

Synthesis of Highly Functionalized Fluorinated Cispentacin Derivatives

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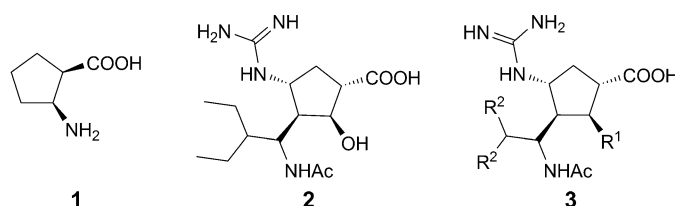
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Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

Fluorinated highly functionalized cispentacin derivatives were synthesised starting from an unsaturated bicyclic β -lactam through C=C bond functionalization *via* the dipolar cycloaddition of a nitrile oxide, isoxazoline opening, and fluorination by OH/F exchange.

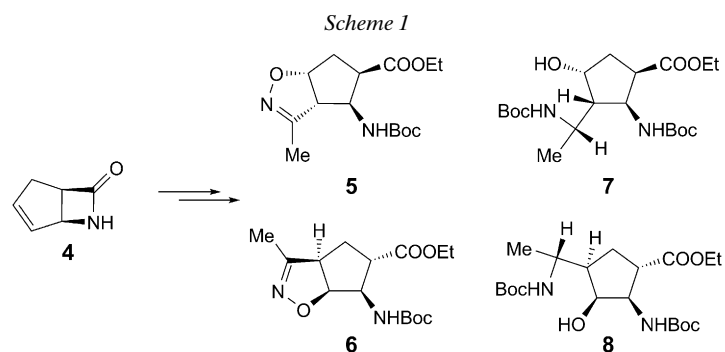
Introduction. – As a result of their biological potential, cyclic β -amino acids are of considerable importance in medicinal chemistry. As conformationally restricted derivatives, they are building blocks for the construction of biologically active peptides [1][2]. They include cispentacin (**1**), an important potent antifungal [1a][1b]. Multisubstituted aminocyclopentanecarboxylic acids such as Peramivir (**2**) and related analogs **3** ($R^1 = \text{H, OH}$; $R^2 = \text{Et, Pr}$) exhibit strong antiviral properties [3].



Fluorinated α - and acyclic β -amino acids comprise an expanding area of research, with increasing impact in both chemistry and biochemistry. They are valuable in medicinal chemistry as enzyme inhibitors, antitumour agents, or antibiotics [4][5]. Only a small number of fluorinated cyclic β -amino acids have been prepared so far, this being particularly true for the five-membered derivatives [6].

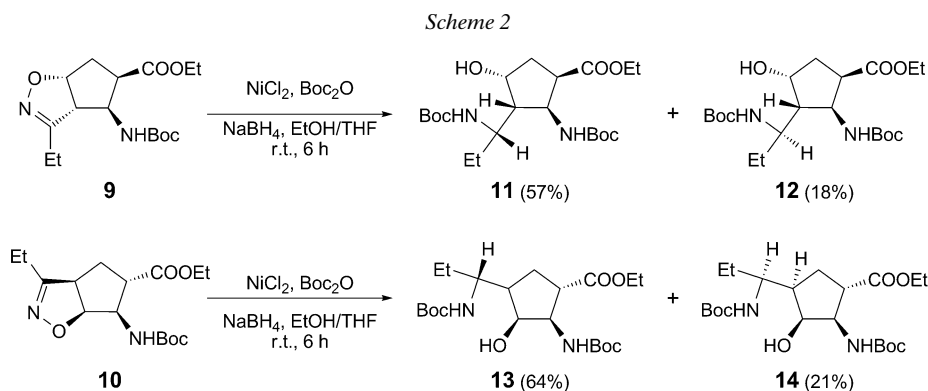
We recently reported the synthesis of highly functionalized cispentacin stereoisomers **7** and **8** from bicyclic β -lactam **4** by means of the regio- and stereoselective 1,3-dipolar cycloaddition of a nitrile oxide (acetonitrile *N*-oxide) to ethyl *cis*- and *trans*-2-aminocyclopentene-3-carboxylates, followed by the stereoselective opening of the isoxazoline ring (*Scheme 1*) [7].

Results and Discussion. – Our current aim was to synthesize highly functionalized regio- and stereoisomers of F-containing five-membered cyclic β -amino acid deriva-



tives from bicyclic β -lactam **4** through selective transformation of its C=C bond by the dipolar cycloaddition of a nitrile oxide, followed by reductive isoxazoline opening and H/F exchange.

Accordingly, novel OH-containing, multifunctionalized β -aminocyclopentanecarboxylates were prepared by reductive ring opening of the isoxazoline skeleton of **9** and **10** [8] (*Scheme 2*). In contrast to our earlier experiments on Me-substituted compounds (*cf. Scheme 1*) [7], the reductive isoxazoline opening of Et-substituted *cis*- and *trans*-isoxazoline-fused derivatives **9** and **10** under similar experimental conditions, with NaBH_4 in the presence of NiCl_2 in EtOH/THF, did not prove to be 100% stereoselective. Both transformations furnished two diastereoisomers, **11** (*Fig. 1*) and **12**, or **13** and **14**, in a ratio of 3 : 1, the major products, **11** and **13**, respectively, resulting from H attack on the isoxazoline from the same face of the carbamate (*Scheme 2*; for several related transformations, see [3]). The products **11** + **12** and **13** + **14** were separated and isolated by column chromatography on SiO_2 .



New multifunctionalized hydroxylated cispentacin analogs containing a longer alkyl chain were next prepared by cycloaddition of the nitrile oxide formed from 2-ethylbutyraldehyde oxime in the presence of *N*-chlorosuccinimide (NCS; *Huisgen's* conditions) to ethyl *cis*- and *trans*-2-aminocyclohexenecarboxylates, **15** and **18**,

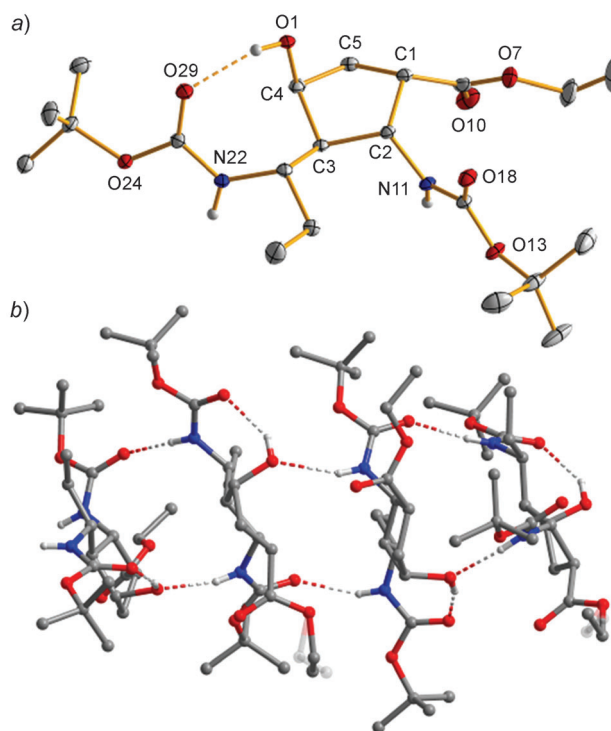


Fig. 1. a) *Molecular structure of compound 11*. Only one of two similar molecules in the asymmetric unit is presented. b) *Ball-and-stick model of 11 showing inter- and intramolecular H-bonds*. Thermal ellipsoids have been drawn at 30% probability level, and the C–H H-atoms are omitted for clarity.

respectively (*Scheme 3*). The cycloaddition to **15** gave isoxazoline-fused amino ester regioisomers **16/17** in a ratio of 7.5 : 1 (*Scheme 3*), the major product containing the O-atom of the isoxazoline skeleton farther from the carbamate group (for analogous transformations, see [8a]). The products were separated by chromatography. Similarly as with other nitrile oxides [8b], the cycloaddition to the *trans* counterpart **18** selectively afforded only cycloadduct **19** (*Scheme 3*).

Analogously to **9** and **10**, the reductive ring openings of isoxazoline-fused *cis*- and *trans*-amino esters **16** and **19**, respectively, with $\text{NaBH}_4/\text{NiCl}_2$ each furnished two products, **20** (*Fig. 2*; the H_2O adduct of the compound)/**21**, or **22/23**, respectively, in a ratio of 2 : 1 and 3 : 1, which were separated by column chromatography (*Scheme 4*).

Introduction of a F-atom in the skeleton of the major isomers of the synthesized highly-functionalized cispentacin derivatives possessing a OH substituent was achieved through H/F exchange with *Deoxo-Fluor*[®] (= bis(2-methoxyethyl)aminosulfur trifluoride) as reagent.

Fluorination of **7**, **11**, and **20** in dry toluene at 0° for 2 h afforded the corresponding fluorinated compounds with inversion, **24a–24c**, and the elimination products **25a–25c**, respectively (for analogous experimental results, see [6a][6b] and ref. cit. therein; *Scheme 5*), which were separated by column chromatography. No experimental

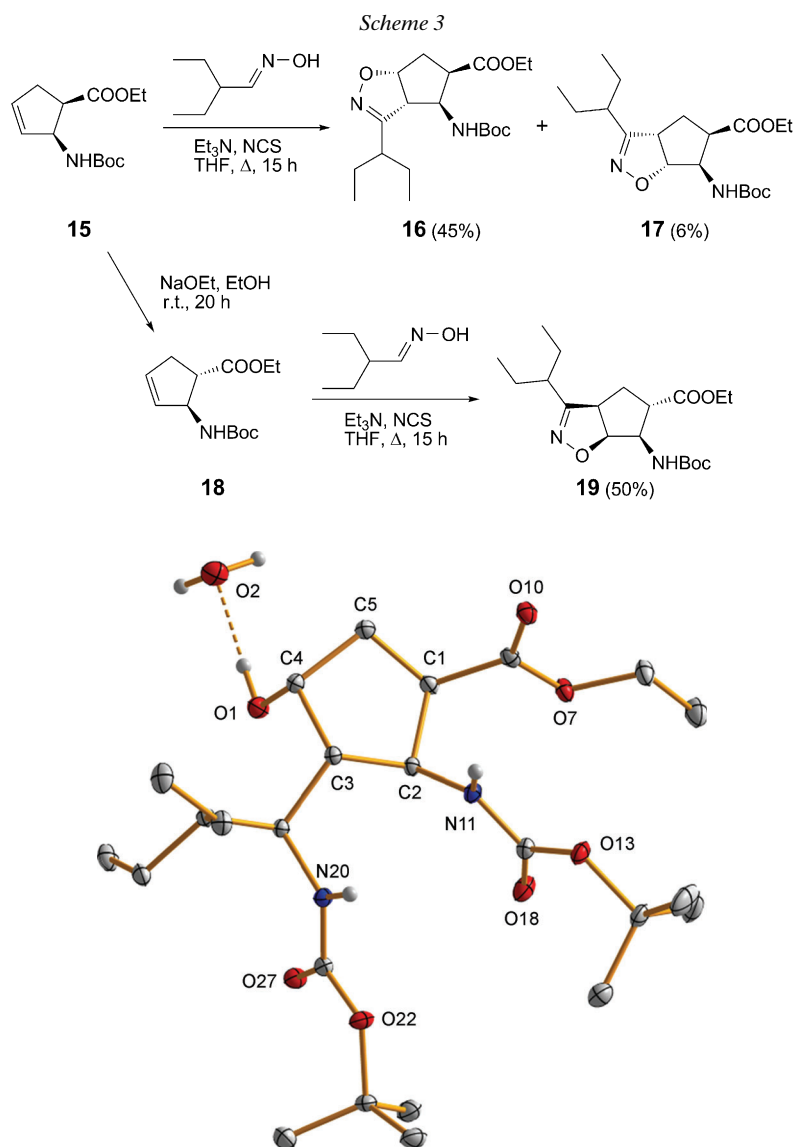
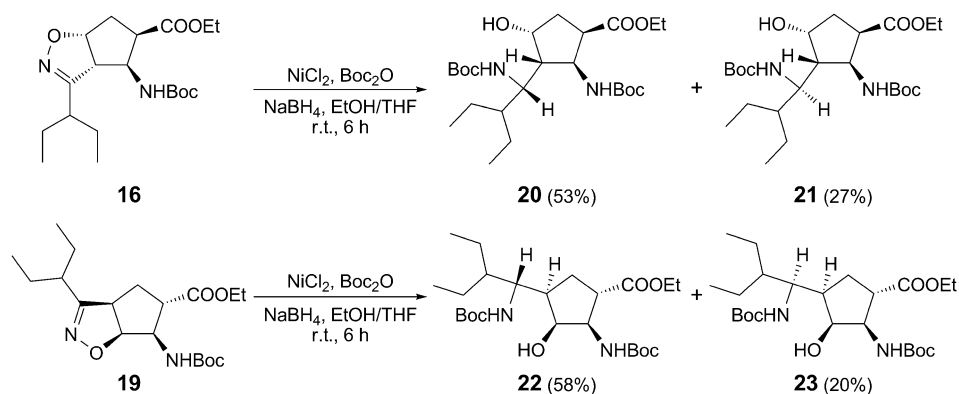


Fig. 2. Molecular structure of compound $20 \cdot \text{H}_2\text{O}$. Thermal ellipsoids have been drawn at 30% probability level, and the C–H H-atoms are omitted for clarity.

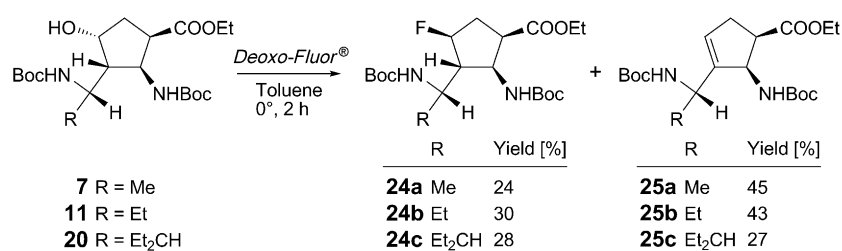
conditions were found under which the large amounts of elimination products could be avoided.

Under similar conditions, fluorination of the *trans* counterparts **8**, **13**, and **22** provided the required fluorinated products **26a** and **26b**, unfortunately again together with large quantities of elimination products **27a–27c**, respectively (*Scheme 6*).

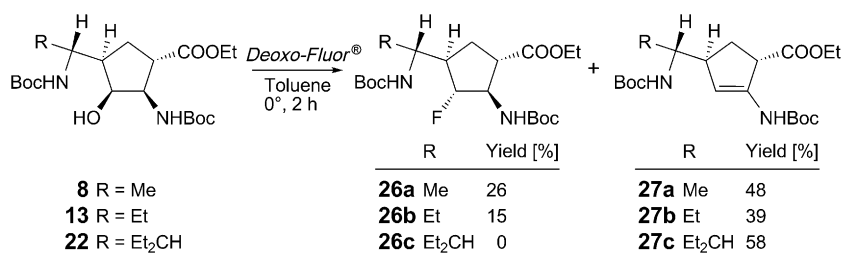
Scheme 4



Scheme 5



Scheme 6



To summarize, highly functionalized fluorinated β -aminocyclopentanecarboxylate regio- and stereoisomers containing multiple stereogenic centers were synthesized from β -aminocyclopentenecarboxylates through the 1,3-dipolar cycloaddition of nitrile oxides and reductive ring opening of the isoxazoline skeleton, followed by H/F exchange. These products may be regarded not only as fluorinated cispentacin derivatives, but as precursors for the preparation of β -amino acid-modified peramivir analogs.

We are grateful to the *Hungarian Research Foundation* (OTKA No. NK81371 and K100530) for financial support.

Experimental Part

General. The chemicals were purchased from *Aldrich*. The solvents were used as received from the supplier. M.p.: *Kofler* apparatus. NMR Spectra: *Bruker DRX 400* spectrometer, chemical shifts, δ , in ppm rel. to TMS as internal standard, with CDCl_3 as solvent. MS: *Finnigan MAT 95S* spectrometer. Elemental analyses: *Perkin-Elmer CHNS-2400 Ser II* elemental analyzer.

Synthesis of 2-Ethylbutyraldehyde Oxime (= (1E)-2-Ethyl-N-hydroxybutan-1-imine). To a soln. of 2-ethylbutyraldehyde (=2-ethylbutanal; 50 mmol) in EtOH (50 ml), dry pyridine (150 mmol), and $\text{NH}_2\text{OH}\cdot\text{HCl}$ (50 mmol) were added, and the mixture was stirred under reflux for 7 h. The mixture was then concentrated under reduced pressure, and the crude residue was purified by column chromatography (CC) on SiO_2 (hexane/AcOEt) to give (1E)-2-ethyl-N-hydroxybutan-1-imine.

General Procedure for the Synthesis of Isoxazoline-Fused β -Aminocyclopentanecarboxylates. To a soln. of amino ester **15** or **18** (19.6 mmol) in THF (70 ml), (1E)-2-ethyl-N-hydroxybutan-1-imine (118 mmol), Et_2NH (19.6 mmol), and *N*-chlorosuccinimide (=1-chloropyrrolidine-2,5-dione; 78.4 mmol) were added, and the mixture was stirred at r.t. for 48 h. The mixture was then diluted with AcOEt (75 ml), washed with H_2O (3×20 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude mixture was purified by CC (SiO_2 ; hexane/AcOEt) to give **16/17** and **19**.

General Procedure for Isoxazoline Ring Opening. To a soln. of dihydroisoxazol **9**, **10**, **16**, or **19** (1.46 mmol) in 10 ml of EtOH/THF 3:1 (v/v), NiCl_2 (2.92 mmol) and Boc_2O (2.92 mmol) were added. After stirring for 10 min, NaBH_4 (2.92 mmol) was added in portions. The mixture was stirred at r.t. for 5 h, and the reaction was then quenched by the addition of H_2O (5 ml). The mixture was filtered through *Celite* pad, and the filtrate was concentrated under reduced pressure. The residue was diluted with AcOEt (30 ml), washed with H_2O (3×10 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The products **11/12**, **13/14**, **20/21**, and **22/23** were purified and separated by CC (SiO_2 ; hexane/AcOEt).

General Procedure for the Synthesis of F-Containing β -Aminocyclopentanecarboxylates. To a soln. of hydroxy compounds **7**, **8**, **11**, **13**, **20**, or **22** (0.5 mmol) in dry toluene (10 ml), *Deoxo-Fluor*[®] soln. (50% in toluene, 0.6 mmol) was added at 0° under Ar. The mixture was stirred at 0° for 2 h, and the mixture was then diluted with AcOEt, washed with sat. NaHCO_3 soln. (3×10 ml), followed by H_2O (2×10 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by CC (SiO_2 ; hexane/AcOEt) to furnish **24a–24c**, **25a–25c**, **26a** and **26b**, and **27a–27c**.

Ethyl (1R,2S*,3S*,4R*)-2-[(tert-Butoxy)carbonylamino]-3-((1S*)-1-[(tert-butoxy)carbonylamino]propyl)-4-hydroxycyclopentanecarboxylate (11).* White solid. Yield: 57%. R_f (hexane/AcOEt) 0.24. M.p. 95–96°. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 0.95 (t, $J=7.36$, Me); 1.30 (t, $J=7.2$, Me); 1.45 (s, 'Bu); 1.49 (s, 'Bu); 1.94–2.16 (m, 2 CH_2); 3.34–3.65 (m, H–C(1)); 3.79–3.89 (m, H–C(3)); 4.12–4.30 (m, H–C(2), CH, CH_2O); 4.44–4.55 (m, H–C(4)); 5.26–5.37 (br. s, NH); 5.61–5.72 (br. s, NH). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 10.9; 13.7; 27.9; 28.0; 28.4; 36.4; 43.8; 50.1; 50.3; 53.8; 60.3; 72.9; 79.3; 79.6; 155.2; 157.3; 174.9. ESI-MS: 431 ($[M+1]^+$). Anal. calc. for $\text{C}_{21}\text{H}_{38}\text{N}_2\text{O}_7$: C 58.58, H 8.90, N 6.51; found: C 58.55, H 8.92, N 6.49.

Ethyl (1R,2S*,3S*,4R*)-2-[(tert-Butoxy)carbonylamino]-3-((1R*)-1-[(tert-butoxy)carbonylamino]propyl)-4-hydroxycyclopentanecarboxylate (12).* White solid. Yield: 18%. R_f (hexane/AcOEt 2:1) 0.33. M.p. 125–127°. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 2.97 (t, $J=7.2$, Me); 1.28 (t, $J=7.1$, Me); 1.43 (s, 'Bu); 1.48 (s, 'Bu); 1.65–1.89 (m, CH_2); 1.96–2.18 (m, CH_2); 3.50–3.61 (m, H–C(1)); 3.66–3.77 (m, H–C(3)); 4.06–4.27 (m, CH, H–C(2), CH_2O); 4.38–4.49 (m, H–C(4)); 4.58–4.72 (br. s, 2 NH). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 10.0; 13.8; 25.3; 27.9; 35.4; 45.6; 50.9; 51.9; 56.6; 60.2; 71.3; 78.9; 79.5; 154.4; 156.7; 174.1. ESI-MS: 431 ($[M+1]^+$). Anal. calc. for $\text{C}_{21}\text{H}_{38}\text{N}_2\text{O}_7$: C 58.58, H 8.90, N 6.51; found: C 59.12, H 8.02, N 6.60.

Ethyl (1R,2S*,3R*,4S*)-2-[(tert-Butoxy)carbonylamino]-4-((1S*)-1-[(tert-butoxy)carbonylamino]propyl)-3-hydroxycyclopentanecarboxylate (13).* White solid. Yield: 64%. R_f (hexane/AcOEt) 0.57. M.p. 216–217°. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 0.96 (t, $J=7.4$, Me); 1.25–1.33 (m, Me); 1.44 (s, 'Bu); 1.49 (s, 'Bu); 1.76–2.38 (m, 2 CH_2); 2.47–2.62 (m, H–C(1)); 2.76–2.96 (m, H–C(4)); 3.10–3.19 (m, H–C(2)); 3.68–3.80 (m, CH); 4.10–4.24 (m, CH_2O); 4.28–4.38 (br. s, NH); 4.42–4.47 (m, H–C(3)); 5.01–5.25 (br. s, NH). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 10.3; 11.1; 27.0; 28.1; 32.4; 33.2; 45.2; 52.3; 50.8; 54.1;

58.8; 72.1; 77.0; 154.5; 156.5; 175.4. ESI-MS: 431 ($[M+1]^+$). Anal. calc. for $C_{21}H_{38}N_2O_7$: C 58.58, H 8.90, N 6.51; found: C 58.57, H 8.91, N 6.49.

Ethyl (1R,2S*,3R*,4S*)-2-[[tert-Butoxy]carbonyl]amino]-4-((1R*)-1-[[tert-butoxy]carbonyl]amino)propyl]-3-hydroxycyclopentanecarboxylate (14)*. Brownish oil. Yield: 21%. R_f (hexane/AcOEt) 0.35. 1H -NMR (400 MHz, $CDCl_3$): 0.96 (*t*, $J = 7.6$, Me); 1.25–1.33 (*m*, Me); 1.45 (*s*, 'Bu); 1.50 (*s*, 'Bu); 1.81–2.15 (*m*, 2 CH_2); 2.24–2.36 (*m*, H–C(4)); 2.74–2.86 (*m*, H–C(1)); 3.69–3.82 (*m*, CH); 4.09–4.26 (*m*, H–C(2), H–C(3), CH_2O); 4.29–4.39 (*br. s*, NH); 5.03–5.20 (*br. s*, NH). ^{13}C -NMR (100 MHz, $CDCl_3$): 10.0; 11.0; 27.9; 28.0; 31.1; 35.5; 45.2; 51.7; 51.1; 56.5; 60.1; 71.6; 78.1; 154.4; 155.5; 174.6. ESI-MS: 453 ($[M+Na]^+$). Anal. calc. for $C_{21}H_{38}N_2O_7$: C 58.58, H 8.90, N 6.51; found: C 58.57, H 8.98, N 6.50.

Ethyl (3aR,4S*,5R*,6aR*)-4-[[tert-Butoxy]carbonyl]amino]-3-(1-ethylpropyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d][1,2]oxazole-5-carboxylate (16)*. Brownish oil. Yield: 45%. R_f (hexane/AcOEt) 0.72. 1H -NMR (400 MHz, $CDCl_3$): 0.90–1.00 (*m*, 2 Me); 1.30 (*t*, $J = 7.1$, Me); 1.47 (*s*, 'Bu); 1.54–1.84 (*m*, 2 CH_2); 2.25–2.41 (*m*, CH_2); 2.46–2.55 (*m*, H–C(5)); 2.94–3.07 (*m*, H–C(3a)); 3.64–3.75 (*m*, CH); 4.16–4.31 (*m*, CH_2O , H–C(4)); 5.06–5.20 (*m*, H–C(6a), NH). ^{13}C -NMR (100 MHz, $CDCl_3$): 11.4; 12.5; 14.5; 24.4; 25.9; 28.6; 31.6; 36.9; 41.0; 45.6; 52.1; 57.1; 61.6; 62.9; 83.7; 155.4; 160.8. ESI-MS: 369 ($[M+1]^+$). Anal. calc. for $C_{19}H_{32}N_2O_5$: C 61.93, H 8.75, N 7.60; found: C 61.92, H 8.76, N 6.758.

Ethyl (3aR,5S*,6S*,6aR*)-6-[[tert-Butoxy]carbonyl]amino]-3-(1-ethylpropyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d][1,2]oxazole-5-carboxylate (17)*. Yellowish oil. Yield: 6%. R_f (hexane/AcOEt) 0.52. 1H -NMR (400 MHz, $CDCl_3$): 1.21–1.33 (*m*, 3 Me); 1.46 (*s*, 'Bu); 1.51–2.20 (*m*, 2 CH_2); 2.32–2.46 (*m*, CH_2); 2.93–3.07 (*m*, H–C(5)); 3.44–3.54 (*m*, H–C(3a)); 4.01–4.24 (*m*, CH, CH_2O); 4.28–4.40 (*m*, H–C(6)); 4.87–4.92 (*m*, H–C(6a)); 5.64–5.80 (*br. s*, NH). ^{13}C -NMR (100 MHz, $CDCl_3$): 10.5; 11.2; 14.5; 23.9; 26.2; 30.0; 31.4; 35.9; 42.1; 44.9; 52.2; 56.9; 59.6; 62.9; 85.0; 155.4; 161.4. ESI-MS: 369 ($[M+1]^+$). Anal. calc. for $C_{19}H_{32}N_2O_5$: C 61.93, H 8.75, N 7.60; found: C 61.91, H 8.76, N 7.61.

Ethyl (3aS,5R*,6S*,6aR*)-6-[[tert-butoxy]carbonyl]amino]-3-(1-ethylpropyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d][1,2]oxazole-5-carboxylate (19)*. White solid. Yield: 50%. R_f (hexane/AcOEt) 0.38. M.p. 95–96°. 1H -NMR (400 MHz, $CDCl_3$): 0.89–1.00 (*m*, 2 Me); 1.29 (*t*, $J = 7.1$, Me); 1.46 (*s*, 'Bu); 1.55–1.74 (*m*, 2 CH_2); 1.97–2.04 (*m*, 1 H of CH_2); 2.14–2.31 (*m*, 1 H of CH_2 , H–C(5)); 2.38–2.49 (*m*, H–C(3a)); 3.62–3.73 (*m*, CH); 4.09–4.34 (*m*, H–C(6), CH_2O); 4.85–4.91 (*m*, H–C(6a)); 5.19–5.26 (*br. s*, NH). ^{13}C -NMR (100 MHz, $CDCl_3$): 10.5; 11.6; 13.6; 23.6; 25.3; 27.8; 29.9; 39.8; 46.4; 50.9; 59.5; 60.6; 79.0; 82.5; 154.6; 162.4; 172.2. ESI-MS: 369 ($[M+1]^+$). Anal. calc. for $C_{19}H_{32}N_2O_5$: C 61.93, H 8.75, N 7.60; found: C 61.95, H 8.74, N 7.59.

Ethyl (1R,2S*,3S*,4R*)-2-[[tert-Butoxy]carbonyl]amino]-3-((1S*)-1-[[tert-butoxy]carbonyl]amino)-2-ethylbutyl)-4-hydroxycyclopentanecarboxylate (20)*. White solid. Yield: 53%. R_f (hexane/AcOEt) 0.26. M.p. 99–100°. 1H -NMR (400 MHz, $CDCl_3$): 0.80–0.93 (*m*, 2 Me); 1.24–1.67 (*m*, 2 'Bu, CH_2); 1.97–2.21 (*m*, 1 H of CH_2 , H–C(1), H–C(3)); 3.31–3.40 (*m*, CH); 3.77–3.89 (*m*, CH); 4.12–4.28 (*m*, H–C(2), CH_2O); 4.40–4.52 (*m*, H–C(4)); 5.28–5.38 (*br. s*, NH); 5.80–5.90 (*br. s*, NH). ^{13}C -NMR (100 MHz, $CDCl_3$): 9.6; 9.9; 13.7; 20.8; 21.4; 27.9; 28.0; 36.5; 43.0; 43.66; 50.1; 50.2; 50.4; 60.4; 73.4; 79.2; 79.5; 155.1; 157.2; 175.1. ESI-MS: 495 ($[M+Na]^+$). Anal. calc. for $C_{24}H_{44}N_2O_7$: C 60.99, H 9.38, N 5.93; found: C 61.01, H 9.39, N 5.94.

Ethyl (1R,2S*,3S*,4R*)-2-[[tert-Butoxy]carbonyl]amino]-3-((1R*)-1-[[tert-butoxy]carbonyl]amino)-2-ethylbutyl)-4-hydroxycyclopentanecarboxylate (21)*. White solid. Yield: 27%. R_f (hexane/AcOEt) 0.53. M.p. 197–198°. 1H -NMR (400 MHz, $CDCl_3$): 0.90–1.03 (*m*, 2 Me); 1.08–1.24 (*m*, 1 H of CH_2); 1.29 (*t*, $J = 7.2$, Me); 1.38–1.59 (*m*, 2 'Bu, CH_2); 1.83–1.95 (*m*, 1 H of CH_2); 1.97–2.21 (*m*, CH_2); 3.51–3.65 (*m*, H–C(1)); 3.89–3.99 (*m*, CH); 4.02–4.73 (*m*, CH, CH_2O , H–C(2), H–C(3), H–C(4)). ^{13}C -NMR (100 MHz, $CDCl_3$): 11.4; 11.5; 14.0; 21.2; 22.7; 27.9; 27.94; 35.0; 41.1; 46.1; 50.6; 51.9; 54.2; 50.2; 71.7; 78.9; 79.8; 154.1; 157.2; 174.0. ESI-MS: 495 ($[M+Na]^+$). Anal. calc. for: $C_{24}H_{44}N_2O_7$: C 60.99, H 9.38, N 5.93; found: C 60.98, H 9.40, N 5.91.

Ethyl (1R,2S*,3R*,4S*)-2-[[tert-Butoxy]carbonyl]amino]-4-((1S*)-1-[[tert-butoxy]carbonyl]amino)-2-ethylbutyl)-3-hydroxycyclopentanecarboxylate (22)*. Yellowish oil. Yield: 58%. R_f (hexane/AcOEt) 0.47. 1H -NMR (400 MHz, $CDCl_3$): 0.90–1.01 (*m*, 2 Me); 1.09–1.34 (*m*, Me, 2 CH_2); 1.46 (*s*, 2 'Bu); 1.92–2.30 (*m*, CH_2 , H–C(1)); 2.76–2.88 (*m*, H–C(4)); 2.94–3.02 (*m*, CH); 3.92–4.03 (*m*, CH); 4.06–4.31 (*m*, H–C(2), H–C(3), CH_2O); 4.35–4.44 (*br. s*, NH); 5.07–5.19 (*br. s*, NH). ^{13}C -NMR (100 MHz, $CDCl_3$): 11.0; 12.0; 14.3; 21.0; 24.3; 26.2; 27.0; 28.4; 44.3; 45.4; 48.0; 51.6; 58.8; 63.0; 73.8; 80.0;

127.0; 142.0; 153.7; 158.1. ESI-MS: 474 ($[M+1]^+$). Anal. calc. for $C_{24}H_{44}N_2O_7$: C 60.99, H 9.38, N 5.93; found: C 60.97, H 9.39, N 5.94.

Ethyl (1R,2S*,3R*,4S*)-2-[(tert-Butoxy)carbonyl]amino]-4-((1R*)-1-[(tert-butoxy)carbonyl]amino)-2-ethylbutyl)-3-hydroxycyclopentanecarboxylate (23)*. White solid. Yield: 20%. R_f (hexane/AcOEt) 0.35. M.p. 137–138°. 1H -NMR (400 MHz, $CDCl_3$): 0.89–1.00 (*m*, 2 Me); 1.29 (*t*, $J=7.1$, Me); 1.40–1.72 (*m*, 2 iBu , 4 CH_2); 1.96–2.52 (*m*, CH_2 , H–C(1), H–C(4), CH); 3.60–3.76 (*m*, CH); 4.07–4.42 (*m*, H–C(2), CH_2O , H–C(3)); 4.84–4.93 (*br. s.*, NH); 5.16–5.30 (*br. s.*, NH). ^{13}C -NMR (100 MHz, $CDCl_3$): 11.5; 11.9; 13.7; 21.2; 22.6; 25.2; 27.9; 27.9; 44.3; 44.7; 46.3; 50.9; 58.8; 60.3; 74.2; 79.1; 126.9; 142.0; 154.9; 156.3. ESI-MS: 474 ($[M+1]^+$). Anal. calc. for $C_{24}H_{44}N_2O_7$: C 60.99, H 9.38, N 5.93; found: C 61.01, H 9.36, N 5.92.

Ethyl (1R,2R*,3S*,4S*)-2-[(tert-Butoxy)carbonyl]amino]-3-((1S*)-1-[(tert-butoxy)carbonyl]amino)ethyl)-4-fluorocyclopentanecarboxylate (24a)*. White solid. Yield: 24%. R_f (hexane/AcOEt) 0.56. M.p. 114–115°. 1H -NMR (400 MHz, $CDCl_3$): 1.23 (*d*, $J=6.9$, Me); 1.27–1.33 (*m*, Me); 1.43–1.49 (*m*, 2 iBu); 2.11–2.42 (*m*, CH_2 , H–C(1)); 3.00–3.08 (*m*, H–C(3)); 4.41–4.28 (*m*, NH, CH, CH_2O); 4.83–5.09 (*m*, H–C(4), H–C(2)); 5.58–5.67 (*br. s.*, NH). ^{13}C -NMR (100 MHz, $CDCl_3$): 14.5; 19.6; 28.8; 34.8; 34.9; 45.2; 46.1; 52.2; 55.9; 56.1; 61.3; 79.1; 79.8; 95.9; 152.8; 173.5. ESI-MS: 419 ($[M+1]^+$). Anal. calc. for $C_{20}H_{33}FN_2O_6$: C 57.40, H 8.43, N 6.69; found: C 57.43, H 8.42, N 5.67.

Ethyl (1R,2R*)-2-[(tert-butoxy)carbonyl]amino]-3-((1S*)-1-[(tert-butoxy)carbonyl]amino)ethyl)cyclopent-3-ene-1-carboxylate (25a)*. White solid. Yield: 45%. R_f (hexane/AcOEt) 0.52. M.p. 83–84°. 1H -NMR (400 MHz, $CDCl_3$): 1.26–1.33 (*m*, 2 Me); 1.42–1.50 (*m*, 2 Me_3C); 2.41–2.52 (*m*, 1 H of CH_2); 2.75–2.86 (*m*, 1 H of CH_2); 3.36–3.45 (*m*, H–C(1)); 4.12–4.22 (*m*, CH_2O); 4.34 (*br. s.*, NH); 4.70–5.08 (*m*, NH, CH, H–C(2)); 5.65 (*s*, H–C(4)). ^{13}C -NMR (100 MHz, $CDCl_3$): 14.6; 21.2; 28.7; 28.8; 33.3; 45.7; 47.7; 57.4; 61.0; 79.9; 121.4; 126.2; 155.5; 158.5; 172.9. ESI-MS: 399 ($[M+1]^+$). Anal. calc. for $C_{20}H_{34}N_2O_6$: C 60.28, H 8.60, N 7.03; found: C 60.26, H 8.61, N 7.04.

Ethyl (1R,2R*,3S*,4S*)-2-[(tert-Butoxy)carbonyl]amino]-3-((1S*)-1-[(tert-butoxy)carbonyl]amino)propyl)-4-fluorocyclopentanecarboxylate (24b)*. White solid. Yield: 30%. R_f (hexane/AcOEt) 0.74. M.p. 103–104°. 1H -NMR (400 MHz, $CDCl_3$): 0.97 (*t*, $J=7.3$, Me); 1.26–1.33 (*m*, Me); 1.44–1.50 (*m*, 2 iBu); 1.57–1.67 (*m*, CH_2); 2.09–2.45 (*m*, CH_2 , H–C(1)); 2.97–3.06 (*m*, H–C(3)); 3.86 (*br. s.*, NH); 4.03–4.28 (*m*, CH_2O , H–C(2)); 4.80–5.03 (*m*, CH, H–C(4)); 5.66–5.76 (*br. s.*, NH). ^{13}C -NMR (100 MHz, $CDCl_3$): 10.5; 13.6; 26.4; 27.9; 34.1; 44.5; 50.9; 51.3; 54.0; 60.5; 78.8; 79.3; 94.5; 95.9; 155.0; 155.9; 173.3. ESI-MS: 434 ($[M+1]^+$). Anal. calc. for $C_{21}H_{37}FN_2O_6$: C 58.31, H 8.62, N 6.48; found: C 58.29, H 8.63, N 6.49.

Ethyl (1R,2R*)-2-[(tert-Butoxy)carbonyl]amino]-3-((1S*)-1-[(tert-butoxy)carbonyl]amino)propyl)cyclopent-3-ene-1-carboxylate (25b)*. Brownish oil. Yield: 43%. R_f (hexane/AcOEt) 0.67. 1H -NMR (400 MHz, $CDCl_3$): 0.91 (*t*, $J=7.5$, Me); 1.29 (*t*, $J=7.2$, Me); 1.42–1.50 (*m*, iBu); 1.62–1.77 (*m*, CH_2); 2.34–2.53 (*m*, 1 H of CH_2); 2.74–2.90 (*m*, 1 H of CH_2); 3.30–3.45 (*m*, H–C(1)); 4.09–4.28 (*m*, CH, CH_2O); 4.78–5.05 (*m*, 2 NH, H–C(2)); 5.65 (*s*, H–C(4)). ^{13}C -NMR (100 MHz, $CDCl_3$): 9.6; 13.8; 26.6; 27.9; 27.9; 32.5; 46.7; 56.6; 60.2; 79.1; 112.5; 115.4; 117.2; 126.4; 154.8; 171.3; 172.2. ESI-MS: 414 ($[M+1]^+$). Anal. calc. for $C_{21}H_{36}N_2O_6$: C 61.14, H 8.80, N 6.79; found: C 61.13, H 8.82, N 6.80.

Ethyl (1R,2R*,3S*,4S*)-2-[(tert-Butoxy)carbonyl]amino]-3-((1S*)-1-[(tert-butoxy)carbonyl]amino)-2-ethylbutyl)-4-fluorocyclopentanecarboxylate (24c)*. White solid. Yield: 28%. R_f (hexane/AcOEt) 0.75. M.p. 115–116°. 1H -NMR (400 MHz, $CDCl_3$): 0.83–0.95 (*m*, 2 Me); 1.17–1.37 (*m*, Me, CH_2); 1.40–1.52 (*m*, 2 iBu , CH_2); 2.10–2.38 (*m*, CH_2 , CH); 2.46–2.62 (*m*, H–C(1)); 2.98–3.09 (*m*, H–C(3)); 3.79–3.90 (*m*, CH); 4.03–4.29 (*m*, H–C(2), CH_2O); 4.82 (*br. s.*, NH); 4.91–5.06 (*m*, H–C(4)); 5.68–5.79 (*br. s.*, NH). ^{13}C -NMR (100 MHz, $CDCl_3$): 9.5; 10.3; 13.6; 20.8; 21.4; 27.9; 34.0; 41.9; 44.7; 51.1; 51.2; 51.5; 60.5; 78.7; 79.2; 95.3; 96.7; 154.9; 156.0; 173.4. ESI-MS: 475 ($[M+1]^+$). Anal. calc. for $C_{24}H_{43}FN_2O_6$: C 60.74, H 9.13, N 5.90; found: C 60.73, H 9.12, N 5.92.

Ethyl (1R,2R*)-2-[(tert-Butoxy)carbonyl]amino]-3-((1S*)-1-[(tert-butoxy)carbonyl]amino)-2-ethylbutyl)cyclopent-3-ene-1-carboxylate (25c)*. White solid. Yield: 27%. R_f (hexane/AcOEt) 0.61. M.p. 94–95°. 1H -NMR (400 MHz, $CDCl_3$): 0.84–1.11 (*m*, 2 Me, CH_2); 1.17–1.36 (*m*, Me, CH_2); 1.39–1.53 (*m*, 2 iBu); 2.40–2.53 (*m*, 1 H of CH_2); 2.76–2.89 (*m*, 1 H of CH_2); 3.36–3.47 (*m*, CH); 4.09–4.25 (*m*, CH_2O); 4.36 (*br. s.*, NH); 4.62–5.07 (*m*, CH, NH, H–C(2)); 5.63–5.65 (*m*, H–C(4)). ^{13}C -NMR (100 MHz, $CDCl_3$): 11.2; 12.2; 13.8; 21.1; 22.2; 27.8; 27.9; 32.4; 42.4; 46.7; 50.3; 56.5; 60.1; 78.8; 78.9; 126.5; 143.1;

154.6; 155.2; 172.1. ESI-MS: 455 ($[M+1]^+$). Anal. calc. for $C_{24}H_{42}N_2O_6$: C 63.41, H 9.31, N 6.16; found: C 63.39, H 9.32, N 6.17.

Ethyl (1R,2S*,3S*,4S*)-2-[(tert-Butoxy)carbonylamino]-4-((1S*)-1-[(tert-butoxy)carbonylamino]ethyl)-3-fluorocyclopentanecarboxylate (26a)*. White solid. Yield: 26%. R_f (hexane/AcOEt) 0.51. M.p. 104–105°. 1H -NMR (400 MHz, $CDCl_3$): 1.17–1.23 (*m*, Me); 1.29 (*t*, $J=7.2$, Me); 1.44–1.49 (*m*, 2 'Bu); 2.09–2.24 (*m*, 1 H of CH_2); 2.27–2.58 (*m*, 1 H of CH_2 , H–C(1)); 2.69–2.94 (*m*, H–C(4)); 3.69–3.89 (*m*, CH); 4.09–4.25 (*m*, CH_2O , H–C(2)); 4.26–4.43 (*br. s.*, NH); 4.65–5.00 (*m*, NH, H–C(3)). ^{13}C -NMR (100 MHz, $CDCl_3$): 13.7; 15.5; 27.9; 33.5; 36.6; 46.5; 48.1; 50.8; 51.5; 51.7; 60.6; 79.2; 103.6; 105.0; 154.8; 172.6. ESI-MS: 419 ($[M+1]^+$). Anal. calc. for $C_{20}H_{35}FN_2O_6$: C 57.40, H 8.43, N 6.69; found: C 57.41, H 8.41, N 6.70.

Ethyl (1R,4R*)-2-[(tert-Butoxy)carbonylamino]-4-((1S*)-1-[(tert-butoxy)carbonylamino]ethyl)cyclopent-2-ene-1-carboxylate (27a)*. White solid. Yield: 48%. R_f (hexane/AcOEt) 0.47. M.p. 129–130°. 1H -NMR (400 MHz, $CDCl_3$): 1.18–1.3 (*m*, Me); 1.26–1.33 (*m*, Me); 1.45–1.48 (*m*, 2 'Bu); 2.29–2.49 (*m*, H–C(1)); 2.57–2.79 (*m*, CH_2); 2.81–2.91 (*m*, H–C(4)); 3.70–3.87 (*m*, NH); 4.15–4.25 (*m*, CH_2O , CH); 4.92–5.01 (*m*, NH); 5.45–5.47 (*m*, H–C(3)). ^{13}C -NMR (100 MHz, $CDCl_3$): 13.7; 19.4; 27.9; 36.77; 44.9; 46.7; 46.6; 50.7; 60.4; 78.0; 79.2; 124.7; 148.3; 154.7; 167.8. ESI-MS: 399 ($[M+1]^+$). Anal. calc. for $C_{20}H_{34}N_2O_6$: C 60.28, H 8.60, N 7.03; found: C 60.30, H 8.59, N 7.02.

Ethyl (1R,2S*,3S*,4S*)-2-[(tert-Butoxy)carbonylamino]-4-((1S*)-1-[(tert-butoxy)carbonylamino]propyl)-3-fluorocyclopentanecarboxylate (26b)*. Brownish oil. Yield: 15%. R_f (hexane/AcOEt) 0.57. 1H -NMR (400 MHz, $CDCl_3$): 0.89–1.02 (*m*, Me); 1.25–1.33 (*m*, Me); 1.44–1.50 (*m*, 2 'Bu); 1.64–1.80 (*m*, CH_2); 2.23–3.06 (*m*, CH_2 , H–C(1), CH); 3.49–3.72 (*m*, H–C(4)); 4.14–4.25 (*m*, CH_2O); 4.29–4.54 (*m*, H–C(2)); 4.57–4.82 (*m*, H–C(3)); 4.97 (*br. s.*, NH); 5.13 (*br. s.*, NH). ^{13}C -NMR (100 MHz, $CDCl_3$): 9.9; 13.7; 22.7; 27.9; 36.8; 47.9; 49.7; 52.9; 53.7; 57.3; 57.5; 60.5; 79.1; 103.8; 105.2; 154.3; 155.8. ESI-MS: 433 ($[M+1]^+$). Anal. calc. for $C_{21}H_{37}FN_2O_6$: C 58.31, H 8.62, N 6.48; found: C 58.30, H 8.61, N 6.50.

Ethyl (1R,4R*)-2-[(tert-Butoxy)carbonylamino]-4-((1S*)-1-[(tert-butoxy)carbonylamino]propyl)cyclopent-2-ene-1-carboxylate (27b)*. White solid. Yield: 39%. R_f (hexane/AcOEt) 0.48. M.p. 121–122°. 1H -NMR (400 MHz, $CDCl_3$): 0.88–1.01 (*m*, Me); 1.24–1.33 (*m*, Me); 1.47 (*s*, 2 'Bu); 1.61–1.90 (*m*, CH_2); 2.09–2.35 (*m*, 1 H of CH_2); 2.53–2.75 (*m*, 1 H of CH_2); 2.77–2.92 (*m*, H–C(1)); 4.07–4.25 (*m*, H–C(4), CH_2O); 4.47 (*br. s.*, NH); 4.56–4.87 (*m*, CH); 4.93–5.05 (*m*, NH); 5.45–5.47 (*m*, H–C(3)). ^{13}C -NMR (100 MHz, $CDCl_3$): 9.8; 13.7; 22.6; 26.1; 27.9; 50.6; 51.5; 57.3; 60.5; 79.0; 103.8; 105.2; 124.6; 154.6; 155.8; 172.7. ESI-MS: 413 ($[M+1]^+$). Anal. calc. for $C_{21}H_{36}N_2O_6$: C 61.14, H 8.80, N 6.79; found: C 61.15, H 8.78, N 6.80.

Ethyl (1R,4R*)-2-[(tert-Butoxy)carbonylamino]-4-((1S*)-1-[(tert-butoxy)carbonylamino]-2-ethylbutyl)cyclopent-2-ene-1-carboxylate (27c)*. Yellowish oil. Yield: 58%. R_f (hexane/AcOEt) 0.48. 1H -NMR (400 MHz, $CDCl_3$): 0.85–1.17 (*m*, 2 Me, CH_2); 1.23–1.39 (*m*, Me, CH_2); 1.46 (*s*, 2 'Bu); 1.58–1.68 (*m*, CH_2); 2.41–2.90 (*m*, CH, H–C(1), CH); 3.51–3.61 (*m*, H–C(4)); 4.07–4.22 (*m*, CH_2O); 4.37 (*br. s.*, NH); 4.49 (*br. s.*, NH); 5.63–5.64 (*m*, H–C(3)). ^{13}C -NMR (100 MHz, $CDCl_3$): 10.8; 11.2; 13.7; 21.5; 22.6; 27.8; 27.9; 34.4; 43.1; 50.2; 52.0; 57.11; 60.4; 78.5; 79.1; 103.2; 105.5; 153.9; 155.8; 171.7. ESI-MS: 455 ($[M+1]^+$). Anal. calc. for $C_{24}H_{42}N_2O_6$: C 63.41, H 9.31, N 6.16; found: C 63.44, H 9.30, N 6.14.

X-Ray Crystallographic Studies. Crystallographic data for the compounds **11** and **20** were collected with *Agilent Supernova* diffractometer equipped with *Atlas* area detector using CuK_{α} radiation ($\lambda = 1.54184 \text{ \AA}$). Empirical absorption correction, using spherical harmonics implemented in SCALE3 ABSPACK scaling algorithm, was applied for both compounds with CrysAlisPro program package [9]. The structures were solved by direct methods using SIR97 [10] program, and full-matrix, least-squares refinements on F^2 were performed using the SHELXL-97 [11] program. Molecular structure figures were drawn with Diamond3 program [12]. Selected crystallographic data collected in CCDC-902350 and -902351 contain the supplementary crystallographic data for **11** and **20**. These data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html>, or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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