Synthesis of highly functionalized β-aminocyclopentanecarboxylate stereoisomers by reductive ring opening reaction of isoxazolines

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Abstract

A rapid and simple procedure was devised for the synthesis of multifunctionalized cyclic β-amino esters and γ-amino alcohols via the 1,3-dipolar cycloaddition of nitrile oxides to β-aminocyclopentenecarboxylates. The opening of the isoxazoline reductive ring to the corresponding highly functionalized 2-aminocyclopentanecarboxylates occurred stereoselectively with good yields.

Introduction

Isoxazoline-fused amino acids are important bioactive derivatives in organic and medicinal chemistry (e.g., conformationally restricted aspartate and glutamate analogues) [1-6]. As a consequence of their ability to undergo reductive ring opening, isoxazolines are of interest as precursors for the synthesis of highly functionalized molecules such as β-hydroxyketones [7-10], amino alcohols or amino acids [11-17], etc. The multifunctionalized cyclic amino acids – e.g., the antibiotic Oryzoxymycin [18-21], the antiviral agents Tamiflu [22-33], Zanamivir and 2,3-didehydro-2-deoxy-*N*-acetylneuraminic acid (DANA) [34-38] – are bioactive derivatives of great significance for medicinal chemistry. A promising neuraminidase inhibitor, BCX-1812 (Peramivir), is currently under evaluation

in clinical trials [39-45] (Figure 1). A series of Peramivir analogues has recently been investigated as potential antiviral agents [46,47].

Results and Discussion

We recently reported a regio- and stereoselective procedure for the formation of a series of isoxazoline-fused cispentacin and transpentacin regio- and stereoisomers (**2–6**) from bicyclic β-lactam **1** [48,49] (Scheme 1). The syntheses consisted of a dipolar cycloaddition of nitrile oxide (generated with Boc$_2$O, Et$_3$N and DMAP) to the olefinic bond of *cis*-ethyl 2-amino-cyclopent-3-enecarboxylate derived from **1**, during which the isoxazoline-fused amino ester regio- and stereoisomers (**2** and
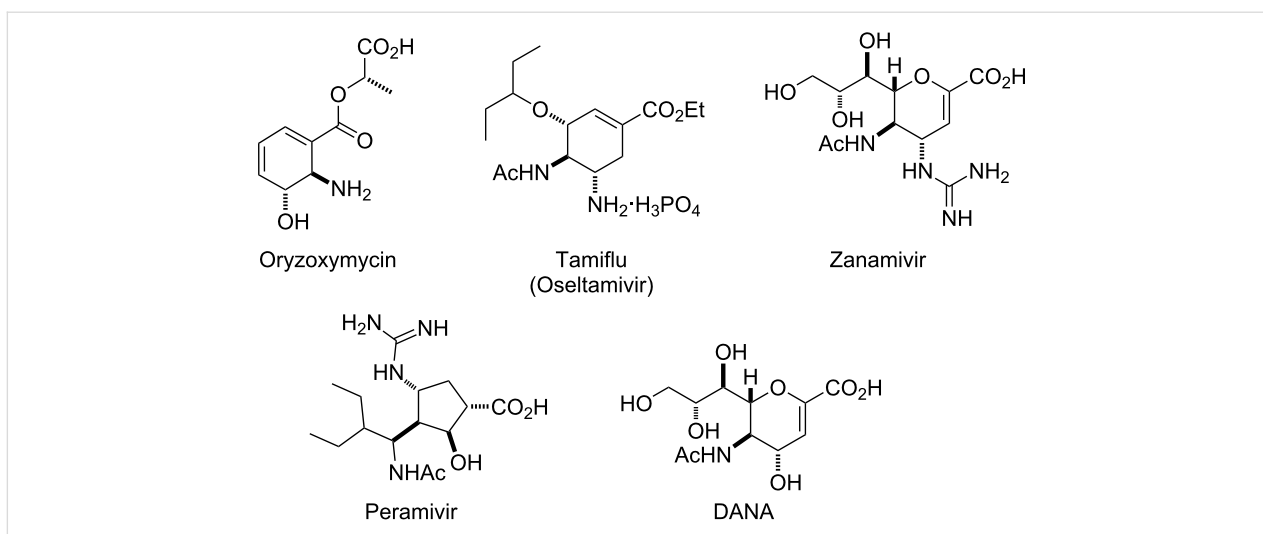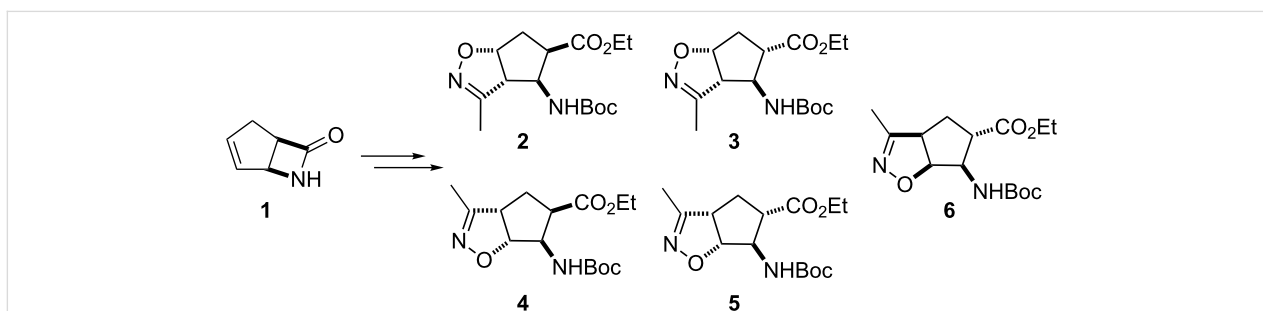
Figure 1: Structures of neuraminidase inhibitors.

Scheme 1: Isoxazoline-fused β-aminocyclopentanecarboxylate regio- and stereoisomers [8].

4) were formed, then separated and isolated. The cycloaddition of nitrile oxide to *trans*-ethyl 2-aminocyclopent-3-enecarboxylate under similar conditions proceeded selectively with the formation of **6**. Epimerization of **2** and **4** afforded *trans* derivatives **3** and **5** [48,49].

Since isoxazoline-functionalized molecules are excellent precursors for the construction of different functional groups through reductive ring cleavage, our recent aim was to synthesize highly functionalized β-aminocyclopentanecarboxylate regio- and stereoisomers from the earlier prepared isoxazoline-fused cispentacin and transpentacin derivatives.

A number of methods are known for the reductive opening of the isoxazoline ring: Catalytic hydrogenation or reduction with Fe in the presence of NH_4Cl, $NaBH_4$, $LiAlH_4$, Raney Ni, $BH_3 \cdot THF$, or $SmI_2/B(OH)_3/H_2O$ [7-17].

For the reduction, we selected model compound **2** from earlier prepared isoxazoline-fused cispentacin stereoisomers to execute the reduction under different conditions. The isoxazoline-fused

derivative was treated with the above-mentioned reducing agents. Unfortunately, neither transformation nor isoxazoline opening with ester reduction was observed. When the reduction was carried out with $NaBH_4$ in EtOH, three products were obtained: The epimerized isoxazoline-fused amino carboxylate **7** and amino alcohols **8** and **9** which were separated by chromatography and isolated (Scheme 2).

Thus, this reaction did not lead to the formation of highly functionalized isoxazoline ring-opened β-amino ester either. When ammonium formate in EtOH in the presence of Pd/C was investigated for the reduction of **2**, the ring opening resulted in carbonyl compound **10** in rather low yield through the corresponding hydroxyimine intermediate, followed by elimination and saturation (Scheme 3).

Combinations of $NaBH_4$ (as a mild and selective reducing agent) with cobalt, nickel, iridium or rhodium halide have previously been employed for cleavage of the isoxazoline ring system, which is otherwise inert to $NaBH_4$ without such metal halide additives [50]. Accordingly, we investigated the reduc-
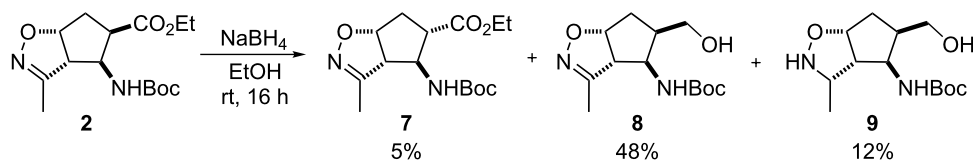
Scheme 2: Treatment of isoxazoline-fused amino ester **2** with NaBH$_4$.
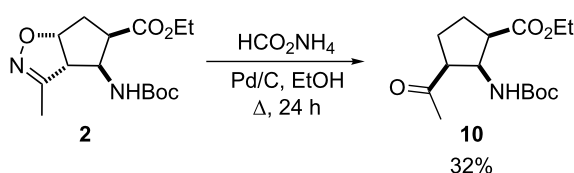
Scheme 3: Reduction with Pd/C in the presence of HCO$_2$NH$_4$.

tion of isoxazoline-fused amino ester stereoisomers **2** [48,49] with NaBH$_4$ in the presence of NiCl$_2$ (Scheme 4), which was found to be a suitable reducing system.

The reduction carried out by adding NaBH$_4$ to a mixture of NiCl$_2$ and isoxazoline derivative **2** in EtOH/H$_2$O, followed by amino group protection with Boc$_2$O, selectively afforded only isoxazoline-opened product **12** as a single diastereomer in good yield. The reaction was exothermic and deposited a black granular precipitate, reflecting the presence of metal boride. The product was purified by column chromatography and the structure of **12** was certified by X-ray analysis (Figure 2).

The isoxazoline opening occurred with the formation of a new stereocenter at a one-carbon distance from C-3. In accordance with earlier results [39-47], the hydrogenation of the isoxazoline proceeded through hydrogen attack from the carbamate side (*cis* to −NHBoc) of the cyclopentane skeleton. This was confirmed by X-ray analysis of **12**.

In order to increase the number of multifunctionalized amino ester stereoisomers, we next examined the reductions of isoxazoline-fused cispentacin and transpentacin stereoisomers (**3**–**6**)
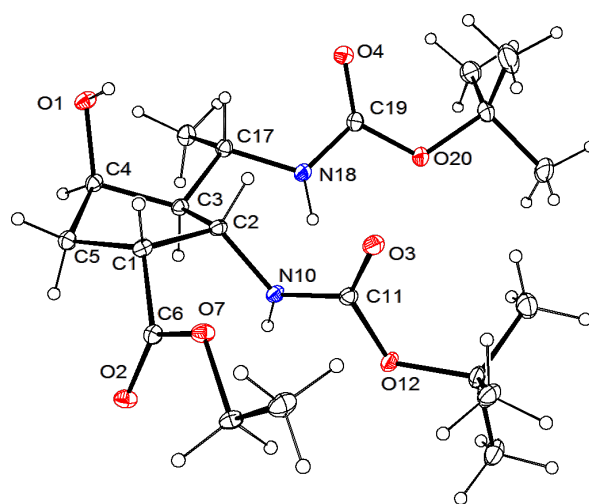

Figure 2: ORTEP diagram of **12** showing the atomic labeling scheme. The thermal ellipsoids are drawn at the 20% probability level.

[49]. Reactions were carried out similarly with NaBH$_4$ in the presence of NiCl$_2$ in EtOH/H$_2$O and led selectively to the corresponding multifunctionalized amino esters **13**–**16** in good yields (Scheme 5) as single diastereoisomers.

Conclusion

The present work has furnished a facile and efficient stereoselective reduction of isoxazoline-fused cyclic β-amino esters to multifunctionalized 2-aminocyclopentanecarboxylates through the use of NaBH$_4$/NiCl$_2$ as reducing agent. As Peramivir related derivatives, highly functionalized cyclic amino esters may be regarded as promising bioactive compounds.
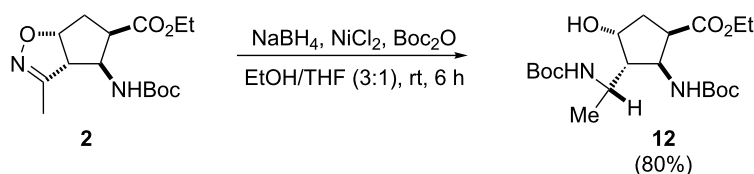
Scheme 4: Transformation of isoxazoline-fused cispentacin stereoisomer **2** into multifunctionalized β-amino acid derivative **12**.
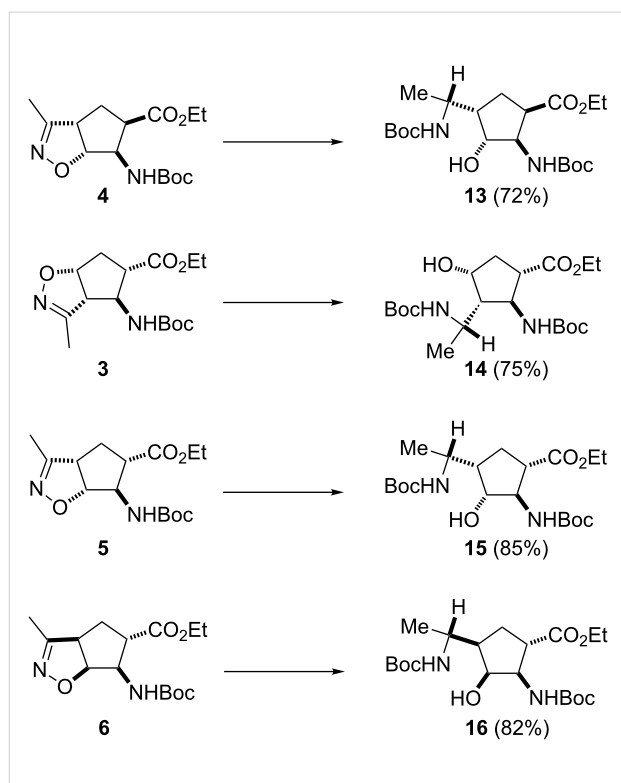
Scheme 5: Synthesis of multifunctionalized β-amino acid derivatives **13–16**. Reaction conditions: NaBH₄, NiCl₂, Boc₂O, EtOH/H₂O, rt, 6 h.

Experimental

The chemicals were purchased from Aldrich. The solvents were used as received from the supplier. Melting points were determined with a Kofler apparatus. NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer in deuterated DMSO or CDCl₃. Chemical shifts are expressed in ppm (δ) from the signal of internal tetramethylsilane. Mass spectra were recorded on a Finnigan MAT 95S spectrometer. Elemental analyses were recorded on a Perkin-Elmer CHNS-2400 Ser II Elemental Analyzer. FTIR spectra were recorded on a Perkin-Elmer Spectrum 100 instrument. Cycloadducts **2–6** were synthesized according to previously published procedures [8].

General procedure for the synthesis of compounds **8** and **9**

To a solution of izoxazoline-fused β-aminocyclopentane-carboxylate **2** (0.96 mmol) in dry EtOH (15 mL) NaBH₄ (2.88 mmol) was added and the reaction mixture was stirred under reflux for 16 h. The reaction was quenched by the addition of H₂O (10 mL) and then, the mixture was concentrated under reduced pressure. The reaction mixture was diluted with H₂O (20 mL), washed with EtOAc (3 × 15 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc) giving **8** and **9**.

General procedure for the synthesis of **10**

To a stirred solution of isoxazoline-fused β-aminocyclopentane-carboxylate **2** (1.6 mmol) in dry EtOH (15 mL), HCOONH₄ (3.2 mmol) and Pd/C (0.10 g) were added and the reaction mixture was stirred under reflux for 24 h. The mixture was filtered through a celite pad and the filtrate was evaporated in vacuo. The crude residue was diluted with EtOAc (30 mL), washed with H₂O (3 × 15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc), giving **10**.

General procedure for isoxazoline ring opening

To a stirred solution of isoxazoline-fused β-aminocyclopentane-carboxylates **2–6** (0.96 mmol) in 8 mL of EtOH/THF (v:v = 3:1), NiCl₂ (1.92 mmol) and Boc₂O (1.92 mmol) were added. After stirring for 10 min, NaBH₄ (1.92 mmol) was added in portions. The reaction mixture was further stirred for 6 h at room temperature and the reaction was quenched by the addition of H₂O (5 mL). The reaction mixture was filtered through a celite pad and the filtrate was evaporated in vacuo. The crude residue was diluted with EtOAc (30 mL), washed with H₂O (3 × 15 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc), giving the corresponding reduced product.

***tert*-Butyl (3a*R**,4*R**,5*R**,6a*R**)-[5-(hydroxymethyl)-3-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazol-4-yl]carbamate (8):** Light-yellow oil; yield 48% (124 mg); R_f 0.35 (*n*-hexane/EtOAc); IR (KBr) ν/cm⁻¹: 3344, 3265, 2979, 1678, 1563, 1184; ¹H NMR (400 MHz, CDCl₃) δ 1.45 (s, 3H, CH₃), 1.56 (s, 9H, CH₃), 1.65–1.72 (m, 2H, CH₂), 2.19–2.25 (m, 1H, H-5), 2.75–2.81 (m, 1H, H-3a), 3.19–3.25 (m, 1H, H-6a), 3.59–3.71 (m, 1H, H-4), 3.63–3.72 (m, 2H, CH₂), 5.42 (br s, 1H, N-H), OH group not observed – exchanged; ¹³C NMR (100 MHz, CDCl₃) δ 16.0, 28.6, 30.2, 32.5, 43.0, 44.4, 59.2, 63.9, 78.0, 155.2, 155.6; MS (ESI) *m/z*: 293 [M + Na]⁺; Anal. calcd for C₁₃H₂₂N₂O₄: C, 57.76; H, 8.20; N, 10.36; found: C, 57.60; H, 8.07; N, 10.23.

***tert*-Butyl (3*S**,3a*R**,4*R**,5*R**,6a*R**)-[5-(hydroxymethyl)-3-methylhexahydro-2*H*-cyclopenta[*d*]isoxazol-4-yl]carbamate (9):** Colorless oil; yield 12% (31 mg); R_f 0.29 (*n*-hexane/EtOAc); IR (KBr) ν/cm⁻¹: 3460, 3331, 2978, 1683, 1531, 1174; ¹H NMR (400 MHz, CDCl₃) δ 0.98–1.05 (m, 3H, CH₃), 1.36 (s, 9H, CH₃), 1.55–1.75 (m, 2H, CH₂), 2.22–2.27 (m, 1H, H-5), 2.38–2.47 (m, 1H, H-3a), 2.78–2.86 (m, 1H, H-3), 3.17–3.24 (m, 1H, H-6a), 3.59–3.69 (m, 1H, H-4), 3.36–3.68 (m, 2H, CH₂), 5.32 (br s, 1H, N-H), 6.12 (br s, 1H, N-H), OH group not observed – exchanged; ¹³C NMR (100 MHz, CDCl₃) δ 15.0,

27.1, 29.0, 35.8, 42.4, 51.7, 57.2, 62.6, 77.4, 80.4, 155.6; MS (ESI) *m/z*: 295 [M + Na]$^+$; Anal. calcd for $C_{13}H_{24}N_2O_4$: C, 57.33; H, 8.88; N, 10.29; found: C, 57.20; H, 8.71; N, 10.42.

Ethyl (1*R**,2*S**,3*S**)-3-acetyl-2-(*tert*-butoxycarbonyl-amino)cyclopentanecarboxylate (10): White solid; yield 32% (153 mg); mp 109–110 °C; R_f 0.62 (*n*-hexane/EtOAc); IR (KBr) ν/cm^{-1}: 3354, 2978, 1716, 1684, 1531, 1171; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.29 (t, *J* = 7.54 Hz, 3H, CH$_3$), 1.41 (s, 9H, CH$_3$), 1.59–1.71 (m, 2H, CH$_2$), 1.74–1.95 (m, 2H, CH$_2$), 2.05 (s, 3H, CH$_3$), 2.83–2.97 (m, 1H, H-1), 3.01–3.15 (m, 1H, H-3), 4.18–4.29 (m, 2H, OCH$_2$), 4.31–4.44 (m, 1H, H-2), 5.76 (br s, 1H, N-H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.98, 20.05, 25.76, 29.31, 31.21, 43.97, 46.01, 52.70, 82.01, 155.67, 176.01, 206.52; MS (ESI) *m/z*: 322 [M + Na]$^+$; Anal. calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68; found: C, 60.05; H, 8.35; N, 4.54.

Ethyl (1*R**,2*S**,3*S**,4*R**)-2-(*tert*-butoxycarbonyl)-3-((*S**)-1-(*tert*-butoxycarbonyl)ethyl)-4-hydroxycyclopentanecarboxy-late (12): White solid; yield 80% (320 mg); mp 120–121 °C; R_f 0.22 (*n*-hexane/EtOAc 1:1); IR (KBr) ν/cm^{-1}: 3457, 3348, 2982, 1720, 1698, 1531, 1160; ^{1}H NMR (400 MHz, DMSO) δ 0.96 (t, *J* = 7.34 Hz, 3H, CH$_3$), 1.27–1.33 (m, 3H, CH$_3$), 1.45–1.50 (m, 18H, CH$_3$), 1.94–2.02 (m, 2H, CH$_2$), 2.07–2.16 (m, 1H, H-4), 3.30–3.39 (m, 1H, H-1), 3.80–3.89 (m, 1H, CH), 4.13–4.23 (m, 2H, OCH$_2$), 4.24–4.30 (m, 1H, H-2), 4.44–4.56 (m, 1H, H-3), 5.28–5.35 (m, 1H, NH), 5.61–5.72 (m, 1H, NH), OH group not observed – exchanged; ^{13}C NMR (100 MHz, CDCl$_3$) δ 11.7, 14.6, 28.8, 28.9, 29.3, 30.1, 31.8, 37.3, 44.6, 51.1, 54.6, 61.2, 73.7, 80.1, 80.4, 155.0, 156.5, 172.0; MS (ESI) *m/z*: 418 [M + 2H]$^+$; Anal. calcd for $C_{20}H_{36}N_2O_7$: C, 57.67; H, 8.71; N, 6.73; found: C, 57,44; H, 8.86; N, 6.58.

Ethyl (1*R**,2*R**,3*R**,4*S**)-2-(*tert*-butoxycarbonyl)-4-((*R**)-1-(*tert*-butoxycarbonyl)ethyl)-3-hydroxycyclopentanecarboxy-late (13): White solid; yield 72% (288 mg); mp 129–130 °C; R_f 0.59 (*n*-hexane/EtOAc 1:1); IR (KBr) ν/cm^{-1}: 3479, 3347, 3353, 1725, 1685, 1662, 1531, 1163; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.17–1.29 (m, 6H, CH$_3$), 1.40–1.46 (m, 18H, CH$_3$), 1.79–1.91 (m, 1H, CH$_2$), 2.05–2.19 (m, 2H, CH$_2$, H-1), 3.26–3.34 (m, 1H, H-4), 3.86–4.01 (m, 2H, H-2, CH), 4.08–4.19 (m, 3H, OCH$_2$, H-3), 4.53 (br s, 1H, N-H), 5.05 (br s, 1H, N-H), OH group not observed – exchanged; ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.6, 21.1, 28.4, 28.7, 28.8, 44.0, 46.6, 60.5, 61.2, 67.5, 77.6, 80.2, 86.4, 156.1, 156.4, 174.8; MS (ESI) *m/z*: 418 [M + 2H]$^+$; Anal. calcd for $C_{20}H_{36}N_2O_7$: C, 57.67; H, 8.71; N, 6.73; found: C, 57.50; H, 8.98; N, 6.39.

Ethyl (1*S**,2*S**,3*S**,4*R**)-2-(*tert*-butoxycarbonyl)-3-((*S**)-1-(*tert*-butoxycarbonyl)ethyl)-4-hydroxycyclopentanecarboxy-

late (14): White solid; yield 75% (300 mg); mp 144–145 °C; R_f 0.3 (*n*-hexane/EtOAc 1:1); IR (KBr) ν/cm^{-1}: 3420, 3363, 2980, 1692, 1537, 1185; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.26–1.33 (m, 6H, CH$_3$), 1.43–1.48 (m, 18H, CH$_3$), 1.82–1.93 (m, 1H, CH$_2$), 1.98–2.15 (m, 1H, H-1), 2.24–2.36 (m, 1H, CH$_2$), 2.76–2.89 (m, 1H, H-3), 3.58–3.72 (m, 1H, H-4), 3.93–4.05 (m, 1H, H-2), 4.15–4.25 (m, 3H, OCH$_2$, CH), 4.87 (br s, 1H, N-H), 5.09 (br s, 1H, N-H), OH group not observed – exchanged; ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.5, 21.4, 28.8, 28.9, 35.9, 45.7, 49.1, 52.3, 54.5, 58.3, 73.4, 80.1, 152.5, 156.8, 172.6; MS (ESI) *m/z*: 418 [M + 2H]$^+$; Anal. calcd for $C_{20}H_{36}N_2O_7$: C, 57.67; H, 8.71; N, 6.73; found: C, 57.41; H, 8.37; N, 6.59.

Ethyl (1*S**,2*R**,3*R**,4*S**)-2-(*tert*-butoxycarbonyl)-4-((*R**)-1-(*tert*-butoxycarbonyl)ethyl)-3-hydroxycyclopentanecarboxy-late (15): White solid; yield 85% (340 mg); mp 141–142 °C; R_f 0.46 (*n*-hexane/EtOAc 1:1); IR (KBr) ν/cm^{-1}: 3426, 3378, 3333, 2979, 1688, 1718, 1703, 1522, 1176; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.21–1.30 (m, 6H, CH$_3$), 1.40–1.46 (m, 18H, CH$_3$), 1.84–1.97 (m, 2H, CH$_2$, H-4), 2.03–2.20 (m, 2H, CH$_2$, H-1), 2.54 (q, *J* = 9.10 Hz, 1H, H-2,), 3.73–3.82 (m, 1H, H-3), 3.87–4.04 (m, 2H, N-H, CH), 4.10–4.22 (m, 2H, OCH$_2$), 4.83 (br s, 1H, N-H), OH group not observed – exchanged; ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.1, 20.0, 27.5, 28.7, 28.8, 45.6, 46.1, 46.8, 60.9, 62.5, 78.1, 80.1, 80.3, 154.0, 156.4, 174.6; MS (ESI) *m/z*: 418 [M + 2H]$^+$; Anal. calcd for $C_{20}H_{36}N_2O_7$: C, 57.67; H, 8.71; N, 6.73; found: C, 57.91; H, 8.46; N, 6.58.

Ethyl (1*S**,2*R**,3*S**,4*R**)-2-(*tert*-butoxycarbonyl)-4-((*S**)-1-(*tert*-butoxycarbonyl)ethyl)-3-hydroxycyclopentanecarboxy-late (16): White solid; yield 82% (328 mg); mp 166–167 °C; R_f 0.32 (*n*-hexane/EtOAc 1:1); IR (KBr) ν/cm^{-1}: 3485, 3368, 3353, 2975, 1733, 1681, 1667, 1533, 1167; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.17–1.31 (m, 6H, CH$_3$), 1.38–1.46 (m, 18H, CH$_3$), 1.79–2.15 (m, 3H, CH$_2$, H-1, H-4), 2.72–2.87 (m, 1H, CH$_2$), 3.77–4.03 (m, 1H, CH), 4.06–4.23 (m, 4H, H-2, H-3, OCH$_2$), 4.37–4.48 (m, 1H, N-H), 4.88 (br s, 1H, N-H), OH group not observed – exchanged; ^{13}C NMR (100 MHz, CDCl$_3$) 14.6, 21.6, 28.7, 28.8, 47.2, 49.0, 59.9, 61.2, 61.6, 69.4, 74.7, 80.0, 85.9, 117.5, 156.1, 158.8, 171.3; MS (ESI) *m/z*: 418 [M + 2H]$^+$; Anal. calcd for $C_{20}H_{36}N_2O_7$: C, 57.67; H, 8.71; N, 6.73; found: C, 57.43; H, 8.40; N, 6.95.

X-ray crystallographic study of 12: Crystallographic data were collected at 123 K with a Nonius-Kappa CCD area detector diffractometer, using graphite-monochromatized Mo K$_a$ radiation (λ = 0.71073 Å) as reported earlier [51]. **Crystal data for 12,** $C_{20}H_{36}N_2O_7$, M_r = 416.51, triclinic, space group *P*−1 (no. 2), *a* = 9.3765(2), *b* = 13.7078(4), *c* = 18.7792(4) Å, α = 96.609(2), β = 95.261(1), γ = 100.965(1), *V* =

2337.9(1) Å^3, T = 123 K, Z = 4, μ(Mo K$_\alpha$) = 0.089 mm^{-1}, 9120 unique reflections (R_{int} = 0.034) which were used in calculations. The final *R1* (for the data with $F^2 > 2\delta(F^2)$) was 0.042 and *wR2*(F^2) (all data) was 0.111.

The SHELXL-97 program [52] was used to solve the structure by direct methods and to perform full-matrix, least-squares refinements on F^2. The unit cell of **12** contains two molecules with slightly different conformations. The CH hydrogen atoms were included at fixed distances from their host atoms with fixed displacement parameters. The NH and OH hydrogen atoms were refined isotropically. The deposition number CCDC 845835 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223-336-033; Email: deposit@ccdc.cam.ac.uk].

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