3.26 (ddd, J = 7.5, 9.2, 9.6 Hz, 1 H, 1-H), 3.92 (dd, J = 6.1, 6.3 Hz, 1 H, 3-H), 4.21–4.29 (m, 2 H, 3-H, 4-H) ppm. ^{13}C NMR (100 MHz, D_2O, 30 °C): δ = 32.9, 44.9, 54.1, 71.9, 72.0, 177.2 ppm. $C_6H_{11}NO_4$ (161.16): calcd. C 44.72, H 6.88, N 8.69; found C 44.95, H 6.71, N 8.89.

(1*R*,2*R*,3*S*)-2-Amino-3-hydroxycyclopentanecarboxylic Acid (+)-(8) and (1*R*,2*R*,3*S*,4*R*)-2-Amino-3,4-dihydroxycyclopentanecarboxylic Acid (–)-(14): The same synthetic route as used for the racemic compounds **8** and **14** was applied, starting from *cis*-2-aminocyclopentenecarboxylic acid hydrochloride [(+)-(**5**)],[39] via intermediate (+)-**6** or (–)-**13b**. The ^{1}H NMR spectroscopic data for the intermediates and products are similar to those for the racemates.

Ethyl (1*R*,2*S*)-2-Aminocyclopent-3-enecarboxylate Hydrochloride (+)-(3): White crystals, m.p. 89–91 °C, $[\alpha]_D^{20}$ = +85.4 (c = 0.5, EtOH).

Ethyl (1*R*,2*S*)-2-Acetylaminocyclopent-3-enecarboxylate (+)-(4a): White crystals, m.p. 109–111 °C, $[\alpha]_D^{20}$ = +33.5 (c = 0.5, EtOH).

Ethyl (3a*R*,4*R*,6*R*,6a*R*)-6-Bromo-2-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopentaoxazole-4-carboxylate (+)-(6): Yellow oil, $[\alpha]_D^{20}$ = +71.1 (c = 0.5, CH_2Cl_2).

Ethyl (3a*R*,4*R*,6a*S*)-2-Methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopentaoxazole-4-carboxylate (+)-(7): Yellow oil, $[\alpha]_D^{20}$ = +96.8 (c = 0.5, EtOH).

(1*R*,2*R*,3*S*)-2-Amino-3-hydroxycyclopentanecarboxylic Acid (+)-(8): White crystals, m.p. 228 °C (dec.), $[\alpha]_D^{20}$ = +28.4 (c = 0.584, H_2O).

Ethyl (1*R*,2*S*)-2-*tert*-Butoxycarbonylaminocyclopent-3-enecarboxylate (+)-(4b): Colourless crystals, m.p. 89–90 °C, $[\alpha]_D^{20}$ = +45.1 (c = 0.5, EtOH).

Ethyl (1*R*,2*R*,3*S*,4*R*)-2-*tert*-Butoxycarbonylamino-3,4-dihydroxycyclopentanecarboxylate (–)-(13b): White crystals, m.p. 118–120 °C, $[\alpha]_D^{20}$ = –117.2 (c = 0.5, EtOH).

(1*R*,2*R*,3*S*,4R)-2-Amino-3,4-dihydroxycyclopentanecarboxylic Acid (–)-(14): White crystals, m.p. 223 °C (dec.), $[\alpha]_D^{20}$ = –112.6 (c = 0.5, H_2O).

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