SYNTHESIS OF DESIGNED FUNCTIONAL MODELS OF BLEOMYCIN INCORPORATING IMIDAZOLE - CONTAINING LEXITROPSINS AS NOVEL DNA RECOGNITION SITES

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Abstract - Synthesis and characterization of compounds **1a - d**, designed functional models for the antitumor antibiotic bleomycin, in which AMPHIS serves as the metal complexing subunit, chiral 1,2-*trans*-disubstituted cyclopropane as linkers and imidazole-containing lexitropsins as DNA sequence selective binding sites, are described.

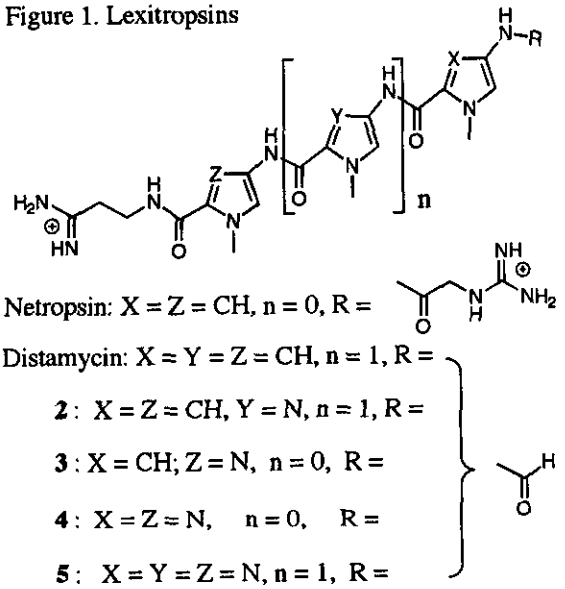
INTRODUCTION

Netropsin and distamycin (Figure 1) are two naturally occurring oligopeptide antibiotics known to act by blocking the template function of DNA through recognizing a sequence consisting of 4 - 5 adjacent AT base pairs in the minor groove of B-DNA double helix.[1] Detailed studies of the molecular recognition of netropsin and distamycin with double helical DNA have made it possible to design the synthetic analogs, so-called "lexitropsins" i.e. information reading agents, where GC recognizing elements have been incorporated to alter the DNA sequence selectivity in varying degrees. For instance, structural modification of netrposin and distamycin by replacement of *N*-methylpyrrole units (Py) with a increasing numbers of other five-mumbered aromatic heterocyclic systems, such as *N*-methylimidazole (Im) led to the lexitropsins such as **2 - 5** with a increasing capacity to recognize and accept GC sites.[1a,2] There is current interest in the design and synthesis of DNA-targeted therapeutic agents which incorporate netropsin and distamycin moieties as sequence recognition motifs.[3] Such polypyrrolamides have been conjugated with synthetic DNA-active cores which simulate the

function of chemotherapeutic agents obtained from natural sources such as enediyne,[4] porphyrin[5] and bleomycin[6] *etc.*

The bleomycins (BLM) and their semisynthetic analogs peplomycin and liblomycin are a family of glycopeptide antitumor antibiotics which are clinically used in combination chemotherapy against several types of cancer (Figure 1).[7] The therapeutic effect of BLM is believed to arise from its ability to cleave double-stranded DNA at '5-GT-3' and '5-GC-3' sites by the abstraction of the H-4' atom of the deoxyribose moiety in pyrimidine residues through a process involved with a redox-active metal ion such as Fe^{2+} and a source of oxygen.[8]

Figure 1. Lexitropsins



Extensive studies on the molecular level indicated that the bithiazole moiety in the side-chain may contribute to the site specificity.[8] This recognition has stimulated studies to design BLM models by replacing the bithiazole moiety to incorporate oligonucleotide,[9] protein[10] and distamycin.[6] Ohno *et al.* have reported a series of synthetic models of bleomycin, PYML(6)-distamycins (Figure 3), where the sequence selectivity is apparently dominated by the distamycin moiety.[6]

We have reported our studies on the design, synthesis and DNA sequence selective cleavage studies of AMPHIS-distamycins (Figure 3).[11] Amongst the compounds studied, hybrid **6** in which the metal complexing subunit AMPHIS and the distamycin-derived carrier are tethered by chiral 1,2-*trans*-cyclopropanedicarboxamide (CPA) showed the highest efficiency of DNA cleavage (Figure 3).[11b] High resolution polyacrylamide sequencing gel studies demonstrated that the recognition of the DNA sequence is dominated by the oligopeptide carriers.[11c,d] We report herein examples where lexitropsins rather than distamycin and netropsin are conjugated into DNA-cleaving molecules constituting the synthesis of BLM functional models with imidazole-containing lexitropsin moieties as DNA recognition sites.

RESULTS AND DISCUSSION

Lown *et al.* and Nishiwaki *et al.* have established the synthetic approaches of poly-*N*-methylpyrrole and poly-*N*-methylimidazole lexitropsins.[12] We found that the lexitropsin moieties **21a - d** are efficiently synthesized by the combination of the intermediates, *N*-methylimidazole **7**, *N*-methylpyrrole **9** reported by Nishiwaki *et al.*[12c] and **8** which was obtained quantitatively by refluxing **7** in methanol. Compound **8** was reduced to amine **10** in

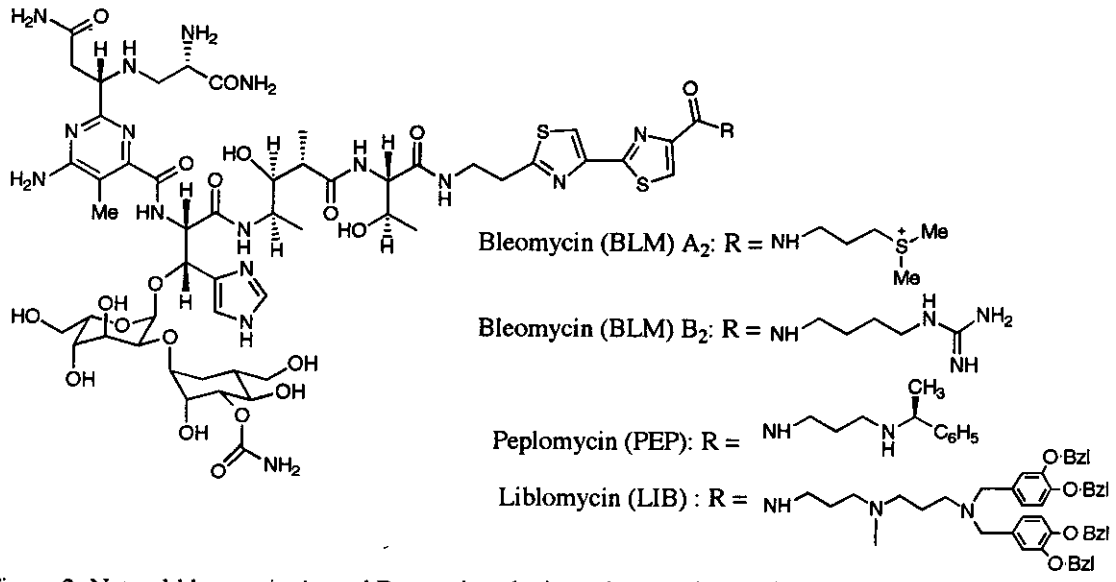
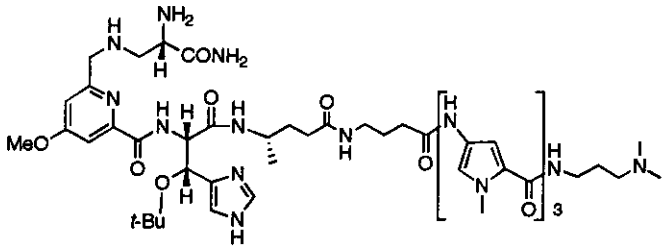


Figure 2: Natural bleomycin A_2 and B_2; semisynthetic analogs pepleomycin and libleomycin



PYML(6)-(4*R*-APA)-DST

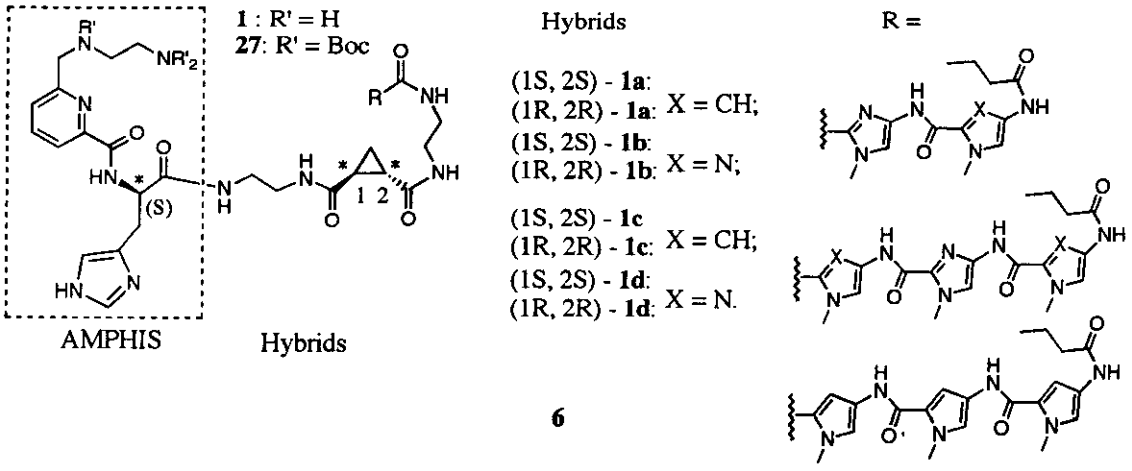
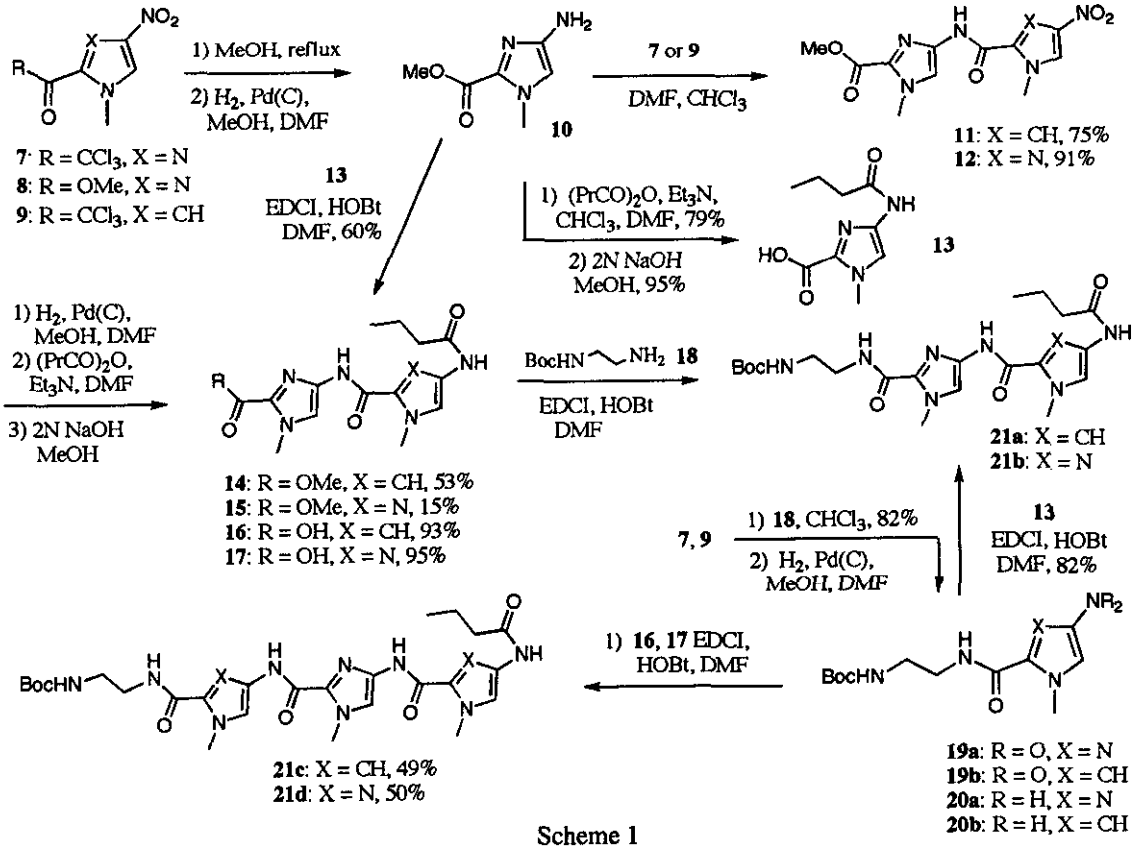


Figure 3. PLMY (6)-DST, previously reported compound **6** and the hybrids synthesized

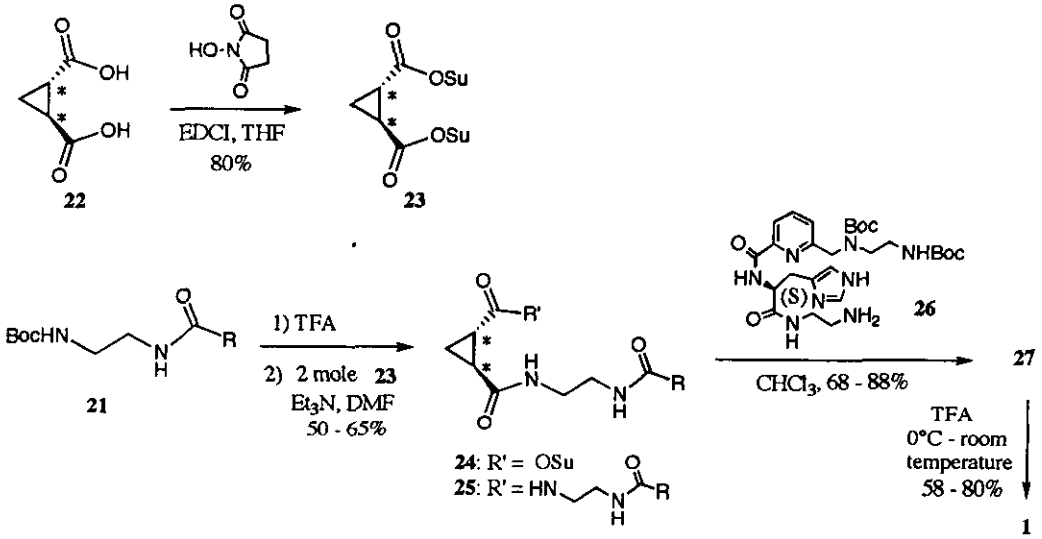
a hydrogen atmosphere in the presence of 10% Pd(C) and **10** was immediately condensed with **7** and **9** in DMF and chloroform, affording **11** and **12** in yields of 75% and 91% respectively from **7**. Catalytic hydrogenation of **11** in DMF and methanol, followed by acylation with butyric anhydride in the presence of triethylamine provided the methyl ester **14** in 53% yield, which was hydrolyzed to acid **16** in a yield of 93%. A similar procedure, however, only gave 15% of **15** owing to the complex products of the hydrogenation of **12**. Compound **15** was obtained in modest from the coupling reaction of amine **10** with acid **13** which was synthesized by the acylation of **10** followed by hydrolysis. Intermediate **15** was converted into corresponding acid **17** in a yield of 95% by hydrolysis. Coupling reaction of acids **16** and **17** with amine **18**[11a,c] in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole



Scheme 1

hydrate (HOBt) in DMF afforded lexitropsin moieties **21a - b** quantitatively. Reactions of **7, 9** with **18** provided nitro compounds **19** which were reduced into **20** quantitatively before use. Compound **21b** was also obtained directly by coupling of **20a** with **13** (82% yield). Lexitropsin moieties **21c - d** were obtained in modest yields from the similar coupling reactions of **20b, a** with **16** and **17** respectively.

The cyclopropane linkers were incorporated by optically pure active ester **23**,[13] which can be prepared by the reaction of (1*S*, 2*S*)- and (1*R*, 2*R*)-1,2-cyclopropanedicarboxylic acid **22**[14] with *O*-succinimidyl-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate in the presence of diisopropylethylamine. They were however more conveniently synthesized in 70% yield by the coupling of the acid **22** with *N*-hydroxysuccinimide in THF in the presence of EDCI. Condensation of amine-TFA salts, derived from the deprotection of **21a - d** with excess of chiral active esters **23** in DMF by adding triethylamine in portions, afforded mono active esters (1*S*, 2*S*)-, (1*R*, 2*R*)-**24** in yields of 50 - 67%, with the formation of diamide **25** as a minor product. Condensation of **24** with the metal-coordinating part (*S*)-AMPHIS-NH_2 **26**[11a,c] in chloroform provided (1*S*, 2*S*)-, (1*R*, 2*R*)-**27** in 70 - 88% yields. Deprotection of **27** with trifluoroacetic acid at 0°C for 30 minutes and purification of the residues on a column of Amberlite XAD-2 resin afforded the final hybrids (1*S*, 2*S*)-, (1*R*, 2*R*)-**1a - d** in 58 - 78% yields.



Scheme 2

A study of the cleavage of supercoiled covalently closed circular DNA by **1a - d** in the presence of Fe(II) ion was conducted by a mobility shift assay using agarose gel electrophoresis experiment. After incubation of the drug-Fe(II) complexes with PM2 DNA (0.5 A_{260}) and 1,4-dithiothreitol (1 mM) in 50 mM of sodium cacodylate buffer for 30 minutes, the reaction mixtures were loaded on a 1% agarose gel. Under the experimental conditions, the complexes of **1a**, **1c**, **1d** at 40 μM and **1b** at 160 μM converted CCC DNA (form I) mainly to OC DNA (form II).

EXPERIMENTAL

Chemistry. Melting points were determined with an Electrothermal apparatus and are uncorrected. ^{1}H-nmr spectra were recorded at ambient temperature on a Bruker WH-300 and Varian Unity 500 MHz spectrometer respectively. Fast atom bombardment high-resolution mass spectra (FABHRms) were recorded on a modified

MS-50 mass spectrometer equipped with a VG 11-250J data system. Accurate masses were calculated interactively with the data system using a reference (such as CsI in glycerol) peaks. FT-ir spectra were recorded on a Perkin Elmer 1760 spectrophotometer interfaced to a PE 7700 microcomputer. Optical rotations were measured on P. E. 241 polarimeter at sodium-D-line (589 nanometers) at ambient temperature. Analytical thin-layer chromatography was performed on silica-coated plastic plates (silica gel 60 F-254, Merck) and visualized under uv light. Preparative separations were performed by flash chromatography on silica gel (Merck, 70-230 or 230-400 mesh). Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl. Anhydrous dimethylformamide (DMF), 98% 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole hydrate (HOBt) were purchased from Aldrich. Trifluoracetic acid (TFA) was purchased from Caledon. All other solvents were used as received and were reagent grade where available.

Methyl 4-(1-methyl-4-nitro-2-pyrrolyl)carboxamido-1-methyl-2-imidazolecarboxylate (**11**):

A suspension of **7** (1.090 g, 4 mmol) in methanol (15 ml) was refluxed for 30 min and then concentrated into 3 ml under reduced pressure. After 10% Pd(C) (370 mg) and DMF (2 ml) were added, the mixture was stirred at room temperature in a hydrogen atmosphere (H_2-balloon) for 2 h. The black suspension was filtered and evaporated *in vacuo*. The residue thus obtained was mixed with **9** (1.086 g, 4 mmol) and chloroform (5 ml), and the solution was stirred overnight. The solid residue was collected, washed with chloroform and dried *in vacuo* to afford **11** (887 mg, 75%) as a yellowish powder. mp 210°C (decomp.); ir (film) ν_{max} 3133 (br), 2955 (*w*), 1717 (*s*), 1666 (*s*), 1553 (*s*), 1315 (*s*), 1123 (m) cm^{-1}; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ 8.50 (br, 1H, -CONH-), 7.60 (d, J = 2.0 Hz, 1H), 7.52 (s, 1H), 7.10 (d, J = 2.0 Hz, 1H), 4.00 (s, 6H), 3.92 (s, 3H); Anal. Calcd for $C_{12}H_{13}N_5O_5$: C, 46.90; H, 4.26; N, 22.80; Found: C, 46.98; H, 4.19; N, 22.74.

Methyl 4-(1-methyl-4-nitro-2-imidazolyl)carboxamido-1-methyl-2-imidazolecarboxylate (**12**):

Compound **8** (1.50 g, 8.11 mmol) was treated in a similar way as described for **11** in the presence of 0.50 g of 10% Pd(C). The resulting DMF solution of **10** was mixed with chloroform (10 ml) and **7** (2.10 g, 8.11 mmol). After the exothermic reaction ceased, the mixture was stirred for another 1 h, the suspension was filtered and the solid residue was washed with dichloromethane. The title compound was obtained as white powder (2.269 g, 91%). mp 218 -219 °C; ir (film) ν_{max} 1718 (m), 1667 (m), 1538 (s), 1455 (m), 1426 (m), 1381 (m), 1312 (m), 1299 (*w*), 1275 (*m*), 1123 (*m*), 828 (*m*) cm^{-1}; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ 10.88 (s, 1H, -CONH-), 8.62 (s, 1H), 7.72 (s, 1H), 4.00 (s, 3H), 3.93 (s, 3H), 3.80 (s, 3H). Anal. Calcd for $C_{11}H_{12}N_6O_5$: C, 42.86; H, 3.92; N, 27.27; Found: C, 42.81; H, 3.96; N, 27.20.

Methyl 4-(4-butyrylamino-1-methyl-2-pyrrolyl)carboxamido-1-methyl-2-imidazolecarboxylate (**14**):

A suspension of **11** (849 mg, 2.88 mmol) and 10% Pd(C) (400 mg) in DMF (5 ml) and methanol (3 ml) was hydrogenated at room temperature with a H_2-balloon until the starting material disappeared as indicated by tlc detection. The mixture was filtered and the filtrate evaporated under reduced pressure to remove methanol. The DMF solution was mixed with butyric anhydride (0.71 ml, 4.32 mmol), triethylamine (0.60 ml, 4.32 mmol), chloroform (6 ml), and stirred at room temperature overnight. The reaction mixture was diluted with chloroform (50 ml), washed with water, saturated aqueous $NaHCO_3$ and dried on anhydrous Na_2SO_4. Purification of the residue by flash chromatography on silica column eluted with dichloromethane / methanol (20:1) provided ester **14** (511 mg, 53%) as yellowish powder. mp 83 - 84°C; ir (film) ν_{max} 3138 (br), 1692 (s), 1539 (s), 1314 (s), 1255 (m), 1113 (m), 749 (m) cm^{-1}; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ 9.22 (s, 1H, -CONH-), 9.02 (s, 1H, -CONH-), 7.50 (s, 1H), 7.26 (d, J = 2.0 Hz, 1H), 6.68 (d, J = 2.0 Hz, 1H), 3.92 (s, 3H), 3.82 (s, 6H), 2.20

(t, J = 7.5 Hz, 2H), 1.63 (sex, J = 7.5 Hz, 2H), 0.90 (t, J = 7.5 Hz, 3H); Anal. Calcd for $C_{16}H_{21}N_5O_4$: C, 55.32; H, 6.09; N, 20.17; Found: C, 55.22; H, 6.01; N, 19.98.

4-Butyrylamino-1-methyl-2-imidazolecarboxylic acid (**13**):

DMF solution (5 ml) of amine **10** obtained from the hydrogenation of **8** (2.035 g, 11.00 mmol) was treated with chloroform (15 ml), butyric anhydride (2.70 ml, 16.5 mmol) and triethylamine (2.3 ml, 16.5 mmol). After being stirred at room temperature overnight, the solution was evaporated *in vacuo* to remove DMF and the residue was dissolved in dichloromethane (90 ml), washed with saturated aqueous sodium bicarbonate and dried on anhydrous Na_2SO_4. The residue was purified by flash chromatography on silica gel, eluted with dichloromethane / methanol (20:1) and recrystallized from hexane / methanol (7:1). Methyl 4-butyrylamino-1-methyl-2-imidazolecarboxylate was obtained as yellowish crystals (1.95 g, 79%). mp 120 -121 °C; ir (film) ν_{max} 3212 (br), 3078 (w), 2961 (w), 1717 (s), 1684 (m), 1561 (s), 1456 (m), 1376 (w), 1273 (m), 1202 (w), 1126 (m) cm^{-1}; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ 7.87 (br, 1H, -CONH-), 7.50 (s, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 2.33 (t, J = 7.5 Hz, 2H), 1.75 (sex, J = 7.5 Hz, 2H), 1.00 (t, J = 7.5 Hz, 3H); Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.31; H, 6.71; N, 18.66; Found: C, 53.29; H, 6.67; N, 18.54. The ester (1.25 g, 5.56 mmol) was hydrolyzed in 0.5 N NaOH in 75% methanol (15 ml) at room temperature for 30 min, and subsequently diluted with water (20 ml). The solution was evaporated under reduced pressure to remove methanol, washed with ether and the aqueous phase was acidified with 6N hydrochloric acid to pH 4. The white deposit was collected and dried *in vacuo* over P_2O_5. The title compound was obtained as white powder (1.110 g, 95%). mp 254 °C (decomp.); ir (film) ν_{max} 3500 (br), 2959 (w), 2700 (br), 1639 (s), 1571 (s), 1343 (m), 1212 (m), 805 (w) cm^{-1}; ^{1}H-nmr (DMSO-d_6, 300 MHz) δ 10.30 (s, 1H, -CONH-), 7.30 (s, 1H), 3.87 (s, 3H), 2.22 (t, J = 7.5 Hz, 2H), 1.56 (t, J = 7.5 Hz, 2H), 0.87 (t, J = 7.5 Hz, 3H). This was employed in the next step without further purification.

Methyl 4-(4-butyrylamino-1-methyl-2-imidazolyl)carboxamido-1-methyl-2-imidazolecarboxylate (**15**):

A solution of the acid **13** (0.397 g, 1.88 mmol), HOBt (0.297 g, 2.2 mmol) and EDCI (0.422 g, 2.2 mmol) in DMF (4 ml) was stirred at room temperature for 30 min and then amine **9** obtained from **8** (0.370 g, 2.0 mmol), was added. After being stirred overnight, the mixture was evaporated and the residue was dissolved in dichloromethane (30 ml), washed with saturated aqueous sodium carbonate, water and dried on anhydrous Na_2SO_4. Concentration of the solution provided a solid which was washed with ether. The title compound was obtained as yellowish powder (0.432 g, 66%). mp 212 -214 °C; ir (film) ν_{max} 3275 (br), 2960 (w), 1716 (m), 1672 (m), 1563 (m), 1534 (s), 1474 (m), 1275 (m), 1125 (m), 731 (w) cm^{-1}; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ 9.45 (s, 1H, -CONH-), 7.85 (s, 1H, -CONH-), 7.55 (s, 1H), 7.45 (s, 1H), 4.03 (s, 3H), 3.95 (s, 3H), 2.35 (t, J = 7.5 Hz, 2H), 1.75 (sex, J = 7.5 Hz, 2H), 1.00 (t, J = 7.5 Hz, 3H); Anal. Calcd for $C_{15}H_{20}N_6O_4$: C, 51.71; H, 5.79; N, 24.13; Found: C, 51.77; H, 5.88; N, 23.96.

4-(4-Butyrylamino-1-methyl-2-pyrrolyl)carboxamido-1-methyl-2-imidazolecarboxylic acid (**16**):

A suspension of **14** (495 mg, 1.427 mmol), 0.4 N NaOH in 50% methanol (10 ml, 4 mmol) was stirred at room temperature for 1 h. The clear solution was evaporated to remove methanol, diluted with water (10 ml) and extracted with ethyl acetate (2 X 10 ml). The organic layer was extracted with water (5 ml) and the combined aqueous layer was cooled on an ice-water bath, acidified with dilute hydrochloric acid to pH 3 and then filtered. The solid residue was dissolved in methanol and evaporated. The residue was washed with ether and dried *in vacuo*. The Acid **16** (442 mg, 93%) was obtained as yellowish powder. mp 160°C (decomp.); ir

(film) ν_{max} 3247 (br), 2960 (w), 1658 (s), 1566 (s), 1552 (s), 1402 (m), 1351 (m), 1211 (w), 1102 (w), 832 (w) cm^{-1}; ^{1}H-nmr (DMSO-d_6, 300 MHz) δ 10.34 (s, 1H, -CONH-), 9.78 (s, 1H, -CONH-), 7.42 (s, 1H), 7.24 (d, J = 2.0 Hz, 1H), 6.88 (d, J = 2.0 Hz, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 2.20 (t, J = 7.5 Hz, 2H), 1.56 (sex, J = 7.5 Hz, 2H), 0.88 (t, J = 7.5 Hz, 3H); Anal. Calcd for $C_{15}H_{19}N_5O_4$: C, 54.04; H, 5.74; N, 21.01; Found: C, 53.96; H, 5.69; N, 20.91.

4-(4-Butyrylamino-1-methyl-2-imidazolyl)carboxamido-1-methyl-2-imidazolecarboxylic acid (**17**):

The acid **17** (0.197 g, 95%) was obtained from the ester **15** (0.216 g, 0.621 mmol) in the similar procedure as described for **16**. mp 130 - 131 °C; ir (film) ν_{max} 3400 (br), 2925 (w), 1671 (s), 1542 (s), 1452 (m), 1369 (m), 1216 (w), 783 (w) cm^{-1}; ^{1}H-nmr (DMSO-d_6, 300 MHz) δ 10.33 (s, 1H, -CONH-), 9.60 (s, 1H, -CONH-), 7.62 (s, 1H), 7.50 (s, 1H), 3.96 (s, 3H), 3.92 (s, 3H), 2.27 (t, J = 7.5 Hz, 2H), 1.56 (sex, J = 7.5 Hz, 2H), 0.88 (t, J = 7.5 Hz, 3H); Anal. Calcd for $C_{14}H_{18}N_6O_4$: C, 50.29; H, 5.43; N, 25.14; Found: C, 50.15; H, 5.40; N, 24.99.

N-(2-*t*-Butoxycarboxamido)ethyl 4-(4-butyrylamino-1- methyl-2- pyrrolyl)carboxamido- 1-methyl- 2-imidazolecarboxamide (**21a**):

A solution of acid **16** (150 mg, 0.450 mmol), amine **18** (87 mg, 0.541 mmol), EDCI (104 mg, 0.541 mmol), HOBt (73 mg, 0.541 mmol) in DMF (3 ml) was stirred at room temperature overnight. DMF was removed by evaporation *in vacuo* and the residue was dissolved in dichloromethane (30 ml), washed with saturated aqueous $NaHCO_3$, water and dried on anhydrous Na_2SO_4. The product **21a** (209 mg, 98%) was separated by flash chromatography on silica column eluted with dichloromethane / methanol (20:1) as a yellowish foam. R_f (CH_2CL_2:MeOH = 9:1) 0.47; ir (film) ν_{max} 3297 (br), 2965 (w), 2934 (w), 1658 (s), 1531 (s),1466 (m), 1446 (m), 1366 (w), 1249 (w), 1162 (m) cm^{-1}; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ: 8.75 (br, 1H, -CONH-), 8.00 (br, 1H, -CONH-), 7.70 (br, 1H, -CONH-), 7.40 (s, 1H), 7.35 (s, 1H), 6.68 (s, 1H), 5.24 (br, 1H, -CONH-), 3.98 (s, 3H), 3.90 (s, 6H), 3.50 (m, 2H), 3.37(m, 2H), 2.33 (t, J = 7.5 Hz, 2H), 1.75 (sex, J = 7.5 Hz, 2H), 1.40 (s, 9H), 1.00 (t, J = 7.5 Hz, 3H); HRMS m/z calcd for $C_{22}H_{33}N_7O_5$ (M^+): 475.2543, found: 475.2530. This was employed in the next step without further purification.

N-(2-*t*-Butoxycarboxamido)ethyl 4-nitro-1-methyl-2-imidazolecarboxamide (**19a**):

A solution of **7** (1.500 g, 5.5 mmol) and amine **18** (0.969 g, 6.05 mmol) in chloroform (20 ml) was stirred at room temperature for 30 min. The mixture was evaporated and the solid residue was collected, then washed with ether. the title compound was obtained as a white powder (1.420 g, 82%). mp 143 -145 °C; ir (film) ν_{max} 3369 (br), 2978 (w), 2935 (w), 1677 (s), 1540 (s), 1383 (m), 1309 (m), 1252 (m), 1168 (m), 1001 (w) cm^{-1}; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ 7.77 (s, 1H), 7.51 (br, 1H, -CONH-), 4.80 (br, 1H, -CONH-), 4.13 (s, 3H), 3.49 (m, 2H), 3.33 (m, 2H), 1.40 (s, 9H). Anal. Calcd for $C_{12}H_{19}N_5O_5$: C, 46.00; H, 6.11; N, 22.36; Found: C, 45.89; H, 6.06; N, 22.31.

N- (2-*t*-Butoxycarboxamido)ethyl 4-(4- butyrylamino-1 -methyl-2- imidazolyl)carboxamido-1- methyl-2-imidazolecarboxamide (**21b**):

A solution of acid **13** (0.500 g, 2.37 mmol), HOBt (0.352 g, 2.61 mmol) and EDCI (0.500 g, 2.61 mmol) in DMF (5 ml) was stirred at room temperature for 30 min. To this was added a DMF solution of the amine **20a** obtained from the hydrogenation of **19a** (0.742 g, 2.37 mmol) in methanol (7 ml) and DMF (5 ml) in the presence of 10% Pd(C) (0.200 g). After being stirred at room temperature overnight, the mixture was evaporated to remove DMF and the residue was dissolved in chloroform (20 ml), washed with water, saturated

aqueous sodium bicarbonate and dried on anhydrous Na_2SO_4. Purification of the residue on silica column eluted with dichloromethane / methanol (20:1 - 10:1) provided the title compound as a white powder (0.930 g, 82%). R_f (CH_2Cl_2:MeOH = 9:1) 0.50; ir (film) ν_{max} 3301 (br), 2966 (w), 1673 (s), 1532 (s),1469 (m), 1366 (w), 1170 (w) cm^{-1}; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ 9.25 (br, 1H, -CONH-), 8.51 (br, 1H, -CONH-), 8.18 (br, 1H, -CONH-), 7.47 (s, 1H), 7.42 (s, 1H), 5.25 (br, 1H, -CONH-), 4.03 (s, 3H), 4.00 (s, 3H), 3.55 (m, 2H), 3.40 (m, 2H), 2.43 (t, J = 7.5 Hz, 2H), 1.78 (sex, J = 7.5 Hz, 2H), 1.40 (s, 9H), 1.01 (t, J = 7.5 Hz, 3H); HRms m/z calcd for $C_{21}H_{32}N_8O_5$ (M^+): 476.2496, found: 476.2498. This was employed in the next step without further purification.

N- (2-*t*-Butoxycarboxamido)ethyl 4-[4 -(4-butyrylamino-1 -methyl-2- pyrrolyl)carboxamido-1- methyl-2-imidazolyl]carboxamido-1-methyl-2-pyrrolecarboxamide (**21c**):

A suspension of **19b**[11a,c] (154 mg, 0.495 mmol), 10% Pd(C) (50 mg) in methanol (3 ml) and DMF (2 ml) was stirred at room temperature in a hydrogen atmosphere supplied from H_2-balloon for 2 h. The mixture was then filtered and evaporated under reduced pressure to give a DMF solution of **20b**. To this was added the acid **16** (150 mg, 0.450 mmol), EDCI (95 mg, 0.495 mmol), HOBt (67 mg, 0.495 mmol) and DMF (5 ml). After being stirred overnight, the mixture was evaporated *in vacuo* to remove DMF and the residue was dissolved in chloroform (50 ml), washed with water and dried on anhydrous Na_2SO_4. Flash chromatography on silica column by elution with dichloromethane / methanol (20:1) provided **21c** (133 mg, 49%) as amorphous foam. R_f (CH_2Cl_2:MeOH = 9:1) 0.40; ir (film) ν_{max} 3296 (br), 2964 (w), 2935 (w), 1652 (s), 1533 (s), 1444 (m), 1365 (m), 1251 (w), 1167 (w) cm^{-1}; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ 9.30 (br, 1H, -CONH-), 8.65 (br, 1H, -CONH-), 8.17 (br, 1H, -CONH-), 7.43 (s, 1H), 7.37 (s, 1H), 7.04 (br, 1H, -CONH-), 6.77 (s, 1H), 6.70 (s, 1H), 4.01 (s, 3H), 3.90 (s, 3H), 3.86 (s, 6H), 3.53 (m, 2H), 3.40 (m, 2H), 2.40 (t, J = 7.5 Hz, 2H), 1.78 (sex, J = 7.5 Hz, 2H), 1.45 (s, 9H), 1.04 (t, J = 7.5 Hz, 3H); FABHRms m/z calcd for $C_{28}H_{39}N_9O_6$ (M^+): 597.3023, found: 597.3030. This was employed in the next step without further purification.

N- (2-*t*-Butoxycarboxamido]ethyl 4-[4- (4- butyrylamino-1- methyl-2- imidazolyl)carboxamido-1- methyl-2-imidazolyl]carboxamido-1-methyl-2-imidazolecarboxamide (**21d**):

A solution of the acid **17** (0.260 g, 0.778 mmol), HOBt (0.116 g, 0.856 mmol) and EDCI (0.164 g, 0.856 mmol) in DMF (6 ml) was stirred at room temperature for 30 min and to this was added the amine **20a** obtained from the hydrogenation of **19a**[11a,c] (0.268 g, 0.856 mmol). After being stirred at room temperature overnight, the mixture was evaporated to remove DMF and the residue was dissolved in chloroform (50 ml), washed with water and dried on anhydrous Na_2SO_4. Concentration of the solution afforded a yellowish powder which was washed with ether and dried *in vacuo*. **21d** was obtained as yellowish powder (0.230 g, 50%). R_f (CH_2Cl_2:MeOH = 9:1) 0.55; ir (film) ν_{max} 3325 (br), 1673 (s), 1532 (s), 1465 (m) cm^{-1}; ^{1}H-nmr ($CDCl_3$:CD_3OD = 5:1, 300 MHz) δ 7.26 (s, 1H), 7.19 (s, 1H), 7.13 (s, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.19 (t, J = 6.0 Hz, 2H), 3.03 (t, J = 6.0 Hz, 2H), 2.10 (t, J = 7.5 Hz, 2H), 1.48 (sex, J = 7.5 Hz, 2H), 1.16 (s, 9H), 0.75 (t, J = 7.5 Hz, 3H); FABHRms m/z calcd for $C_{26}H_{37}N_{11}O_6H$ (M^++H): 600.3007, found: 600.3026. This was employed in the next step without further purification.

Preparation of *O*-succinimidyl cyclopropanedicarboxylate (**23**):

To a solution of (+)-(1*S*, 2*S*)-**22**[14] (580 mg, 4.46 mmol) and *N*-hydroxysuccinimide (1.28 g, 11.15 mmol) in anhydrous THF (5 ml) was added dropwise EDCI (2.14 g, 11.15 mmol) in chloroform (5 ml). After being stirred overnight, the mixture was diluted with dichloromethane (30 ml), washed with water, saturated aqueous

sodium bicarbonate and dried on anhydrous Na_2SO_4. Concentration of the solution provided a solid residue which was washed with methanol and dried *in vacuo* to give (1*S*, 2*S*)-**23** (1.19 g, 82%) as a white powder. The spectral and physical data are identical with those reported.[13] (1*R*, 2*R*)-**23** (1.12 g, 78%) was obtained in the same procedure.

General procedure for the synthesis of (**24**):

Compounds **21a - d** in trifluoroacetic acid was stirred at 0°C for 30 min and subsequently evaporated *in vacuo* to remove the solvent. Washing the residue with ether and drying *in vacuo* resulted in the amine-TFA salts quantitatively as yellowish powder.

To a stirred solution of the amine-TFA salts and 2 equivalents of active ester **23** in DMF was added triethylamine by microsyringe. After being stirred for 2 h, the mixture was evaporated and the residue was dissolved in chloroform, washed with water and dried on anhydrous Na_2SO_4. The products were isolated as amorphous foam by flash chromatography on silica column eluted with dichloromethane / methanol (10:1).

SuO-CPA-ImPy (**24a**): Compound **21a** (200 mg, 0.421 mmol) afforded 213 mg of the corresponding amine-TFA salt. The latter material (100 mg, 0.198 mmol) reacted with (1*R*, 2*R*)-**23** (128 mg, 0.396 mmol), triethylamine (60 µl) in DMF (2 ml), resulting in (1*R*, 2*R*)-**24a** (77 mg, 67%): R_f (CH_2Cl_2:MeOH = 8.5:1.5) 0.59; $[\alpha]^{20}_D$ -59° (c 0.89, $CHCl_3$); ir (film) ν_{max} 3385 (br), 2926 (w), 1736 (s), 1654 (s), 1539 (s), 1405 (m), 1208 (m), 668 (m) cm^{-1}; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ: 10.27 (s, 1H, -CONH-), 9.80 (s, 1H, -CONH-), 8.62 (t, J = 3.0 Hz, 1H, -CONH-), 8.07 (t, J = 3.0 Hz, 1H, -CONH-), 7.50 (s, 1H), 7.38 (d, J = 2.0 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 3.93 (s, 3H), 3.82 (s, 6H), 3.48 - 3.42 (m, 4H), 2.82 (s, 4H), 2.33 (m, 1H), 2.23 (m, 1H), 2.21 (t, J = 7.5 Hz, 2H), 1.60 (sex, J = 7.5 Hz, 2H), 1.50 (m, 1H), 1.40 (m, 1H), 0.90 (t, J = 7.5 Hz, 3H); FABHRms m/z calcd for $C_{26}H_{32}N_8O_8H$ (M^++H): 585.2421, found: 585.2450. (1*S*, 2*S*)-**24a** (65% yield) was obtained in the same procedure.

SuO-CPA-ImIm (**24b**): Compound **21b** (500 mg, 1.05 mmol), deprotected in trifluoroacedic acid (3 ml), provided the amine-TFA salt (439 mg). 150 mg of the latter (0.306 mmol), reacted with (1*S*, 2*S*)-**23** (149 mg, 0.459 mmol) in the presence of triethylamine (90 µl), to afford (1*S*,2*S*)-**24b** (94 mg, 53%): R_f (CH_2Cl_2:MeOH = 9:1) 0.45; $[\alpha]^{20}_D$ +1.9° (c 0.62, MeCN:MeOH = 4:1); ir (film) ν_{max} 3298 (br), 2961 (w), 1780 (w), 1741 (s), 1665 (s), 1565 (s), 1535 (s), 1476 (m), 1368 (m), 1205 (m), 1075 (w), 769 (w) cm^{-1}; ^{1}H-nmr (DMSO-d_6, 300 MHz) δ 10.30 (s, 1H, -CONH-), 9.32 (s, 1H, -CONH-), 8.62 (br m, 1H, -CONH-), 8.34 (br m, 1H, -CONH-), 7.53 (s, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 3.33 - 3.26 (m, 4H), 2.81 (s, 4H), 2.29 (t, J = 7.5 Hz, 2H), 2.30 (m, 1H), 2.21 (m, 1H), 1.59 (sex, J = 7.5 Hz, 2H), 1.51 (m, 1H), 1.39 (m, 1H), 0.88 (t, J = 7.5 Hz, 3H); FABHRms m/z calcd for $C_{30}H_{36}N_{12}O_9H$ (M^++H): 709.2806, found: 709.2796. (1*R*, 2*R*)-**24b** (50% yield) was obtained in the same procedure.

SuO-CPA-PyImPy (**24c**): Deprotection of **21c** (120 mg, 0.201 mmol) in trifluoroacetic acid (2 ml) gave the amine-TFA salt (125 mg), 62 mg of which reacted with (1R, 2R)-**23** (65 mg, 0.200 mmol) and triethylamine (20 µl), resulting in (1*R*, 2*R*)-**24c** (45 mg, 67%): R_f (CH_2Cl_2:MeOH = 8.5:1.5) 0.55; $[\alpha]^{20}_D$ -50° (c 0.46, MeOH); ir (film) ν_{max} 3301 (br), 2961 (w), 1739 (s), 1655 (s), 1530 (s), 1445 (m), 1364 (m), 1207 (m), 1101 (m), 753 (m) cm^{-1}; ^{1}H-nmr (DMSO-d_6, 300 MHz) δ 10.25 (s, 1H, -CONH-), 9.98 (s, 1H, -CONH-), 9.78 (s, 1H, -CONH-), 8.62 (t, J = 3.0 Hz, 1H, -CONH-), 8.10 (t, J = 3.0 Hz, 1H, -CONH-), 7.52 (s, 1H), 7.27 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 3.98 (s, 3H), 3.83 (s, 6H), 3.80 (s, 3H), 3.23 (m, 4H), 2.81 (s, 4H), 2.32 (m, 1H), 2.22 (m, 1H), 2.20 (t, J = 7.5 Hz,

2H), 1.58 (sex, J = 7.5 Hz, 2H), 1.50 (m, 1H), 1.38 (m, 1H), 0.90 (t, J = 7.5 Hz, 3H); FABHRms m/z calcd for $C_{32}H_{38}N_{10}O_9H$ (M^++H): 707.2901, found: 707.2894. (1*S*, 2*S*)-**24c** (64%) was obtained in the same procedure.

SuO-CPA-ImImIm (**24d**): Compound **21d** (200 mg, 0.334 mmol), treated with trifluoroacedic acid (3 ml), afforded the corresponding amine -TFA salt (203 mg). The latter (100 mg, 0.167 mmol) reacted with (1*S*, 2*S*)-**23** (108 mg, 0.334 mmol) in the presence of triethylamine (60 µl) and provided (1*S*,2*S*)-**24d** (63 mg, 53%). R_f (CH_2Cl_2:MeOH = 9:1) 0.50; $[\alpha]^{20}_D$ +54° (c 0.35, $CHCl_3$:MeOH = 7:3); ir (film) ν_{max} 3331 (br), 2959 (w), 1779 (w), 1738 (s), 1672 (s), 1539 (s), 1475 (m), 1369 (w), 1205 (m), 1102 (w), 1074 (w) cm^{-1}; ^{1}H-nmr (DMSO-d_6, 300 MHz) δ 10.35 (s, 1H, -CONH-), 9.63 (s, 1H, -CONH-), 9.60 (s, 1H, -CONH-), 8.60 (t, J = 4.5 Hz, 1H, -CONH-), 8.33 (t, J = 4.5 Hz, 1H, -CONH-), 7.64 (s, 1H), 7.53 (s, 1H), 7.52 (s, 1H), 4.00 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H), 3.28 (m, 4H), 2.80 (s, 4H), 2.30 (m, 1H), 2.28 (t, J = 7.5 Hz, 2H), 2.21 (m, 1H), 1.59 (sex, J = 7.5 Hz, 2H), 1.51 (m, 1H), 1.39 (m, 1H), 0.88 (t, J = 7.5 Hz, 3H); FABHRms m/z calcd for $C_{25}H_{31}N_9O_8H$ (M^++H): 586.2374, found: 586.2356. (1*R*, 2*R*)-**24d** (62%) was obtained in the same procedure.

General procedure for the synthesis of (**27**):

Active esters **24** and 1.5 equivalents of **26** in chloroform or THF was stirred at room temperature overnight. The mixture was concentrated and subjected to flash chromatography on silica column eluting with dichloromethane / methanol (8.5:1.5 - 8:2). The product was obtained as amorphous powder.

(*S*)-bis(Boc)-AMPHIS-CPA-ImPy (**27a**): Reaction of (1*S*, 2*S*)-**24a** (40 mg, 0.0685 mmol) with **26** (59 mg, 0.103 mmol) in chloroform (2 ml) afforded (1*S*, 2*S*)-**27** (62 mg, 87%): R_f (CH_2Cl_2:MeOH = 8:2) 0.37; $[\alpha]^{20}_D$ +32° (c 0.87, $CHCl_3$); ir (film) ν_{max} 3301 (br), 2974 (w), 2934 (w), 1653 (s), 1527 (s),1449 (m), 1366 (m), 1246 (m), 1165 (m), 754 (m) cm^{-1}; ^{1}H-nmr (DMSO-d_6, 300 MHz) δ 10.25 (s, 1H, -CONH-), 9.77 (s, 1H, -CONH-), 8.73 (br, 1H, -CONH-), 8.38 (br, 2H, -CONH-), 8.20 (br, 1H, -CONH-), 8.03 (t, J = 6.0 Hz, 1H, -CONH-), 7.95 (dd, J = 14.0Hz, J = 7.0 Hz, 1H), 7.88 (m, 1H), 7.82 (br s, 1H), 7.48 (s, 1H), 7.39 (dd, J = 14.0 Hz, J = 7.0 Hz, 1H), 7.26 (d, J = 2.0 Hz, 1H), 6.92 (s, 1H), 6.90 (d, J = 2.0 Hz, 1H), 6.85 (br, 1H, -CONH-), 4.63 (dd, J = 14.0 Hz, J = 6.0 Hz, 1H), 4.52 (d, J = 18.0 Hz, 1H), 4.49 (d, J = 18.0 Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H), 3.40 - 3.00 (m, 14H), 2.21 (t, J = 7.5 Hz, 2H), 1.93 (t, J = 8.0 Hz, 2H), 1.58 (sex, J = 7.5 Hz, 2H), 1.42 (s, 4.5H,*t*-Bu), 1.35 (s, 9H), 1.24 (s, 4.5H,*t*-Bu), 1.03 (t, J = 8.0 Hz, 2H), 0.90 (t, J = 7.5 Hz, 3H); FABHRms m/z: calcd for $C_{49}H_{69}N_{15}O_{11}H$ (M^++H): 1044.5379, found: 1044.5349. For (1*R*, 2*R*)-**27a** (86%): R_f (CH_2Cl_2:MeOH = 8:2) 0.37; $[\alpha]^{20}_D$ -11° (c 0.99, $CHCl_3$); ir (film) ν_{max} 3303 (br), 2974 (w), 2934 (w), 1657 (s), 1529 (s), 1449 (m), 1406 (m), 1366 (w), 1246 (w), 1165 (w), 754 (w) cm^{-1}; ^{1}H-nmr (DMSO-d_6, 500 MHz) δ 10.25 (s, 1H, -CONH-), 9.80 (s, 1H, -CONH-), 8.74 (br, 1H, -CONH-), 8.40 (br, 2H, -CONH-), 8.21 (br s, 1H, -CONH-), 8.02 (br, 1H, -CONH-), 7.95 (m, 1H), 7.88 (m, 1H), 7.80 (br s, 1H), 7.49 (s, 1H), 7.38 (m, 1H), 7.26 (d, J = 2.0 Hz, 1H), 6.90 (br s, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.86 (br, 1H, -CONH-), 4.62 (dd, J = 11.0 Hz, J = 6.0 Hz, 1H), 4.50 (m, 2H), 3.91 (s, 3H), 3.81 (s, 3H), 3.40 - 3.00 (m, 14H), 2.20 (t, J = 7.5 Hz, 2H), 1.91 (t, J = 6.5 Hz, 2H), 1.57 (sex, J = 7.5 Hz, 2H), 1.42 (s, 4.5H, *t*-Bu), 1.35 (s, 9H), 1.24 (s, 4.5H, *t*-Bu), 1.10 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H); FABHRms m/z calcd for $C_{49}H_{69}N_{15}O_{11}H$ (M^++H): 1044.5379, found: 1044.5375.

(*S*)-bis(Boc)-AMPHIS-CPA-ImIm (**27b**): The reaction of (1*S*, 2*S*)-**24b** (40 mg, 0.0684 mmol) with (**26**) (51 mg, 0.0889 mmol) in chloroform (2 ml) provided (1*S*, 2*S*)-**27b** (50 mg, 70%): R_f (CH_2Cl_2:MeOH = 8:2)

0.47; $[\alpha]^{20}_D$ +3.4° (c 0.97, $CHCl_3$); ir (film) ν_{max} 3305 (br), 2974 (w), 2935 (w), 1667 (s), 1532 (s),1478 (m), 1367 (m), 1246 (m), 1168 (m), 754 (m) cm^{-1}; ^{1}H-nmr (DMSO-d_6, 300 MHz) δ 10.30 (s, 1H, -CONH-), 9.30 (s, 1H, -CONH-), 8.75 (br, 1H, -CONH-), 8.38 (br, 2H, -CONH-), 8.30 (t, J = 5.5 Hz, 1H, -CONH-), 8.19 (br, 1H, -CONH-), 7.96 (m, 1H), 7.71 (br s, 1H), 7.51 (s, 2), 7.39 (m, 1H), 6.87 (s, 1H), 6.84 (br, 1H, -CONH-), 4.62 (dd, J = 12.0 Hz, J = 6.5 Hz, 1H), 4.50 (m, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 3.40 - 3.25 (m, 6H), 3.25 - 3.07 (m, 6H), 3.03 (m, 2H), 2.28 (t, J = 7.5 Hz, 2H), 1.93 (t, J = 7.0 Hz, 2H), 1.59 (sex, J = 7.5 Hz, 2H), 1.42 (s, 4.5H, *t*-Bu), 1.35 (s, 9H), 1.23 (s, 4.5H, *t*-Bu), 1.03 (m, 2H), 0.89 (t, J = 7.5 Hz, 3H); FABHRms m/z calcd for $C_{48}H_{68}N_{16}O_{11}H$ (M^++H): 1045.5332, found: 1045.5326; For (1*R*, 2*R*)-**27b** (57%): R_f (CH_2Cl_2:MeOH = 8:2) 0.47; $[\alpha]^{20}_D$ +4.0° (*c* 1.10, $CHCl_3$); *ir (film)* ν_{max} 3305 (br), 2974 (w), 1669 (s), 1533 (s), 1477 (m), 1452 (m), 1367 (m), 1246 (w), 1168 (w), 754 (m) cm^{-1}; ^{1}H-nmr (DMSO-d_6, 300 MHz) δ 10.30 (s, 1H, -CONH-), 9.30 (s, 1H, -CONH-), 8.74 (br, 1H, -CONH-), 8.40 (br, 1H, -CONH-), 8.37 (t, J = 5.0 Hz, 1H, -CONH-), 8.30 (t, J = 5.0 Hz, 1H, -CONH-), 8.19 (br s, 1H, -CONH-), 7.96 (m, 1H), 7.89 (m, 1H), 7.71 (br s, 1H), 7.51 (s, 2H), 7.38 (m, 1H), 6.87 (s, 1H), 6.84 (br, 1H, -CONH-), 4.61 (dd, J = 12.0 Hz, J = 6.5 Hz, 1H), 4.51 (m, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 3.41 - 2.99 (m, 14H), 2.28 (t, J = 7.5 Hz, 2H), 1.93 (t, J = 7.0 Hz, 2H), 1.59 (sex, J = 7.5 Hz, 2H), 1.42 (s, 4.5H, *t*-Bu), 1.35 (s, 9H), 1.24 (s, 4.5H, *t*-Bu), 1.03 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H); FABHRms m/z found: 1045.5353.

(*S*)-bis(Boc)-AMPHIS-CPA-PyImPy (**27c**): Reaction of (1*S*, 2*S*)-**24c** (35 mg, 0.0496 mmol) with **26** (43 mg, 0.0744 mmol) in THF (2 ml) afforded (1S, 2S)-**27c** (48 mg, 83%): R_f (CH_2Cl_2:MeOH = 8:2) 0.37; $[\alpha]^{20}_D$ +16° (*c* 0.92, $CHCl_3$); *ir (film)* ν_{max} 3296 (br), 3006 (w), 2974 (w), 2935 (w), 1657 (s), 1531 (s),1451 (m), 1406 (m), 1366 (m), 1247 (m), 1167 (m), 755 (m) cm^{-1}; ^{1}H-nmr (DMSO-d_6, 500 MHz) δ 10.23 (s, 1H, -CONH-), 9.96 (s, 1H, -CONH-), 9.78 (s, 1H, -CONH-), 8.76 (br, 1H, -CONH-), 8.38 (br, 2H, -CONH-), 8.19 (br s, 1H, -CONH-), 8.06 (br, 1H, -CONH-), 7.96 (m, 1H), 7.89 (m, 1H), 7.76 (br s, 1H), 7.53 (s, 1H), 7.39 (m, 1H), 7.27 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.89 (s, 1H), 6.84 (br, -CONH-, 1H), 4.63 (dd, J = 13.0 Hz, J = 6.5 Hz, 1H), 4.50 (m, 2H), 3.97 (s, 3H), 3.83 (s, 6H), 3.81 (s, 3H), 3.40 - 3.00 (m, 14H), 2.21 (t, J = 7.5 Hz, 2H), 1.94 (t, J = 7.0 Hz, 2H), 1.58 (sex, J = 7.5 Hz, 2H), 1.42 (s, 4.5H), 1.35 (s, 9H), 1.23 (s, 4.5H, *t*-Bu), 1.04 (m, 2H), 0.89 (t, J = 7.5 Hz, 3H); FABHRms m/z calcd for $C_{55}H_{75}N_{17}O_{12}H$ (M^++H): 1166.5859, found: 1166.5832. For (1*R*, 2*R*)-**27c** (75%): R_f (CH_2Cl_2:MeOH = 8:2) 0.37; $[\alpha]^{20}_D$ +8.6° (c 0.96, $CHCl_3$); ir (film) ν_{max} 3302 (br), 2974 (w), 2934 (w), 1655 (s), 1534 (s), 1464 (m), 1406 (m), 1366 (m), 1247 (m), 1166 (w), 755 (m) cm^{-1}; ^{1}H-nmr (DMSO-d_6, 500 MHz) δ 10.22 (s, 1H, -CONH-), 9.96 (s, 1H, -CONH-), 9.77 (s, 1H, -CONH-), 8.74 (br, 1H, -CONH-), 8.38 (br, 2H, -CONH-), 8.21 (br s, 1H, -CONH-), 8.07 (br, 1H, -CONH-), 7.97 (dd, J = 13.0 Hz, J = 6.0 Hz, 1H), 7.89 (m, 1H), 7.82 (br s, 1H), 7.53 (s, 1H), 7.39 (dd, J = 13.0 Hz, J = 8.0 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.90 (s, 1H), 6.84 (br, 1H, -CONH-), 4.63 (q, J = 7.0 Hz, 1H), 4.50 (m, 2H), 3.97 (s, 3H), 3.83 (s, 6H), 3.81 (s, 3H), 3.42 - 2.98 (m, 14H), 2.21 (t, J = 7.5 Hz, 2H), 1.93 (dd, J = 7.0 Hz, J = 4.0 Hz, 2H), 1.58 (sex, J = 7.5 Hz, 2H), 1.42 (s, 4.5H, *t*-Bu), 1.35 (s, 9H), 1.23 (s, 4.5H, *t*-Bu), 1.04 (m, 2H), 0.89 (t, J = 7.5 Hz, 3H); FABHRms m/z found: 1166.5858.

(*S*)-bis(Boc)-AMPHIS-CPA-ImImIm (**27d**): Compound (1*R*, 2*R*)-**24d** (40 mg, 0.0565 mmol) reacted with **26** (49 mg, 0.0848 mmol) in chloroform (2 ml) provided (1*R*,2*R*)-**27d** (57 mg, 86%): R_f (CH_2Cl_2:MeOH = 8:2) 0.51; $[\alpha]^{20}_D$ +130° (c 1.02, $CHCl_3$); ir (film) ν_{max} 3300 (br), 2974 (w), 2935 (w), 1672 (s), 1536 (s), 1478

(m), 1434 (w), 1367 (m), 1169 (w), 753 (m) cm^{-1}; ^{1}H-nmr (DMSO-d_6, 500 MHz) δ 10.34 (s, 1H, -CONH-), 9.63 (s, 1H, -CONH-), 9.60 (s, 1H, -CONH-), 8.74 (br, 1H, -CONH-), 8.36 (br, 2H, -CONH-), 8.31 (t, J = 6.0 Hz, 1H, -CONH-), 8.21 (br s, 1H, -CONH-), 7.96 (m, 1H), 7.89 (m, 1H), 7.65 (br s, 1H), 7.62 (s, 1H), 7.53 (s, 1H), 7.52 (s, 1H), 7.39 (dd, J = 12.0 Hz, J = 6.0 Hz, 1H), 6.94 (s, 1H), 6.84 (m, 1H, -CONH-), 4.64 (dd, J = 12.0 Hz, J = 6.0 Hz, 1H), 4.50 (m, 2H) 4.01 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H), 3.40 - 2.98 (m, 14H), 2.29 (t, J = 7.5 Hz, 2H), 1.93 (t, J = 7.0 Hz, 2H), 1.58 (sex, J = 7.5 Hz, 2H), 1.42 (s, 4.5H, *t*-Bu), 1.35 (s, 9H), 1.23 (s, 4.5H, *t*-Bu), 1.03 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H); FABHRms m/z calcd for $C_{53}H_{73}N_{19}O_{12}H$ (M^++H): 1168.5764, found: 1167.5745; For (1*S*, 2*S*)-**27d** (88%): R_f(CH_2Cl_2:MeOH = 8:2) 0.51; $[\alpha]^{20}_D$ -13° (c 0.62, $CHCl_3$); ir (film) ν_{max} 3301 (br), 2973 (w), 2934 (w), 1667 (s), 1532 (s), 1477 (m), 1367 (m), 1246 (w), 1169 (w), 753 (w) cm^{-1}; ^{1}H-nmr (DMSO-d_6, 500 MHz) δ 10.34 (s, 1H, -CONH-), 9.62 (s, 1H, -CONH-), 9.60 (s, 1H, -CONH-), 8.74 (br, 1H, -CONH-), 8.38 (br, 2H, -CONH-), 8.30 (t, J = 6.0 Hz, 1H, -CONH-), 8.18 (br s, 1H, -CONH-), 7.96 (m, 1H), 7.88 (m, 1H), 7.70 (br s, 1H), 7.65 (s, 1H), 7.53 (s, 1H), 7.50 (s, 1H), 7.38 (dd, J = 12.0 Hz, J = 6.0 Hz, 1H), 6.86 (s, 1H), 6.83 (m, 1H, -CONH-), 4.62 (dd, J = 12.0 Hz, J = 6.0 Hz, 1H), 4.50 (m, 2H) 4.01 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H), 3.40 - 2.98 (m, 14H), 2.29 (t, J = 7.5 Hz, 2H), 1.93 (t, J = 7.0 Hz, 2H), 1.59 (sex, J = 7.5 Hz, 2H), 1.42 (s, 4.5H, *t*-Bu), 1.35 (s, 9H), 1.23 (s, 4.5H, *t*-Bu), 1.03 (m, 2H), 0.89 (t, J = 7.5 Hz, 3H); FABHRms m/z found: 1167.5731.

General procedure for the synthesis of (**1**):

Compound **27** in trifluoroacetic acid was stirred at 0°C for 45 min and the solution was evaporated *in vacuo* to remove the solvent. The residue was dissolved in water, basified with aqueous ammonia solution to pH 9 and loaded on a column of Amberlite XAD-2 resin. This was initially washed with distilled water until the fraction collected became neutral and subsequently with methanol to elute the product. Concentration of the methanolic fraction and drying *in vacuo* provided the final product.

(*S*)-AMPHIS-CPA-ImPy (**1a**): Compound (1*S*, 2*S*)-**27a** (55 mg, 0.0527 mmol), deprotected in TFA (1 ml), resulted in (1*S*, 2*S*)-**1a** (33 mg, 74%): R_f (AcOH:*n*-BuOH:H_2O = 1:1:1) 0.39; $[\alpha]^{20}_D$ -25° (c 0.55, MeOH); ^{1}H-nmr (DMSO-d_6, 500 MHz) δ 9.78 (s, 1H, -CONH-), 8.94 (br m, 1H, -CONH-), 8.42 (br s, 1H, -CONH-), 8.39 (t, J = 5.0 Hz, 1H, -CONH-), 8.16 (br, 1H, -CONH-), 8.04 (t, J = 5.0 Hz, 1H, -CONH-), 7.93 (t, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.48 (s, 1H), 7.27 (d, J = 2.0 Hz, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.82 (s, 1H), 4.57 (m, 1H), 3.92 (s, 3H), 3.86 (s, 2H), 3.81 (s, 3H), 3.50 - 3.24 (m, 4H), 3.20 (m, 2H), 3.10 (m, 2H), 3.02 (m, 2H), 2.65 (t, J = 6.0 Hz, 2H), 2.57 (t, J = 6.0 Hz, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.92 (d, J = 5.0 Hz, 1H), 1.91 (d, J = 5.0 Hz, 1H), 1.57 (sex, J = 7.5 Hz, 2H), 1.02 (d, J = 5.0 Hz, 1H), 1.01 (d, J = 5.0 Hz, 1H), 0.88 (t, J = 7.5 Hz, 3H); FABHRms m/z calcd for $C_{39}H_{53}N_{15}O_7H$ (M^++H): 844.4331, found: 844.4319; For (1*R*, 2*R*)-**1a** (78%): R_f (AcOEt:*n*-BuOH:H_2O = 1:1:1) 0.39; $[\alpha]^{20}_D$ +44° (c 0.71, MeOH); ^{1}H-nmr (DMSO-d_6, 300 MHz) δ 10.25 (s, 1H, -CONH-), 9.77 (s, 1H, -CONH-), 8.93 (br, 1H, -CONH-), 8.40 (br m, 2H, -CONH-), 8.16 (br m, 1H, -CONH-), 8.03 (br m, 1H, -CONH-), 7.92 (t, J = 7.5 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.54 (s, 1H), 7.49 (s, 1H), 7.27 (d, J = 2.0 Hz, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.82 (s, 1H), 4.58 (m, 1H), 3.91 (s, 3H), 3.85 (s, 2H), 3.81 (s, 3H), 3.30 - 2.95 (m, 10H), 2.65 (t, J = 6.0 Hz, 2H), 2.56 (t, J = 6.0 Hz, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.93 (d, J = 7.5 Hz, 1H), 1.91 (d, J = 7.5 Hz, 1H), 1.57 (sex, J = 7.5 Hz, 2H), 1.02 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H); FABHRms m/z found: 844.4317.

(*S*)-AMPHIS-CPA-ImIm (**1b**): The reaction of (1*R*, 2*R*)-**27b** (35 mg, 0.0335 mmol) in TFA (1 ml) provided (1*R*, 2*R*)-**1b** (18 mg, 64%): R_f (AcOH:*n*-BuOH:H_2O = 1:1:1) 0.40; $[\alpha]^{20}_D$ -20° (c 0.31, MeOH); ^{1}H-nmr (DMSO-d_6, 500 MHz) δ 10.30 (s, 1H, -CONH-), 8.93 (br, 1H, -CONH-), 8.40 (br, 2H, -CONH-), 8.33 (br, 1H, -CONH-), 8.18 (br, 1H, -CONH-), 7.92 (t, J = 7.5 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.53 (s, 1H), 7.51 (s, 2H), 6.80 (s, 1H), 4.56 (m, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 3.87 (s, 2H), 3.40 - 2.98 (m, 10H), 2.64 (t, J = 5.5 Hz, 2H), 2.55 (t, J = 5.5 Hz, 2H), 2.28 (t, J = 7.5 Hz, 2H), 1.92 (t, J = 7.0 Hz, 2H), 1.56 (sex, J = 7.5 Hz, 2H), 1.01 (t, J = 7.0 Hz, 2H), 0.87 (t, J = 7.5 Hz, 3H); FABHRms m/z calcd for $C_{38}H_{52}N_{16}O_7H$ (M^++H): 845.4283, found: 845.4274. For (1*S*, 2*S*)-**1b** (60%): R_f (AcOH:*n*-BuOH:H_2O = 1:1:1) 0.40; $[\alpha]^{20}_D$ +36° (c 0.22, MeOH); ^{1}H-nmr (DMSO-d_6, 300 MHz) δ 10.30 (s, 1H, -CONH-), 8.95 (br, 1H, -CONH-), 8.40 (br, 2H, -CONH-), 8.31 (br, 1H, -CONH-), 8.16 (br, 1H, -CONH-), 7.93 (t, J = 7.5 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.54 (s, 1H), 7.51 (s, 2H), 6.80 (s, 1H), 4.55 (m, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.86 (s, 2H), 3.30 - 3.97 (m, 10H), 2.69 (t, J = 5.5 Hz, 2H), 2.59 (t, J = 5.5 Hz, 2H), 2.28 (t, J = 7.5 Hz, 2H), 1.92 (t, J = 7.0 Hz, 2H), 1.56 (sex, J = 7.5 Hz, 2H), 1.02 (t, J = 7.0 Hz, 2H), 0.88 (t, J = 7.5 Hz, 3H); FABHRms m/z found: 845.4267.

(*S*)-AMPHIS-CPA-PyImPy (**1c**): Deprodection of (1*S*, 2*S*)-**27c** (50 mg, 0.0429 mmol) in TFA (1 ml) provided (1*S*, 2*S*)-**1c** (25 mg, 60%): R_f (AcOEt:*n*-BuOH:H_2O = 1:1:1) 0.28; $[\alpha]^{20}_D$ +34° (c 0.76, MeOH); ^{1}H-nmr (DMSO-d_6, 500 MHz) δ 10.24 (br s, 1H, -CONH-), 9.94 (br s, 1H, -CONH-), 9.78 (s, 1H, -CONH-), 8.94 (br, 1H, -CONH-), 8.40 (br, 2H, -CONH-), 8.16 (br, 1H, -CONH-), 8.07 (br, 1H, -CONH-), 7.93 (t, J = 7.0 Hz, 1H), 7.83 (d, J = 7.0 Hz, 1H), 7.62 (d, J = 7.0 Hz, 1H), 7.55 (s, 1H), 7.53 (s, 1H), 7.27 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 6.82 (s, 1H), 4.60 (m, 1H), 3.97 (s, 3H), 3.86 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 3.50 - 3.10 (m, 6H), 3.08 (m, 2H), 3.04 (m, 2H), 2.70 (t, J = 6.0 Hz, 2H), 2.60 (t, J = 6.0 Hz, 2H), 2.21 (t, J = 7.5 Hz, 2H), 1.93 (dd, J = 8.0 Hz, J = 4.0 Hz, 2H), 1.58 (sex, J = 7.5 Hz, 1H), 1.03 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H); FABHRms m/z calcd for $C_{45}H_{59}N_{17}O_8H$ (M^++H): 966.4811, found: 966.4787; For (1*R*, 2*R*)-**1c** (76%): R_f (AcOEt:*n*-BuOH:H_2O = 1:1:1): 0.28; $[\alpha]^{20}_D$ -18° (c 0.26, MeOH); ^{1}H-nmr (DMSO-d_6, 300 MHz) δ 10.24 (br s, -CONH-, 1H), 9.97 (br s, -CONH-, 1H), 9.80 (s, -CONH-, 1H), 8.93 (br, -CONH-, 1H), 8.37 (br, 2H, -CONH-), 8.16 (br, 1H, -CONH-), 8.08 (br m, 1H, -CONH-), 7.94 (t, J = 7.0 Hz, 1H), 7.86 (d, J = 7.0 Hz, 1H), 7.63 (d, J = 7.0 Hz, 1H), 7.55 (s, 1H), 7.53 (s, 1H), 7.27 (d, J = 2.0 Hz, 1H), 7.24 (d, J = 2.0 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 6.82 (s, 1H), 4.55 (m, 1H), 3.96 (s, 3H), 3.87 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.40 - 2.96 (m, 10H), 2.71 (t, J = 5.0 Hz, 2H), 2.61 (t, J = 5.0 Hz, 2H), 2.21 (t, J = 7.5 Hz, 2H), 1.93 (dd, J = 8.0 Hz, J = 4.0 Hz, 2H), 1.58 (sex, J = 7.5 Hz, 1H), 1.03 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H); FABHRms m/z found: 966.4801.

(*S*)-AMPHIS-CPA-ImImIm (**1d**): The reaction of (1*S*, 2*S*)-**27d** (46 mg, 0.0395 mmol) in TFA (1 ml) provided (1*S*, 2*S*)-**1d** (22 mg, 58%): R_f (AcOEt:*n*-BuOH:H_2O = 1:1:1) 0.18; $[\alpha]^{20}_D$ +36° (c 0.22, $CHCl_3$:MeOH = 7:3); ^{1}H-nmr (DMSO-d_6, 300 MHz) δ 10.35 (s, 1H, -CONH-), 8.95 (br, 1H, -CONH-), 8.43 (br, 1H, -CONH-), 8.33 (br, 1H, -CONH-), 8.17 (br, 1H, -CONH-), 7.93 (t, J = 7.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.65 (s, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.55 (s, 1H), 7.54 (s, 1H), 7.53 (s, 1H), 6.82 (s, 1H), 4.61 (m, 1H), 4.02 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.88 (s, 2H), 3.40 - 2.96 (m, 10H), 2.71 (t, J = 6.0 Hz, 2H), 2.60 (t, J = 6.0 Hz, 1H), 2.29 (t, J = 7.5 Hz, 2H), 1.92 (t, J = 7.0 Hz, 2H), 1.58 (sex, J = 7.5 Hz, 2H), 1.03 (m, 2H), 0.89 (t, J = 7.5 Hz, 3H); FABHRms m/z calcd for $C_{43}H_{57}N_{19}O_8H$ (M^++H):

968.4716, found: 968.4736; For (1*R*, 2*R*)-**1d** (60%): R_f (AcOEt:*n*-BuOH:H_2O = 1:1:1) 0.18; $[\alpha]^{20}_D$ -14° (c 0.27, $CHCl_3$:MeOH = 7:3); ^{1}H-nmr (DMSO-d_6, 300 MHz) δ 10.38 (s, 1H, -CONH-), 8.95 (br, 1H, -CONH-), 8.40 (br, 1H, -CONH-), 8.33 (br, 1H, -CONH-), 8.18 (br m, 1H, -CONH-), 7.94 (t, J = 7.0 Hz, 1H), 7.86 (d, J = 7.0 Hz, 1H), 7.66 (s, 1H), 7.64 (d, J = 7.0 Hz, 1H), 7.55 (s, 1H), 7.53 (s, 1H), 7.52 (s, 1H), 6.83 (s, 1H), 4.58 (m, 1H), 4.00 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H), 3.88 (s, 2H), 3.40 - 3.00 (m, 10H), 2.76 (t, J = 6.0 Hz, 2H), 2.64 (t, J = 6.0 Hz, 1H), 2.29 (t, J = 7.5 Hz, 2H), 1.93 (t, J = 6.0 Hz, 2H), 1.58 (sex, J = 7.5 Hz, 2H), 1.02 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H); FABHRms m/z found: 968.4687.

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REFERENCES

1. Review: a) J. W. Lown, *Chemtracts*, 1993, **6**, 205. b) J. W. Lown, *Antiviral Research*, 1992, **17**, 179. c) J. W. Lown, *Anti-Cancer Drug Design*, 1988, **3**, 25. d) J. W. Lown, In Molecular Basis of Specificity in Nucleic Acid-Drug Interactions, B. Pullman, J Jortner Eds., Klumer Acad. Publishers: Dordrecht, Netherlands, 1990, p103.

2. a) T. J. Dwyer, B. H. Geierstanger, Y. bathini, J. W. Lown, and D. E. Wemmer, *J. Am. Chem. Soc.*, 1992, **114**, 5911. b) K. Kissinger, K. Krowicki, J. C. Dabrowiak, and J. W. Lown, *Biochemistry*, 1987, **26**, 5590.

3. Recent reports: a) T. Matsumoto, K. Toyooka, E. Nishiwaki, and M. Shibuya, *Heterocycles*, 1990, **31**, 1629. b) T. Matsumoto, Y. Sakai, K. Toyooka, and M. Shibuya, *Heterocycles*, 1992, **33**, 135. c) T. Matsumoto, Y. Utsumi, Y. Sakai, K. Toyooka, and M. Shibuya, *Heterocycles*, 1992, **34**, 1697. d) R. D'Alessio, C. Geroni, G. Biasoli, E. Pesenti, M. Grandi, and M. Mongeli, *BioMed. Chem. Lett.*, 1994, **4**, 1467. e) M. Lee, A. L. Rhodes, M. D. Wyatte, M. D'Incalei, S. Forrow, and A. J. Hartley, *J. Med. Chem.* 1993, **36**, 863. f) T. M. Bregant, J. Groppe, and R. D. Little, *J. Am. Chem. Soc.*, 1994, **116**, 3635. g) P. Herfeld, P. Helissey, and S. Giorgi-Renault, *Bioconjugate Chem.*, 1994, **5**, 67. h) P. B. Dervan, *Science*, 1986, **232**, 464. i) M. Shinomiya, and R. Kuroda, *Tetrahedron Lett.*, 1992, **33**, 2697. j) S. Th. Sigurdsson, S. M. Rink, and P. B. Hopkins, *J. Am. Chem. Soc.*, 1993, **115**, 12633. k) S. Th. Sigurdsson, and P. B. Hopkins, *Tetrahedron*, 1994, **50**, 12065.

4. a) M. F. Semmelhack, and J. J. Gallagher, *J. Org. Chem.*, 1994, **59**, 4357. b) G. Xie, A. R. Morgan, and J. W. Lown, *BioMed. Chem. Lett.*, 1993, **3**, 1565. c) M. Tokuda, K. Fujiwara, T. Gomibuchi, and M. Hirama, *Tetrahedron Lett.*, 1993, **34**, 669.

5. G. Anneheim-Herbelin, M. Perree-Fauvet, A. Gaudemer, P. Helissey, S. Giorgi-Renault, and N. Gresh, *Tetrahedron Lett.*, 1993, **34**, 7263.

6. a) M. Otsuka, T. Masuda, A. Haupt, M. Ohno, T. Shiraki, Y. Sugiura, and K. Maeda, *J. Am. Chem. Soc.*, 1990, **112**, 838. b) T. Owa, A. Haupt, M. Otsuka, S. Kobayashi, N. Tomioka, A. Itai, and M. Ohno, *Tetrahedron*, 1992, **48**, 1193.

7. a) S. K. Carter, T. Ichikawa, G. Mathe, H. Umezawa, Fundamental and clinical studies of bleomycin; University of Tokyo Press, Tokyo, 1976. b) S. K. Carter, S. T. Crooke, and H. Umezawa, Bleomycin: Current status and new developments. Academic Press, New York, 1978 and c) S. M. Hecht, Bleomycin: Chemical, biochemical and biological aspects. Springer-Verlag, New York, 1979. d) B. I. Sikic, M. Rozenweig, S. K. Carter, Bleomycin chemotherapy. Academic Press: Orlando, FL, 1985.

8. a) S. M. Hecht, *Acc. Chem. Res.*, 1986, **19**, 383. b) J. Stubbe and J. W. Kozarich, *Chem. Rev.*, 1987, **87**, 1107. c) L. Huang, J. C. Quada, Jr., and J. W. Lown, *Current Med. Chem.*, 1995, **2**, in press.

9. V. F. Zarytova, D. S. Sergeyev, and T. S. Godovikova, *Bioconjugate Chem.*, 1993, **4**, 189.

10. M. G. Oakley, K. D. Turnbull, and P. B. Dervan, *Bioconjugate Chem.*, 1994, **5**, 242.

11. a) L. Huang, A. R. Morgan, and J. W. Lown, *BioMed. Chem. Lett.*, 1993, **3**, 1751. b) L. Huang, J. C. Quada, Jr., and J. W. Lown, *Tetrahedron Lett.*, 1994, **35**, 5323. c) L. Huang, J. C. Quada, Jr., and J. W. Lown, *Bioconjugate Chem.*, 1995, **6**, 21. d) L. Huang, J. C. Quada, Jr., and J. W. Lown, *BioMed. Chem.*, in press. e) L. Huang, J. C. Quada, Jr., and J. W. Lown, *Heterocycl. Commun.*, 1995, **2**, in press.

12. a) J. W. Lown, and K. Krowicki, *J. Org. Chem.*, 1985, **50**, 3774. b) K. Krowicki and J. W. Lown, *J. Org. Chem.*, 1987, **52**, 3493. c) K. Nishiwaki, and S. Tanaka, H. Lee, and M. Shibuya, *Heterocycles*, 1988, **27**, 1945.

13. M. P. Singh, B. Plouvier, G. C. Hill, J. Gueck, R. T. Pon, and J. W. Lown, *J. Am. Chem. Soc.*, 1994, **116**, 7006.

14. a) A. Misumi, K. Iwanaga, K. Furuta, and H. Yamamoto, *J. Am. Chem. Soc.*, 1985, **107**, 3343. b) K. Furuta, K. Iwanaga, and H. Yamatmoto, *Org. Synth.*, 1989, **67**, 76.

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