Di-, Tri- and Tetrapeptide-Linked Dicatechol Derivatives

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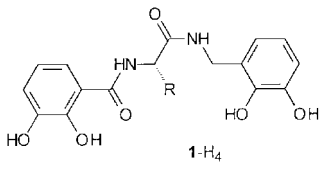
Abstract: Di-, tri- and tetrapeptide linked dicatechol derivatives are prepared by subsequent coupling of 2,3-dimethoxybenzoic acid (**2**), peptides **3** and 2,3-dimethoxybenzylamine (**5**) using classical activating conditions (EDC/HOBt or DDC/HOSu). In the final step the methyl ethers at the veratrol units are cleaved to afford the free catechol derivatives **7**, which are potential ligands for metal complexes with well defined fixed conformations at the peptide spacers.

Key words: amides, peptides, ligands, supramolecular chemistry

The three-dimensional structure of a protein is crucial for its function as a molecular machine. Structurally different domains of a peptide (α-helix, turns, loops, β-sheet) combine in a well defined manner to enable the folding of the protein. However, the folding mechanisms of peptides are not very well understood.[1] In some cases the coordination of metal ions to the peptides supports the formation of specific structures in natural and artificial proteins and leads to the fixation of more stable structures than hydrogen bonding alone does.[2]

Just recently we described the preparation of amino acid-bridged dicatechol derivatives **1**-H_4[3] (Figure 1) which form double-stranded dinuclear titanium(IV) complexes $[(\mathbf{1})_2Ti_2(OR)_2]^{2-}$ with two alcoholate coligands present. Despite the possible and initially observed formation of seven different isomers, only one isomer is obtained as the thermodynamically favored major species. Conformational considerations show, that the three-dimensional structure of the amino acid residue in the spacer is influenced by the stereochemistry at the metal centers.[4]



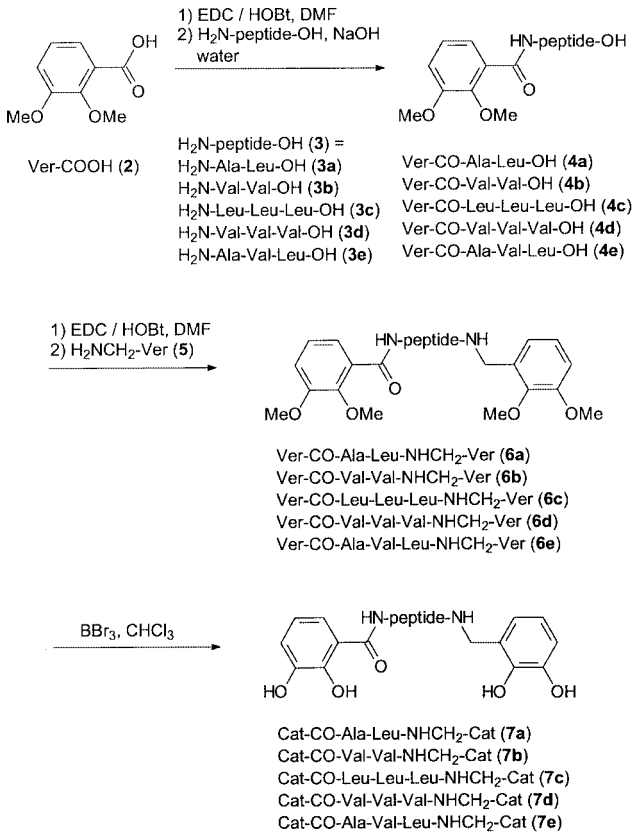
1-H_4

Figure 1 Chemical structure of the amino acid-bridged dicatechol derivative **1**-H_4

To go further, we now introduce di-, tri-, and tetrapeptide sequences as spacers in dicatechol derivatives. With appropriate metal ions we should be able to induce loop-, sheet-, or helix-type structures in the ligand strands. In this paper we present the straightforward synthesis of the peptide-bridged dicatechol derivatives which are highly interesting candidates for peptide/metal complex hybrides with well-defined three-dimensional structures.

The peptide-bridged dicatechol ligands **7** are prepared using standard peptide coupling strategies[5] with EDC/HOBt[6] (or DCC/HOSu)[7] as activating agents. Hereby the di- **7a**,**b** and tripeptide derivatives **7c**–**e** are synthesized in three step procedures by coupling first 2,3-dimethoxybenzoic acid (veratryl-3-carboxylic acid = Ver-CO_2H) (**2**) to the N-terminus and subsequently 2,3-dimethoxybenzylamine (3-aminomethylveratrol = H_2NCH_2-Ver) (**5**) to the C-terminus of the corresponding di- or tripeptide. In the last step the methyl ethers of **6a**–**e** are cleaved with BBr_3[8] and the deprotected peptide-bridged dicatechol ligands **7a**–**e** are liberated (Scheme 1).

The intermediate monoveratrole substituted peptides **4a**–**e** are not isolated in analytically pure form. However, the material, which was obtained was pure enough for further transformations and in most cases could be characterized spectroscopically. Purification can easily be performed on



Scheme 1

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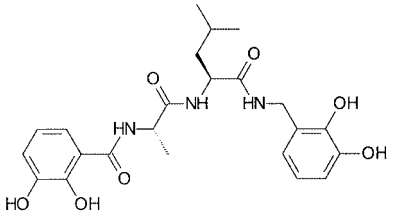
the bisveratrole derivatives **6a**–**e** by simply recrystallizing them from the appropriate solvent.

As dipeptide we have chosen to introduce alanyl-leucine and valyl-valine. Hereby the formations of the diveratrole derivatives proceed in 41% (**6a**) and 52% yield (**6b**) over two steps. The methyl ether cleavage is performed in close to quantitative yield and the dipeptide bridged dicatechols **7a** and **7b** are obtained as beige solids, which decompose between 80 °C and 100 °C (Figure 2).



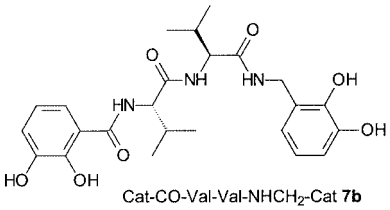


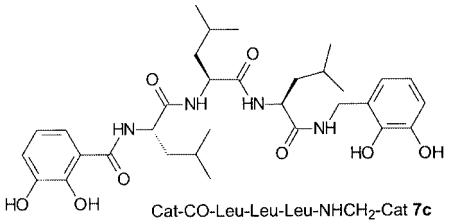
Figure 2 Chemical structures of dipeptide-bridged dicatechols **7a** and **7b**

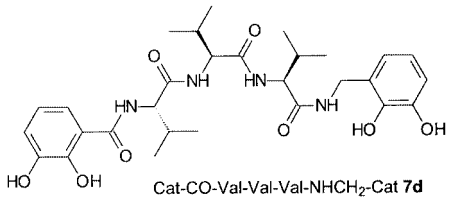
With alanyl-leucine as spacer **7a**, an amino acid sequence is present which possesses two sterically less demanding amino acids while in the valyl-valine derivative **7b** two sterically highly demanding amino acids are introduced. Upon metal binding this might lead to different conformations at the strands.

Three different dicatechol derivatives **7c**–**e** are prepared which bear tripeptide spacers (Figure 3). Again one sterically less hindered spacer with the Leu-Leu-Leu sequence **7c** and one more demanding with the Val-Val-Val linker **7d** is introduced. As a third example a compound with three different amino acid residues (Ala-Val-Leu) **7e** is prepared.

The diveratrole ligand precursors **6c**–**e** are synthesized in a two step sequence without purification of the intermediate monoveratrole derivatives **4c**–**e** similar to the synthesis of the dipeptide bridged ligands. Hereby yields of 59% (**6c**), 49% (**6d**) and 39% (**6e**) are obtained after the two step sequence followed by recrystallization of the peptide-bridged diveratrols. The final ether cleavage again proceeds in close to quantitative yield. The Val-Val-Val linked compound **7d** melts at 176–180 °C while the other derivatives decompose at 110 °C (**7c**) or 90 °C (**7e**), respectively.

As an example of a tetrapeptide derivative, we synthesized the Phe-Leu-Phe-Leu bridged dicatechol **7f** in a four step procedure. The intermediate peptides with a N-terminal 2,3-dimethoxybenzoate substituent **4f** and **8f** are not





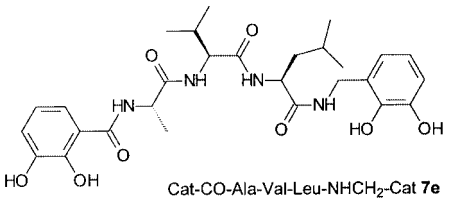
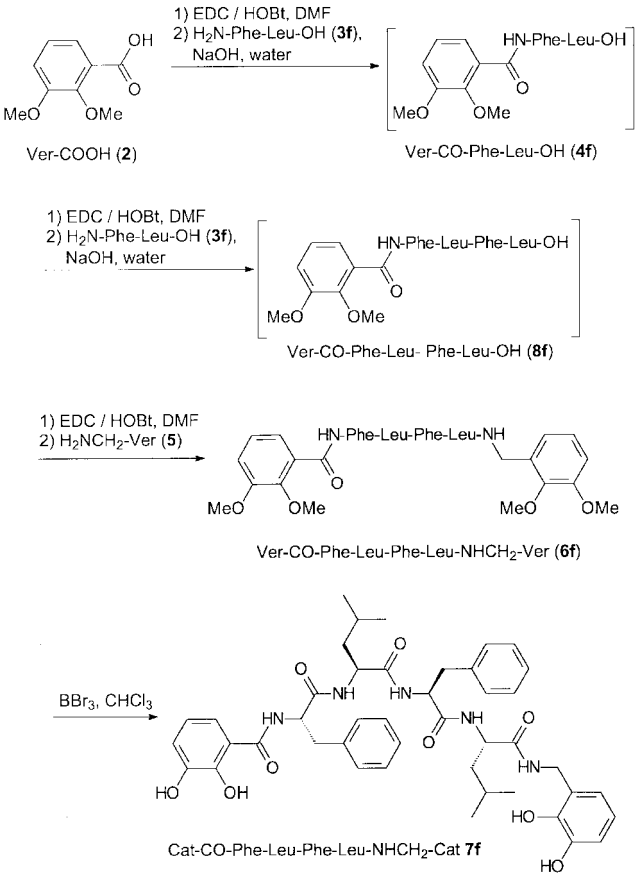


Figure 3 Chemical structures of tripeptide-bridged dicatechols **7c**–**e**

obtained in analytically pure form. The first intermediate to be purified by crystallization is the tetrapeptide linked diveratrol **6f** (Scheme 2).



Scheme 2

In the first reaction step 2,3-dimethoxybenzoic acid (**2**) is coupled with phenylalanyl-leucine (**3f**) by EDC/HOBt activation to obtain the veratryl dipeptide **4f**. The same reaction step is repeated with **4f** and **3f** to generate the tetrapeptide **8f**. Activation of the acid function of **8f** (EDC/HOBt) and addition of 2,3-dimethoxybenzylamine (**5**) results in the formation of the tetrapeptide bridged diveratrole **6f**, which after recrystallization from methanol is isolated in 36% yield over three steps. Deprotection of the methyl ethers is performed using BBr_3 and the dicatechol **7f** finally is obtained on a half gram scale in 97% yield.

Herein we presented the simple synthesis of several di-, tri- or tetrapeptide linked dicatechol derivatives **7a**–**f**, which are potential ligands for mono- or oligonuclear metal complexes. The preparations follow straightforward peptide coupling protocolls using EDC/HOBt (or DCC/HOSu) as amide coupling reagents. Different peptide linkers were used to introduce different sterical demands in the ligand spacer. In future studies the ligands will be used to obtain coordination compounds in which by metal coordination either sheet **A**,[9] turn **B**[10] or helical structures **C**[11] should be geometrically fixed (for a schematic representation, see Figure 4).

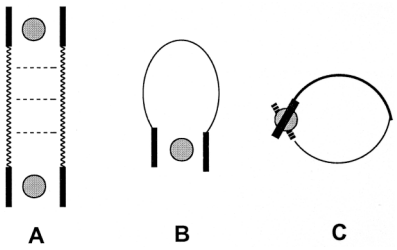


Figure 4 Schematic representation of geometrically fixed metal coordination

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX 500 spectrometer using DEPT techniques for the assignment of the multiplicity of carbon atoms. FT-IR spectra were recorded by diffuse reflection (KBr) on a Bruker IFS spectrometer. UV-vis spectra were recorded on a Perkin Elmer Lambda 2 spectrometer. Mass spectra (positive FAB; EI, 70 eV) were taken on a Finnigan MAT 90 mass spectrometer. Elemental analyses were obtained with a Heraeus CHN-O-Rapid analyzer. Solvents were purified by standard methods. Melting points: Büchi B-540 (uncorrected). Air sensitive compounds were prepared and handled under argon using Schlenk techniques.

Coupling of Peptides 3 with 2,3-Dimethoxybenzoic Acid (2); General Procedure

DMF was cooled to 0 °C and a mixture of EDC [ethyl(dimethylaminopropyl) carbodiimide, 1 equiv], HOBt (1-hydroxybenzotriazole, 1.1 equiv) and 2,3-dimethoxybenzoic acid (**2**; 1 equiv) was added in one portion. Still at 0 °C, the peptide **3** (1 equiv) and a solution of NaOH (1 equiv) in H_2O was added. Warming the mixture to r.t. and stirring overnight was followed by removal of the solvent in vacuum at 20 °C. The residue was dissolved in EtOAc and aq sat. NH_4Cl solution. The layers were separated and the organic layer was washed two times with aq sat. NH_4Cl solution. Evaporation of the solvent yielded the product, which was used for further transformations without purification.

Coupling of *N*-(2,3-Dimethoxybenzoate)-Substituted Peptides 4 and 8 with 2,3-Dimethoxybenzylamine (5); General Procedure

The crude *N*-(2,3-dimethoxybenzoate)-substituted peptide **4** or **8** was dissolved in DMF and the resulting solution was cooled to 0 °C. EDC, HOBt and 2,3-dimethoxybenzylamine (**5**) were added. The mixture was stirred overnight while warming slowly to r.t. The solvent was removed at 20 °C in vacuum and the residue was portioned between EtOAc and aq sat. NH_4Cl solution. The layers were separated, the organic layer was washed two times with aq sat. NH_4Cl solution, and dried ($MgSO_4$). The solvent was distilled off in vacuum and the product was purified by recrystallization.

Methyl Ether Cleavage; General Procedure

The tetramethyl protected compound **6** was dissolved in $CHCl_3$ and cooled to 0 °C. BBr_3 (1 M solution in CH_2Cl_2, 12 equiv) was added slowly and the cooling bath was removed. After stirring overnight MeOH was added and the resulting mixture was stirred for another hour. The solvent was evaporated and the residue dissolved in EtOAc. The solution was washed two times with H_2O and dried ($MgSO_4$). Removal of the solvent provided the pure product **7**.

Preparation of Cat-CO-Ala-Leu-NHCH$_2$-Cat (7a)
Ver-CO-Ala-Leu-OH (4a)

Yield: 1.16 g; colorless oil which was used without further purification.

^{1}H NMR (methanol-d_4): δ = 7.44 (dd, *J* = 7.7, 1.8 Hz, 1 H), 7.13–7.20 (m, 2 H), 4.68 (q, *J* = 7.0, 1 H), 4.47 (dd, *J* = 8.1, 6.9 Hz, 1 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 1.65–1.77 (m, 3 H), 1.47 (d, *J* = 7.1 Hz, 3 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.93 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (methanol-d_4): δ = 175.8 (C), 174.8 (C), 167.2 (C), 154.3 (C), 149.1 (C), 127.8 (C), 125.4 (CH), 122.7 (CH), 117.0 (CH), 61.9 (CH_3), 56.6 (CH_3), 52.1 (CH), 50.3 (CH), 41.5 (CH_2), 26.0 (CH), 23.3 (CH_3), 21.8 (CH_3), 19.1 (CH_3).

MS (EI, 70 eV) *m*/*z*: 366 (4%) [M$^+$], 208 (25%), 165 (100%), 107 (16%), 77 (19%).

HRMS *m*/*z*: [M$^+$] calcd for $C_{18}H_{26}N_2O_6$, 366.1791; found, 366.1794.

Ver-CO-Ala-Leu-NHCH$_2$-Ver (6a)

Yield: 989 mg [41% over two steps starting from H_2N-Ala-Leu-OH (**3a**)], white solid after recrystallization from EtOAc; mp 168–172 °C.

^{1}H NMR ($CDCl_3$): δ = 8.56 (d, *J* = 6.8 Hz, 1 H), 7.56 (dd, *J* = 8.0, 1.5 Hz, 1 H), 6.97–7.13 (m, 4 H), 6.82–6.85 (m, 2 H), 4.72 (pent, *J* = 7.0 Hz, 1 H), 4.45–4.49 (m, 3 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 3.84 (s, 3 H), 1.70–1.74 (m, 1 H), 1.48–1.59 (m, 2 H), 1.44 (d, *J* = 7.0 Hz, 3 H), 0.83 (d, *J* = 6.3 Hz, 3 H), 0.82 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 172.4 (C), 171.7 (C), 165.4 (C), 152.6 (C), 152.6 (C), 147.8 (C), 147.1 (C), 131.7 (C), 125.7 (C), 124.9 (CH), 124.1 (CH), 122.7 (CH), 121.1 (CH), 115.9 (CH), 111.8 (CH), 61.4 (CH_3), 60.7 (CH_3), 56.1 (CH_3), 55.8 (CH_3), 51.9 (CH), 49.4 (CH), 40.7 (CH_2), 38.7 (CH_2), 24.8 (CH), 22.9 (CH_3), 21.8 (CH_3), 17.9 (CH_3).

IR (KBr): 3294, 3084, 2956, 1677, 1629, 1551, 1480, 1261, 1169, 1070, 1018, 1002, 944, 773, 749 cm^{-1}.

MS (+FAB, 3-NBA) *m*/*z*: 516 [MH$^+$], 349, 236, 165, 151, 136.

HRMS *m*/*z*: [M$^+$] calcd for $C_{27}H_{38}N_3O_7$, 516.2710; found, 516.2745.

Anal. Calcd for $C_{27}H_{37}N_3O_7$ (516.6): C, 62.90; H, 7.23; N, 8.15. Found: C, 62.53; H, 7.03; N, 8.44.

Cat-CO-Ala-Leu-NHCH$_2$-Cat (7a)
Yield: 421 mg (~100%); beige solid; mp 80–86 °C (dec.).

^{1}H NMR (methanol-d_4): δ = 7.31 (dd, *J* = 1.4, 8.0 Hz, 1 H), 6.93 (dd, *J* = 1.4, 8.0 Hz, 1 H), 6.72 (t, *J* = 8.0 Hz, 1 H), 6.70 (dd, *J* = 1.8, 7.7 Hz, 1 H), 6.65 (dd, *J* = 1.8, 7.7 Hz, 1 H), 6.61 (t, *J* = 7.7 Hz, 1 H), 4.55 (q, *J* = 7.1 Hz, 1 H), 4.44 (m, 1 H), 4.34 (m, 2 H), 1.68 (m, 1 H), 1.61 (m, 2 H), 1.45 (d, *J* = 7.1 Hz, 3 H), 0.91 (d, *J* = 6.5 Hz, 3 H), 0.88 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (methanol-d_4): δ = 173.8 (C), 173.7 (C), 169.8 (C), 148.5 (C), 145.8 (C), 145.2 (C), 143.1 (C), 124.7 (C), 119.9 (CH), 119.2 (CH), 118.4 (CH), 118.3 (CH), 118.1 (CH), 115.5 (C), 114.2 (CH), 51.8 (CH), 49.5 (CH), 40.4 (CH_2), 38.6 (CH_2), 24.5 (CH_3), 22.0 (CH), 20.5 (CH_3), 16.5 (CH_3).

IR (KBr): 3330, 2958, 2873, 1641, 1536, 1264 cm^{-1}.

MS (+FAB, 3-NBA) *m/z*: 460 [HM$^+$], 482 [NaM$^+$].

Anal. Calcd for $C_{23}H_{29}N_3O_7 \cdot 1.5\ H_2O$ (486.5): C, 56.78; H, 6.63; N, 8.64. Found: C, 56.36; H, 6.27; N, 8.09.

Preparation of Cat-CO-Val-Val-NHCH$_2$-Cat (7b)
Ver-CO-Val-Val-OH (4b)
The peptide coupling is performed with DCC (dicyclohexylcarbodiimide)/HOSu (*N*-hydroxysuccinimide) (instead of EDC/HOBt) in dioxane as coupling reagent. Yield: 994 mg. The crude product is used without purification.

Ver-CO-Val-Val-NHCH$_2$-Ver (6b)
The peptide coupling is performed with DCC/HOSu (instead of EDC/HOBt) in dioxane as coupling reagent. Yield: 360 mg [52% over two steps starting from H_2N-Val-Val-OH (**3b**)]; white solid after recrystallization from MeOH.

^{1}H NMR ($CDCl_3$): δ = 8.55, (d, *J* = 7.4 Hz, 1 NH), 7.59 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.13 (t, *J* = 8.0 Hz, 1 H), 7.07 (dd, *J* = 8.0, 1.6 Hz, 1 H), 6.99 (t, *J* = 8.0 Hz, 1 H), 6.87 (dd, *J* = 8.0, 1.6 Hz, 1 H), 6.85 (dd, *J* = 8.0, 1.6 Hz, 1 H), 6.56 (t, *J* = 8.7 Hz, 1 NH), 4.47 (m, 3 H, two overlapping signals), 4.28 (dd, *J* = 8.7, 5.9 Hz, 1 H), 3.96 (s, 3 H), 3.91 (s, 3 H), 3.91 (s, 3 H), 3.86 (s, 3 H), 2.31 (m, 1 H), 2.24 (m, 1 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.84 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 171.3 (C, double intensity), 170.4 (C), 165.6(C), 152.6 (C), 147.8 (C), 131.6 (C), 125.9 (C), 124.5 (CH), 124.2 (CH) 122.9 (CH), 121.3 (CH), 115.9 (CH), 112.0 (CH), 78.0 (C), 61.7 (CH_3), 60.7 (CH_3), 59.8 (CH), 58.5 (CH), 56.2 (CH_3), 55.8 (CH_3), 38.8 (CH_2), 30.4 (CH), 30.3 (CH), 19.6 (CH_3), 19.3 (CH_3), 17.9 (CH_3), 17.7 (CH_3).

UV-Vis (MeOH): λ_{max} = 277, 279, 295 nm.

MS (EI, 70 eV) *m/z*: 529 (12%) [M$^+$], 265 (57%), 165 (100%).

HRMS *m/z*: [M$^+$] calcd for $C_{28}H_{39}N_3O_7$, 529.2778; found, 529.2792.

Anal. Calcd for $C_{28}H_{39}N_3O_7$ (529.6): C, 63.50; H, 7.42; N, 7.93. Found: C, 63.21; H, 7.36; N, 7.84.

Cat-CO-Val-Val-NHCH$_2$-Cat (7b)
Yield: 87 mg (97%); beige solid; mp 93–98 °C (dec.).

^{1}H NMR (methanol-d_4): δ = 7.33 (dd, *J* = 7.9, 1.5 Hz, 1 H), 6.94 (dd, *J* = 7.9, 1.5 Hz, 1 H), 6.73 (t, *J* = 7.9 Hz, 1 H), 6.70 (dd, *J* = 7.7, 1.7 Hz, 1 H), 6.66 (dd, *J* = 7.7, 1.7 Hz, 1 H), 6.61 (t, *J* = 7.7 Hz, 1 H), 4.43 (d, *J* = 7.6 Hz, 1 H), 4.33 (s, 2 H), 4.16 (d, *J* = 8.0 Hz, 1 H), 2.16 (m, 1 H), 2.05 (m, 1 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (methanol-d_4): δ = 173.9 (C), 173.8 (C), 170.4 (C), 149.1 (C), 147.2 (C), 146.7 (C), 144.6 (C), 126.1 (C), 121.5 (CH), 120.0 (CH) 120.0 (CH), 119.9 (CH), 119.7 (CH), 117.6 (C), 115.7 (CH), 60.4 (CH), 60.4 (CH), 39.8 (CH_2), 32.0 (CH), 31.8 (CH) 19.8 (CH_3), 19.6 (CH_3), 19.0 (CH_3), 18.9 (CH_3).

IR (KBr): 3285, 2967, 1640, 1535, 1480, 1335, 1261, 1184, 1078, 741 cm^{-1}.

UV-Vis (MeOH): λ_{max} = 201, 247, 281, 313 nm.

MS (EI, 70 eV) *m/z*: 473 (2%) [M$^+$].

HRMS *m/z*: [M$^+$] calcd for $C_{24}H_{31}N_3O_7$ (473.5), 473.2162; found, 473.2151.

Anal. Calcd for $C_{24}H_{31}N_3O_7 \cdot CH_2Cl_2 \cdot 3\ H_2O$ (612.5): C, 49.02; H, 6.42; N, 6.86. Found: C, 48.56; H, 6.21; N, 6.95.

Preparation of Cat-CO-Leu-Leu-Leu-NHCH$_2$-Cat (7c)
Ver-CO-Leu-Leu-Leu-OH (4c)
Yield: 1.13 g of crude product, which was used without further purification; mp 86–100 °C.

^{1}H NMR (methanol-d_4): δ = 7.39 (dd, *J* = 7.6, 1.9 Hz, 1 H), 7.14–7.20 (m, 2 H), 4.69 (dd, *J* = 8.4, 6.2 Hz, 1 H), 4.49 (dd, *J* = 8.7, 6.4 Hz, 1 H), 4.44 (dd, *J* = 8.5, 6.5 Hz, 1 H), 3.89 (s, 3 H), 3.91 (s, 3 H), 1.61–1.76 (m, 9 H), 0.99 (d, *J* = 6.4 Hz, 6 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 0.91 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (methanol-d_4): δ = 174.4 (C), 174.3 (C, double intensity), 167.8 (C), 154.3 (C), 148.9 (C), 128.3 (C), 125.4 (CH), 122.6 (CH), 116.9 (CH), 62.0 (CH_3), 56.6 (CH_3), 53.4 (CH), 52.9 (CH), 52.0 (CH), 42.6 (CH_2), 41.7 (2 CH_2), 26.1 (CH), 25.9 (CH), 25.8 (CH), 23.5 (2 CH_3), 23.4 (CH_3), 22.3 (CH_3), 22.1 (CH_3), 21.8 (CH_3).

MS (+FAB, 3-NBA) *m/z*: 522 [MH$^+$], 391, 278, 250, 165, 86.

HRMS *m/z*: [M$^+$] calcd for $C_{27}H_{44}N_3O_7$, 522.3179; found, 522.3154.

Ver-CO-Leu-Leu-Leu-NHCH$_2$-Ver (6c)
Yield: 1.06 g [59% over two steps starting from H_2N-Leu-Leu-Leu-OH (**3c**)] as a white solid after recrystallization from MeOH/H_2O; mp 175 °C (dec.).

^{1}H NMR ($CDCl_3$): δ = 8.53 (d, *J* = 6.0 Hz, 1 H), 7.54 (dd, *J* = 7.8, 1.8 Hz, 1 H), 7.06–7.13 (m, 2 H), 6.94–6.97 (m, 2 H), 6.88 (dd, *J* = 7.7, 1.4 Hz, 1 H), 6.78 (dd, *J* = 8.1, 1.5 Hz, 1 H), 4.56–4.61 (m, 2 H), 4.47 (m, 2 H), 4.38 (m, 1 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 3.82 (s, 3 H), 3.82 (s, 3 H), 1.50–1.82 (m, 9 H), 0.96 (d, *J* = 6.1 Hz, 3 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 0.93 (d, *J* = 5.9 Hz, 3 H), 0.86 (d, *J* = 6.5 Hz, 3 H), 0.86 (d, *J* = 6.5 Hz, 3 H), 0.83 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 172.6 (C), 172.1 (C), 171.8 (C), 166.0 (C), 152.6 (C), 152.4 (C), 147.8 (C), 146.9 (C), 132.1 (C), 125.3 (C), 124.5 (CH), 124.0 (CH), 122.6 (CH), 120.7 (CH), 116.1 (CH), 111.4 (CH), 61.5 (CH_3), 60.6 (CH_3), 56.1 (CH_3), 55.7 (CH_3), 53.1 (CH), 52.4 (CH), 51.9 (CH), 40.7 (CH_2), 40.7 (CH_2), 40.6 (CH_2), 38.2 (CH_2), 25.0 (CH_2), 24.9 (3 CH), 23.1 (2 CH_3), 23.0 (CH_3), 22.0 (CH_3), 21.7 (CH_3), 16.6 (CH_3).

IR (KBr): 3269, 3077, 2956, 2871, 2836, 1634, 1579, 1539, 1483, 1430, 1387, 1368, 1310, 1268, 1222, 1170, 1086, 1007, 916, 879, 785, 753, 706 cm^{-1}.

MS (+FAB, 3-NBA) *m/z*: 671 [MH$^+$], 504, 391, 278, 250, 165.

HRMS *m/z*: [M$^+$] calcd for $C_{36}H_{55}N_4O_8$, 671.4020; found, 671.4039.

Anal. Calcd for $C_{36}H_{54}N_4O_8$ (671.9): C, 64.46; H, 8.11; N, 8.35. Found: C, 64.28; H, 7.85; N, 8.73.

Cat-CO-Leu-Leu-Leu-NHCH$_2$-Cat (7c)
Yield: 438 mg (99%); light brown solid; mp 110 °C (dec.).

^{1}H NMR (methanol-d_4): δ = 7.23 (dd, *J* = 8.1, 1.5 Hz, 1 H), 6.94 (dd, *J* = 7.8, 1.5 Hz, 1 H), 6.60–6.74 (m, 4 H), 4.61 (dd, *J* = 9.4, 5.2, 1 H), 4.40–4.45 (m, 2 H), 4.34 (s, 2 H), 1.55–1.76 (m, 9 H), 0.98 (d, *J* = 6.1 Hz, 3 H), 0.95 (d, *J* = 6.2 Hz, 3 H), 0.86-0.92 (m, 12 H).

^{13}C NMR (methanol-d_4): δ = 175.1 (C), 174.9 (C), 174.5 (C), 171.0 (C), 149.6 (C), 147.2 (C), 146.6 (C), 144.5 (C), 126.1 (C), 121.2 (CH), 120.6 (CH), 119.8 (CH, double intensity), 119.7 (CH), 117.1 (C), 115.6 (CH), 53.7 (CH), 53.3 (CH), 53.0 (CH), 41.8 (CH_2), 41.7 (CH_2), 41.4 (CH_2), 39.9 (CH_2), 26.1 (CH), 25.8 (CH), 25.8 (CH), 23.4 (2 CH_3), 23.4 (CH_3), 22.1 (CH_3), 22.0 (CH_3), 21.9 (CH_3).

IR (KBr): 3290, 3090, 2958, 2871, 1642, 1588, 1480, 1369, 1338, 1264, 1173, 1078, 948, 922, 847, 790, 741 cm^{-1}.

MS (+FAB, 3-NBA) *m/z*: 615 [MH$^+$], 476, 363, 250, 222, 137.

HRMS *m/z*: [M$^+$] calcd for $C_{32}H_{47}N_4O_8$ (615.8), 615.3394; found, 615.3412.

Anal. calcd for $C_{32}H_{46}N_4O_8$·2 H_2O (651.8): C, 59.06; H, 7.74; N, 8.61. Found: C, 59.28; H, 7.16; N, 8.38.

Preparation of Cat-CO-Val-Val-Val-NHCH$_2$-Cat (7d)
Ver-CO-Val-Val-Val-OH (4d)
Yield: 1.05 g of crude product which was pure enough for further transformations.

^{1}H NMR (methanol-d_4): δ = 7.43 (dd, *J* = 1.8, 7.8 Hz, 1 H), 7.20 (dd, *J* = 1.8, 7.8 Hz, 1 H), 7.15 (t, *J* = 7.8 Hz, 1 H), 4.59 (m, 1 H), 4.35 (m, 1 H), 4.30 (m, 1 H), 3.31 (s, 3 H), 3.30 (s, 3 H), 2.16 (m, 2 H), 2.07 (m, 1 H), 0.98 (m, 18 H).

^{13}C NMR (methanol-d_4): δ = 174.5 (C), 173.7 (C), 173.5 (C), 167.6 (C), 154.3 (C), 149.0 (C), 127.9 (C), 125.4 (CH), 122.8 (CH), 117.0 (CH), 62.1 (CH_3), 60.3 (CH), 60.0 (CH), 58.9 (CH), 56.6 (CH_3), 32.8 (CH), 32.0 (CH), 31.7 (CH), 19.9 (CH_3), 119.7 (CH_3), 19.6 (CH_3), 19.0 (CH_3), 18.6 (CH_3), 18.3 (CH_3).

MS (EI, 70 eV) *m/z*: 479 ([M$^+$], 0.2) 264 (29), 236 (33), 165 (100).

HRMS *m/z*: [M$^+$] calcd. for $C_{24}H_{37}N_3O_7$, 479.2632; found, 479.2622.

Ver-CO-Val-Val-Val-NHCH$_2$-Ver (6d)
Yield: 985 mg [49% over two steps starting from H_2N-Val-Val-Val-OH (**3d**)] as a grey solid after recrystallization from CH_2Cl_2–MeOH; mp 240 °C (dec.).

^{1}H NMR ($CDCl_3$): δ = 8.74 (d, *J* = 8.4 Hz, 1 H), 8.14 (s br, 2 H), 7.32–7.34 (m, 1 H), 6.97–6.99 (m, 3 H), 6.85–6.89 (m, 2 H), 6.74 (dd, *J* = 7.2, 2.4 Hz, 1 H), 4.93 (dd, *J* = 15.6, 7.8 Hz, 1 H), 4.70 (dd, *J* = 17.4, 8.7 Hz, 1 H), 4.43-4.48 (m, 3 H), 3.89 (s, 3 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 2.03–2.15 (m, 3 H), 0.97 (d, *J* = 6.7 Hz, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 6.7 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 171.5 (2C), 171.3 (C), 165.0 (C), 152.6 (C), 152.4 (C), 147.8 (C), 146.9 (C), 132.0 (C), 126.5 (C), 124.1 (CH), 123.9 (CH), 122.5 (CH), 120.8 (CH), 115.4 (CH), 111.4 (CH), 61.5 (CH_3), 60.6 (CH_3), 58.7 (CH), 58.6 (CH), 58.4 (CH), 56.1 (CH_3), 55.7 (CH_3), 38.1 (CH_2), 31.7 (CH), 31.7 (CH), 31.0 (CH), 19.3 (CH_3), 19.2 (CH_3), 19.0 (CH_3), 18.7 (CH_3), 18.5 (CH_3), 18.3 (CH_3).

IR (KBr): 3275, 3076, 2961, 2836, 1634, 1542, 1482, 1390, 1266, 1226, 1171, 1087, 1004, 748, 715 cm^{-1}.

Cat-CO-Val-Val-Val-NHCH$_2$-Cat (7d)
Yield: 289 mg (96%); grey solid; mp 176–180 °C.

^{1}H NMR (methanol-d_4): δ = 7.34 (dd, *J* = 1.5, 8.1 Hz, 1 H), 6.93 (dd, *J* = 1.5, 7.9 Hz, 1 H), 6.71 (m, 2 H), 6.65 (dd, *J* = 1.5, 7.6 Hz, 1 H), 6.60 (t, *J* = 7.7 Hz, 1 H), 4.48 (d, *J* = 7.8 Hz, 1 H), 4.34 (d, *J* = 14.6 Hz, 1 H), 4.31 (d, *J* = 14.6 Hz, 1 H), 4.25 (d, *J* = 8.3 Hz, 1 H), 4.18 (d, *J* = 8.1 Hz, 1 H), 2.18 (m, 1 H), 2.01 (m, 2 H), 1.00–0.84 (m, 18 H).

^{13}C NMR (methanol-d_4): δ = 173.8 (C), 173.7 (C), 173.5 (C), 170.4 (C), 149.6 (C), 149.2 (C), 147.1 (C), 146.6 (C), 144.5 (C), 126.1 (CH), 121.4 (CH), 120.5 (CH), 119.9 (CH), 119.8 (CH), 117.5 (C), 115.6 (CH), 60.4 (CH), 60.3 (CH), 60.2 (CH), 39.8 (CH_2), 32.0 (CH), 32.0 (CH), 31.9 (CH), 19.9 (CH_3), 19.6 (CH_3), 19.1 (CH_3), 19.0 (CH_3), 19.0 (CH_3), 18.8 (CH_3).

IR (KBr): 3286, 3090, 2965, 1636, 1536, 1372, 1335, 1265, 1077, 743 cm^{-1}.

MS (+FAB) *m/z*: 573 [MH$^+$], 434, 335, 250, 236, 208, 151, 137, 123.

HRMS *m/z*: [M$^+$] calcd for $C_{29}H_{41}N_4O_8$ (573.67), 573.2924; found, 573.2908.

Anal. Calcd for $C_{29}H_{40}N_4O_8$·2.5 H_2O (618.7): C, 56.39; H, 7.34; N, 9.07. Found: C, 56.56; H, 6.93; N, 9.14.

Preparation of Cat-CO-Ala-Val-Leu-NHCH$_2$-Cat (7e)
Ver-CO-Ala-Val-Leu-OH (4e)
Yield: 1.12 g of a waxy slightly yellow solid which was pure enough for further transformations; mp 65 °C.

^{1}H NMR (methanol-d_4): δ = 7.42 (dd, *J* = 2.0, 7.5 Hz, 1 H), 7.15 (m, 2 H), 4.70 (q, *J* = 7.0 Hz, 1 H), 4.46 (t, *J* = 7.5 Hz, 1 H), 4.25 (d, *J* = 7.6 Hz, 1 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 2.11 (m, 1 H), 1.72 (m, 1 H), 1.65 (m, 2 H), 1.44 (d, *J* = 7.0 Hz, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 6.5 Hz, 3 H), 0.91 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (methanol-d_4): δ = 175.7 (C), 174.6 (C), 173.5 (C), 167.3 (C), 154.3 (C), 149.0 (C), 128.0 (C), 125.4 (CH), 122.6 (CH), 116.9 (CH), 61.9 (CH_3), 60.0 (CH), 56.6 (CH_3), 51.9 (CH), 50.5 (CH), 41.4 (CH_2), 32.1 (CH), 25.9 (CH), 23.49 (CH_3), 21.8 (CH_3), 19.7 (CH_3), 18.9 (CH_3), 18.7 (CH_3).

MS (+FAB, 3-NBA) *m/z*: 466 [MH$^+$], 448, 335, 236, 208, 165.

HRMS *m/z*: [M$^+$] calcd for $C_{23}H_{36}N_3O_7$, 466.2553; found, 466.2532.

Ver-CO-Ala-Val-Leu-NHCH$_2$-Ver (6e)
Yield: 730 mg (39% over two steps starting from H_2N-Ala-Val-Leu-OH **3e**) as a beige solid after recrystallization from methanol; mp: 173-180 °C.

^{1}H NMR ($CDCl_3$): δ = 8.80 (d, *J* = 7.0 Hz, 1 H), 8.01 (s br, 1 H), 7.95 (d, *J* = 8.2 Hz, 1 H), 7.41 (dd, *J* = 7.1, 2.4 Hz, 1 H), 7.11 (d, *J* = 8.4 Hz, 1 H), 6.98–7.04 (m, 2 H), 6.84–6.92 (m, 2 H), 6.73 (dd, *J* = 7.9, 1.7 Hz, 1 H), 5.2–5.05 (m, 1 H), 4.77–4.83 (m, 1 H), 4.39–4.52 (m, 3 H), 3.86 (s, 3 H), 3.89 (s, 3 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 2.11 (q, *J* = 6.8 Hz, 1 H), 1.65–1.75 (m, 3 H), 1.40 (d, *J* = 6.9 Hz, 3 H), 0.88–0.93 (m, 12 H).

^{13}C NMR ($CDCl_3$): δ = 172.9 (C), 172.3 (C), 171.3 (C), 164.9 (C), 152.6 (C), 152.4 (C), 147.9 (C), 146.8 (C), 132.0 (C), 125.9 (C), 124.2 (CH), 123.9 (CH), 122.5 (CH), 120.6 (CH), 115.7 (CH), 111.3 (CH), 61.3 (CH_3), 60.6 (CH_3), 58.7 (CH), 56.1 (CH_3), 55.7 (CH_3), 51.8 (CH), 49.5 (CH), 41.2 (CH_2), 38.1 (CH_2), 31.3 (CH), 24.9 (CH), 22.9 (CH_3), 22.0 (CH_3), 19.2 (CH_3), 19.0 (CH_3), 18.1 (CH_3).

IR (KBr): 3281, 3068, 22957, 2873, 1630, 1580, 1545, 1477, 1432, 1388, 1311, 1268, 1230, 1170, 1151, 1091, 1068, 1002, 954, 817, 779, 746, 713 cm^{-1}.

MS (+FAB, 3-NBA) *m/z*: 615 [MH$^+$], 448, 335, 236, 165, 136.

HRMS *m/z*: [M$^+$] calcd for $C_{32}H_{47}N_4O_8$, 615.3394; found, 615.3377.

Cat-CO-Ala-Val-Leu-NHCH$_2$-Cat (7e)
Yield: 613 mg (99%); slightly grey solid; mp 90 °C (dec.).

^{1}H NMR (methanol-d_4): δ = 7.31 (dd, *J* = 1.5, 7.8 Hz, 1 H), 6.93 (dd, *J* = 1.5, 7.8 Hz, 1 H), 6.79 (t, *J* = 8.1 Hz, 1 H), 6.70 (dd, *J* = 1.8, 7.8 Hz, 1 H), 6.65 (dd, *J* = 1.8, 7.8 Hz, 1 H), 6.60 (t, *J* = 7.8 Hz, 1 H), 4.61 (q, *J* = 7.1 Hz, 1 H), 4.44 (dd, *J* = 5.6, 9.4 Hz, 1 H), 4.32 (s, 2 H), 4.18 (d, *J* = 7.4 Hz, 1 H), 2.01 (m, 2 H), 1.59 (m, 2 H), 1.43 (d, *J* = 7.1 Hz, 3 H), 0.91 (d, *J* = 6.5 Hz, 6 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.87 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (methanol-d_4): δ = 173.9 (C), 173.4 (C), 172.1 (C), 169.6 (C), 148.4 (C), 145.8 (C), 145.2 (C), 143.1 (C), 124.7 (C), 119.9 (CH), 119.2 (CH), 118.4 (CH), 118.3 (CH), 118.1 (CH), 115.5 (C), 114.2 (CH), 58.9 (CH), 51.6 (CH), 49.4 (CH), 40.4 (CH_2), 38.5 (CH_2), 30.5 (CH), 24.4 (CH), 22.0 (CH_3), 20.6 (CH_3), 18.3 (CH_3), 17.3 (CH_3), 16.5 (CH_3).

IR (KBr): 3291, 2962, 2874, 1642, 1588, 1533, 1480, 1339, 1265, 1176, 1078, 973, 845, 793, 742 cm^{-1}.

MS (+FAB, 3-NBA) *m/z*: 559 [MH$^+$], 491, 420, 253, 208, 137, 86.

HRMS *m/z*: [M$^+$] calcd for $C_{28}H_{39}N_4O_8$, 559.2768; found, 559.2788.

Anal. Calcd for $C_{28}H_{38}N_4O_8 \cdot 2\ H_2O$ (595.64): C, 56.55; H, 7.12; N, 9.42. Found: C, 56.83; H, 6.70; N, 9.54.

Preparation of Cat-CO-Phe-Leu-Phe-Leu-NHCH$_2$-Cat (7f)
Ver-CO-Phe-Leu-OH (4f)
Yield: 2.78 g of crude product which was used without further purification.

^{1}H NMR (methanol-d_4): δ = 7.07-7.39 (m, 8 H), 4.49 (dd, *J* = 7.8, 0.8 Hz, 1 H), 3.82 (s, 3 H), 3.56 (s, 3 H), 3.28–3.33 (m, 2 H), 3.05 (dd, *J* = 14.1, 7.9 Hz, 1 H), 1.64–1.75 (m, 3 H), 0.94 (d, *J* = 6.4 Hz, 3 H), 0.91 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (methanol-d$_4$): δ = 175.7 (C), 173.4 (C), 167.3 (C), 154.2 (C), 149.2 (C), 138.0 (C), 130.7 (CH), 129.5 (CH), 127.9 (CH), 127.3 (C), 125.3 (CH), 122.7 (CH), 111.1 (CH), 61.7 (CH_3), 56.5 (CH_3), 55.7 (CH), 52.1 (CH), 41.7 (CH_2), 39.0 (CH_2), 26.0 (CH), 23.4 (CH_3), 21.9 (CH_3).

MS (EI, 70 eV) *m/z*: 442 ([M$^+$], 5), 284 (14), 165 (100).

HRMS *m/z*: [M$^+$] calcd for $C_{24}H_{30}N_2O_6$, 442.2104; found, 442.2098.

Ver-CO-Phe-Leu-Phe-Leu-OH (8f)
Yield: 2.24 g crude product which was used without further purification; mp 91 °C.

^{1}H NMR (methanol-d_4): δ = 7.15–7.03 (m, 13 H), 4.76 (m, 1 H), 4.43 (m, 2 H), 4.77 (m, 1 H), 3.69 (s, 3 H), 3.56 (s, 3 H), 2.93 (m, 4 H), 1.65 (m, 6 H), 0.90 (d, *J* = 6.3 Hz, 6 H), 0.89 (d, *J* = 6.4 Hz, 6 H), and further signals of impurities.

MS (+FAB, 3-NBA) *m/z*: 703 [HM$^+$], 725 [NaM$^+$].

HRMS *m/z*: calcd for $C_{39}H_{51}N_4O_8$, 703.3692; found, 703.3707.

Ver-CO-Phe-Leu-Phe-Leu-NHCH$_2$-Ver (6f)
Yield: 1.11 g [36% over three steps starting from H$_2$N-Phe-Leu-OH (**3f**)]; white solid after recrystallization from MeOH; mp 245 °C (dec.).

^{1}H NMR ($CDCl_3$): δ = 7.2–7.0 (m, 13 H), 6.95 (m, 2 H), 6.78 (d, *J* = 7.9 Hz, 1 H), 4.66 (m, 2 H), 4.57 (m, 1 H), 4.50 (m, 2 H), 4.04 (m, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.44 (s, 3 H), 3.13 (m, 2 H), 3.04 (m, 2 H), 1.84 (m, 2 H), 1.69 (m, 2 H), 1.18 (m, 1 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.93 (d, *J* = 6.4 Hz, 3 H), 0.75 (d, *J* = 6.1 Hz, 3 H), 0.70 (d, *J* = 6.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 172.6 (C), 172.5 (C), 172.5 (C), 171.4 (C), 167.1 (C), 152.5 (C), 152.4 (C), 147.9 (C), 146.8 (C), 137.3 (C), 135.6 (C), 132.5 (C), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.4 (CH), 127.6 (CH), 126.6 (CH), 124.6 (CH), 124.4 (C), 124.0 (CH), 122.5 (CH), 120.6 (CH), 116.5 (CH), 111.2 (CH), 61.1 (CH_3), 60.6 (CH_3), 56.3 (CH), 56.1 (CH_3), 55.7 (CH_3), 55.0 (CH), 53.8 (CH), 52.3 (CH), 40.1 (CH_2), 39.9 (CH_2), 38.0 (CH_2), 36.7 (CH_2), 24.9 (CH), 24.7 (CH), 23.5 (CH_3), 22.8 (CH_3), 21.5 (CH_3), 21.1 (CH_3).

IR (KBr): 3268, 3087, 3030, 2956, 2870, 2836, 1691, 1630, 1541, 1482, 1387, 1368, 1267, 1234, 1171, 1085, 1007, 926, 882, 747, 696 cm^{-1}.

MS (+FAB, 3-NBA) *m/z*: 852 [MH$^+$], 685, 572, 425, 312, 165, 151.

HRMS *m/z*: [M$^+$] calcd for $C_{48}H_{62}N_5O_9$, 852.4548; found, 852.4519.

Anal. Calcd for $C_{48}H_{61}N_5O_9$ (852.1): C, 76.66; H, 7.22; N, 8.22. Found: C, 67.33; H, 7.15; N, 8.39.

Cat-CO-Phe-Leu-Phe-Leu-NHCH$_2$-Cat (7f)
Yield: 630 mg (97%); grey solid; mp 125 °C (dec.).

^{1}H NMR (methanol-d_4): δ = 7.25 (m, 5 H), 7.17 (m, 4 H), 7.13 (m, 2 H), 6.93 (dd, *J* = 1.5, 7.8 Hz, 1 H), 6.70 (m, 2 H), 6.63 (m, 2 H), 4.76 (m, 1 H), 4.63 (m, 1 H), 4.43 (m, 1 H), 4.32 (m, 3 H), 3.18 (m, 2 H), 2.98 (m, 2 H), 1.7-1.4 (m, 6 H), 0.89 (d, *J* = 6.2 Hz, 3 H), 0.86 (d, *J* = 6.1 Hz, 3 H), 0.85 (d, *J* = 6.4 Hz, 3 H), 0.82 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (methanol-d_4): δ = 173.5 (C), 173.2 (C), 172.7 (C), 171.9 (C), 169.2 (C), 147.7 (C), 145.7 (C), 145.3 (C), 143.1 (C), 136.8 (C), 136.8 (C), 129.0 (CH), 128.9 (CH), 128.2 (CH), 128.1 (CH), 126.5 (CH), 126.4 (CH), 124.8 (C), 119.8 (CH), 119.2 (CH), 118.7 (CH), 118.5 (CH), 118.4 (CH), 116.1 (C), 114.2 (CH), 55.6 (CH), 54.7 (CH), 52.4 (CH), 51.9 (CH), 40.6 (CH_2), 40.1 (CH_2), 38.5 (CH_2), 37.1 (CH_2), 30.5 (CH), 24.3 (CH), 22.1 (CH_3), 21.9 (CH_3), 20.6 (CH_3), 20.5 (CH_3), one CH_2 can not be observed.

IR (KBr): 3291, 3065, 2958, 2871, 1641, 1587, 1530, 1480, 1456, 1369, 1264, 1078, 1031, 960, 917, 847, 742, 700 cm^{-1}.

MS (+FAB, 3-NBA) *m/z*: 796 [MH$^+$], 657, 544, 397, 284, 256, 137, 120.

HRMS *m/z*: [M$^+$] calcd for $C_{44}H_{54}N_5O_9$, 796.3922; found, 796.3951.

Anal. Calcd for $C_{44}H_{53}N_5O_9 \cdot 2\ H_2O$ (831.9): C, 63.52; H, 6.91; N, 8.42. Found: C, 63.26; H, 6.48; N, 8.34.

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