SYNTHETIC STUDIES TOWARDS THE SYNTHESIS OF WESTERN AND EASTERN CHLOROPEPTIN I, II SUBUNITS

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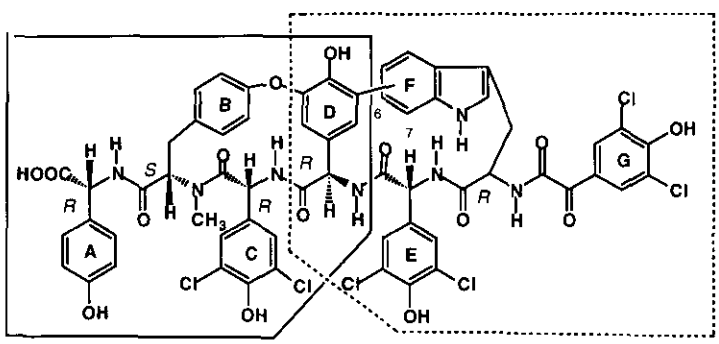
Abstract - The western subunit (16-membered ring) was synthesized by the intramolecular S_NAr reaction while the first 16-membered ring compound was obtained as a model of the eastern subunit *via* an intramolecular Ni^0 mediated coupling reaction.

Chloropeptins I and II are antibiotics produced by Streptomyces sp. WK-3419,[1] whose most important biological activity is related to their ability to inhibit both the cytopathic effect in HIV-1 infected MT 4 cells and the syncytium formation in co-cultured HIV-1 infected MOLT-4 cells. Chloropeptin II, also referred to in the literature as complestatin, was reported to strongly inhibit the hemolysis of complement system sensitized erythrocytes.[2]



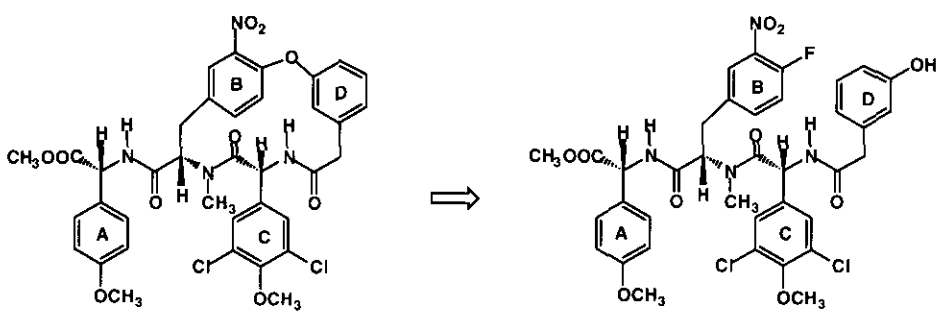
Chloropeptins I, II

The 16-membered cyclotripeptide **BODC** (western subunit) common to chloropeptin I and chloropeptin II is characterized by an *endo* biaryl ether bond connecting tyrosine **B** to the central 4-hydroxyphenylglycine **D**. This amino acid is linked to position 6 or 7 of tryptophane **F** by an *endo* carbon-carbon bond, forming the 17-membered macrocycle of chloropeptin I, or the 16-membered ring of chloropeptin II (eastern subunit). The non-proteinogenic 3, 5-dichloro-4-hydroxyphenylglycine is found in both western and eastern subunits as amino acids **C** and **E**. From acidic degradation[3] and studies combining computer modeling with NMR analysis,[4] relative and absolute configurations[6] have been recently assigned as *(S)*, *(R)*, *(R)* to amino acids **B**, **C** and **D**.

We report here our contribution which includes the synthesis and incorporation of the very racemization prone amino acid **C** in a **BOD** 16-membered polypeptide ring as a model of the western subunit and the first synthesis of a 16-membered ring macropolypeptide **DEF** containing an arylindole key componet, as a simplified model of the eastern subunit of chloropeptin II.

WESTERN SUBUNIT

The very efficient intramolecular S_NAr reaction recently developped in our group and successfully used in the synthesis of monocyclic,[5a-d] bicyclic[5e-g] and tricyclic polypeptides[5h] containing respectively one, two or three *endo* biaryl ether bonds was employed for ring closure of a linear peptide **ABCD** whose terminal aromatic rings carry the functionalities essential for the intramolecular S_NAr reaction leading to the desired **ABODC** cyclised compound.

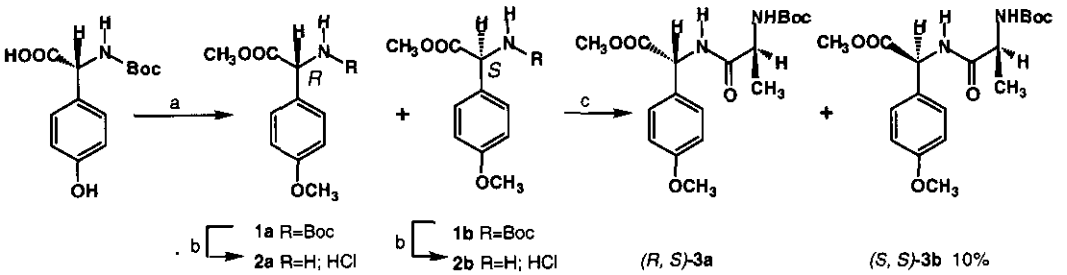


Scheme 1

The synthesis of the precursor **ABCD** involved use of commercially available products : 3-hydroxyphenylacetic acid in place of the central amino acid **D** carrying the nucleophilic chromophore and *(R)*-4-methoxyphenylglycine methyl ester **A** while non proteinogenic amino acids: *(S)*-phenylalanine derivative

B carrying the activated nucleofuge on proper position, and 3,5-dichloro-4-methoxyphenylglycine **C** had to be synthesized.

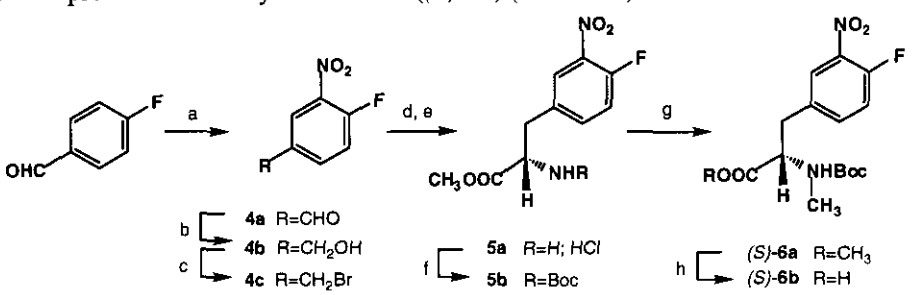
Methylation of *(R)*-*N*-Boc-4-hydroxyphenylglycine by classical procedure to get **1a** did not go to completion, but in acetone and in the presence of tetrabutylammonium iodide,[5a] the expected product was obtained in 90% yield. The extent of epimerization (less than 10%) was deduced from the ratio of the OMe signals in the ^{1}H NMR spectrum of the mixture of peptides (**3a+3b**), obtained by coupling **2a** with *(S)*-*N*-Boc-alanine (Scheme 2).



Reagents and conditions. a: K_2CO_3, $(CH_3)_2SO_4$, tetrabutylammonium iodide, acetone, *90%*; b: *HCl, MeCN, 89%*; c: Et_3N, *(S)-N*-Boc-alanine, HOBT, EDC, CH_2Cl_2, 93%

Scheme 2

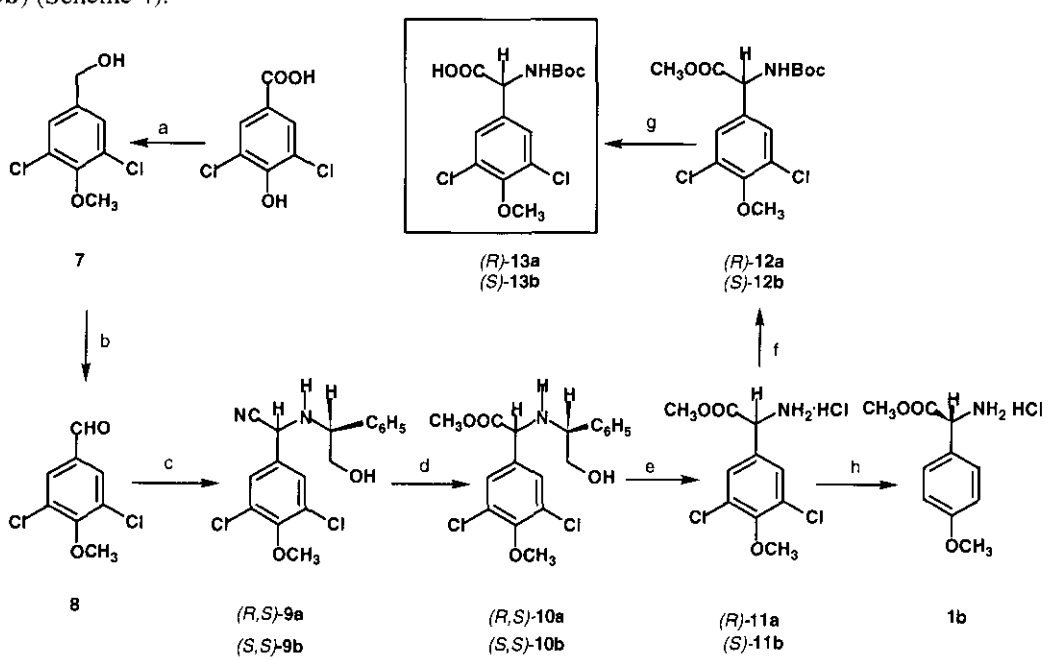
The non-proteinogenic amino acid derivative, *(S)-N*-Boc-*N*-methyl-4-fluoro-3-nitrophenylalanine methyl ester (**6a**) was obtained by methylation of *N*-Boc-4-fluoro-3-nitrophenylalanine methyl ester (**5b**) resulting from alkylation of the *(S)*-Schollköpf bislactim ether with 4-fluoro-3-nitrobenzyl bromide (**4c**)[6]. This electrophilic reagent was prepared in 74% overal yield from 4-fluorobenzaldehyde by nitration to give **4a**, reduction of the formyl function to the alcohol (**4b**) and bromination. *(S)-N*-Boc-4-fluoro-3-nitrophenylalanine methyl ester (**5b**) was efficiently *N*-methylated to give **6a**,[7] the hydrolysis of which provided then the protected *N*-methyl amino acid (*(S)*-**6b**) (Scheme 3).



Reagents and conditions. a: HNO_3, H_2SO_4, 92%; b: $NaBH_4$, CH_3OH, 98%; c: PBr_3, toluene, 82%; d: *(S)*-Schollköpf's reagent, n-C_4H_9Li, CuCN, THF, 20°C, 54%; e: TFA, CH_3CN, H_2O, 65%; f: Boc_2O, $N(C_2H_5)_3$, 54%; g: CH_3I, Ag_2O, DMF, 83%; h: K_2CO_3, CH_3OH, H_2O, 90%.

Scheme 3

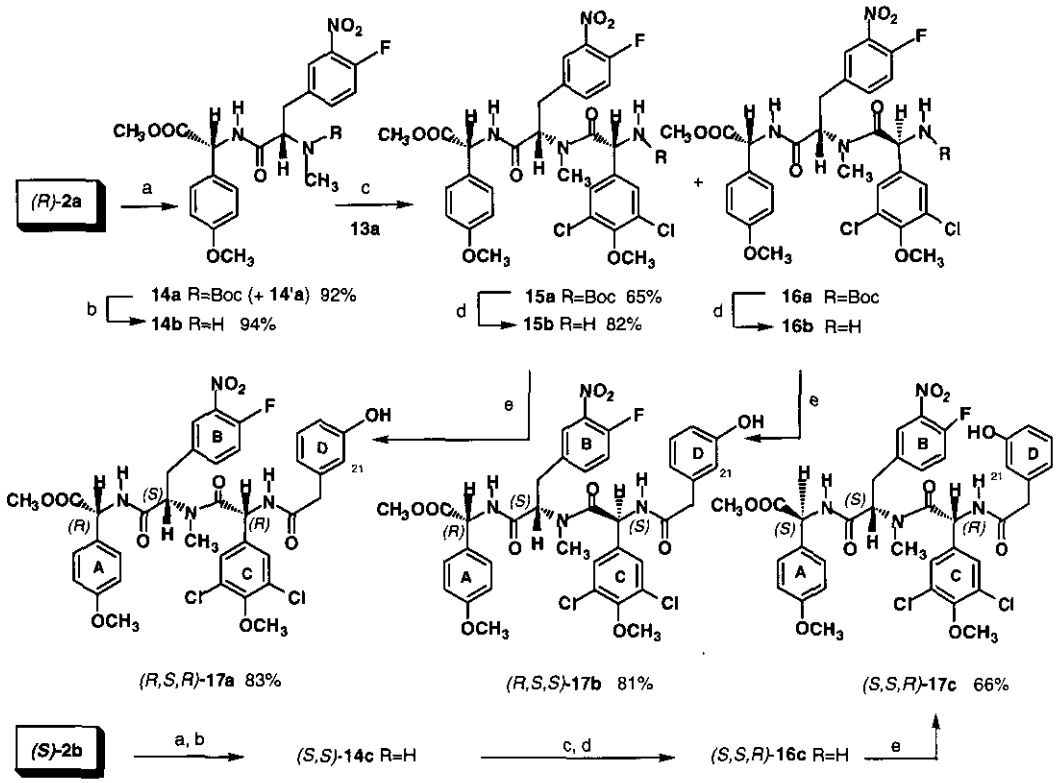
The second non-proteinogenic amino acid, *(R-N*-Boc-3,5-dichloro-4-methoxyphenylglycine methyl ester (*(R)*-**11**) was prepared by standard Strecker methodology.[8] 3-5-Dichloro-4-methoxybenzaldehyde (**8**) obtained by conventional methods from 3-5-dichloro-4-hydroxybenzoic acid was treated with *(R)*-phenylglycinol as chiral agent and subsequently with TMSCN to afford a mixture of two diastereomers (**9a+9b**) (70/30). The low selectivity of this step was partly compensated by the high chemical yield. The major compound (**9a**) was isolated in 64% yield by column chromatography and its absolute configuration was deduced from the ^{1}H NMR spectrum[9] where the benzylic proton appears at higher field than that of the diastereomer (*(S,S)*-**9b**). The conditions used for converting **9a** to **10a** led to a diastereomeric mixture (83/17) of amino esters (**10a+10b**) which was separated by silica gel column chromatography to afford pure **10a** (73%) and **10b** (15%). Oxidative cleavage of the chiral auxiliary afforded the respective amino esters hydrochlorides (*(R)*-**11a**) and (*(S)*-**11b**). The *(R)* configuration of **11a** was confirmed by dehalogenation leading to *(R)*-hydroxyphenylglycine derivative (**1b**) ([α]$_D$=-117°, lit.,[10] [α]$_D$=-100°). *N*-Boc protection of **11a** and **11b** gave pure **12a** and **12b**, whose hydrolysis under controlled basic conditions led to the corresponding *N*H-Boc protected amino acid (*(R)*-**13a**) and (*(S)*-**13b**) (Scheme 4).



Reagents and conditions. a: i) K_2CO_3,$(CH_3)_2SO_4$, DMF; ii) $LiAlH_4$, THF, 88%; b: PCC, CH_2Cl_2, 91%; c: *(S)*-phenylglycinol, TMSCN, $CHCl_3$, 0°C, 90%; d: CH_3OH-HCl, 76%; e: $Pb(OAc)_4$, CH_2Cl_2, CH_3OH, 0°C, 82%; f: Boc_2O, $N(C_2H_5)_2$, THF, 92 %; g: K_2CO_3, CH_3OH, 67%; h: H_2, Pd/C, CH_3OH, 81 %.

Scheme 4

The synthesis of the tripeptide (**15a**) was easily achieved by coupling *(R)*-**2a** containing less than 10% of its epimer (*(S)*-**2b**) with *(S)*-*N*-Boc-4-fluoro-3-nitrophenylalanine (**6b**) to give *(R,S)*-**14a**. A simple TLC separation afforded pure *(R,S)*-**14a** and some amount of the *(S,S)* -diastereomer (**14a'**). Mild deprotection of **14a** provided **14b** in high yield whose coupling with *N*-Boc-*(R)*-3,5-dichloro-4-hydroxyphenylglycine (**13a**) under classical conditions provided an isomeric mixture of tripeptides (*(R,S,R)*-**15a**) and (*(R,S,S)*-**16a**) which was separated by chromatography. The compound (**15a**) was obtained in better yield, without appreciable racemisation by using bromo-tris(pyrrolidino)phosphonium hexafluorophosphate (PyBrop) as a coupling agent.[11] After deprotection, coupling of **15b** with 3-hydroxyphenylacetic acid gave the expected linear precursor (*(R,S,R)*-**17a**); similarly *(R,S,S)*-**17b** was prepared from **16a** for the purpose of comparative macrocyclisation studies (Scheme 5).



Reagents and conditions. a: *(S)*-**6b**, HOBT, EDC, $N(C_2H_5)_3$, CH_2Cl_2; b: TMSCl, NaI, $CHCl_3$; c: **13a**, PyBrOP, CH_2Cl_2, 0°C; d: TMSCl, NaI, $CHCl_3$; e: 3-hydroxyphenylacetic acid, HOBT, EDC, CH_2Cl_2.

Scheme 5

Macrocyclisation studies

The first reaction (entry 1, Table 1) of **17a** under the previously established conditions proceeded slowly. A prolonged reaction time (20 h) was necessary to convert 80% of the starting material, yielding a mixture of six compounds in place of the pair of atropisomers (**18a**) and (**18a'**) normally expected. Comparison of ^{1}H NMR spectrum of the crude mixture with that of the open chain precursor (**17a**) showed several signals between 5.9 and 6.1 ppm, *i.e.* in the range of the upfield shifted H-21 characteristic of 16-membered macropolypeptides containing an *endo* biaryl ether function observed in synthetic compounds[5a-h] and in natural products[3,12] (Table 2). The ratios of the six cyclized compounds remained unchanged after 40 h (entry 2). An interesting observation came from the ^{1}H NMR analysis of the outcome of a reaction carried out with the diastereomeric precursor (*(R,S,S)*-**17b**) which gave the same six products but in different ratios (entry 3). We were thus led to assume that among the four unexpected macrocycles, two at least (a pair of atropisomers of a diastereomeric macrocycle) might originate from racemization of amino acid **C** occuring under the slightly basic reaction conditions applied to the linear peptides (**17a**) and (**17b**).

Table 1. Cyclisation of tetrapeptides (**17a, b, c**)

Entry	Tetrapeptide	Conditions	Conversion %[a]	Cyclized Products[a] **18** %					
				a	**a'**	**b**	**b'**	**c**	**d**
1	**17a**	K_2CO_3, DMF, 20 h	80	18	11	18	11	24	18
2	**17a**	K_2CO_3, DMF, 40 h	90	16	10	19	12	23	20
3	**17b**	K_2CO_3, DMF, 40 h	70	28	12	34	14	6	6
4	**17b**	K_2CO_3, DMF[b]	0						
5	**17b**	Li_2CO_3, THF[b]	0						
6	**17a**	$KHCO_3$, THF[c],40h	70	18	9	23	12	19	19
7	**17b**	$KHCO_3$, THF[c], 2h	100; 60[d]	30	15	37	18	0	0
8	**17c**	$KHCO_3$, THF[c], 40h	100	6	0	6	0	43	45

[a]Ratio obtained from ^{1}H NMR. [b]12-Crown-4. [c]18-Crown-6. [d]Yield of isolated products.

Several reaction parameters were then studied in order to determine the minimal basic conditions compatible with cyclisation. With Li_2CO_3 as a base in DMF (entry 4), or in THF where 12-crown-4 ether was added (entry 5), the linear peptide (*(R,S,S)*-**17b**) did not cyclize. Using $KHCO_3$ in THF where 18-crown-6 was added (entry 6), the linear peptide (*(R,S,R)*-**17a**) was observed to undergo cyclization

giving an almost identical mixture of six products. In contrast, under the same conditions, the intramolecular S_NAr reaction of **17b** took place much faster (entry 7) to give only four products.

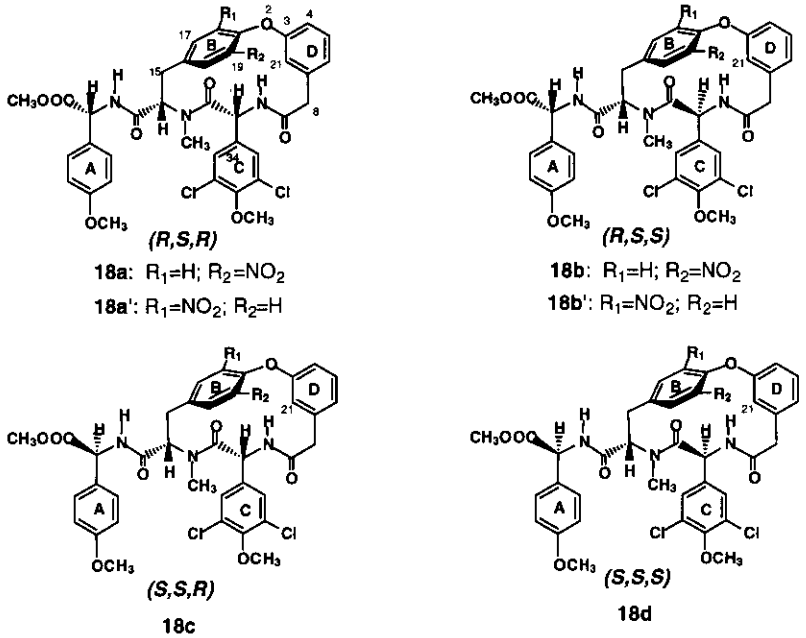


Figure 2

Preparative thin layer chromatography allowed isolation of pure products whose structures where established as pairs of *(R,S,R)* atropisomers (**18a**) and (**18a'**) (natural configuration) and *(R,S,S)* **18b** and **18b'** in almost equal amount. This experiment clearly showed that amino acid **C** had undergone racemization. A separate experiment, in which no racemization of the cyclised product (**18a**) took place under the cyclization conditions clearly indicated that **17a** had racemized prior to cyclization (Figure 2).

Table 2. Characteristic Chemical Shifts in ^{1}H NMR of **18**, and of Chloropeptins I and II

Tetrapeptide			Cyclized Compounds **18**			Chloropeptins		
	N-Me	H-21		*N*-Me	H-21		*N*-Me	H-21
(R,S,R) **17a**	2.98	6.74	**18a**	2.59	6.08	I	2.99	5.70
			18a'	2.65	5.91	II	2.99	5.47
(R,S,R) **17b**	2.93	6.81	**18b**	2.97	6.07			
			18b'	3.00	5.91			
(S,S,R) **17c**	2.74	6.76	**18c**	2.79	5.69			
			18d	3.01	5.69			

With the ^{1}H NMR spectra of pure **18a**, **18a'**, **18b** and **18b'** in hand, we were able to identify four over the six products formed in previous reactions of **17a** (entries 1, 2, 6), and furthermore, to detect unambigously the epimerized *(R,S,S)* precursor (**17b**) in the crude mixture, demonstrating that indeed epimerization of 3,5 dichloro-4-methoxyphenylglycine had occurred prior to cyclisation when the intramolecular S_NAr reaction was particularly slow. Finally, macrocyclisation of the peptide (*(S,S,R)*-**17c**) (entry 8) which was slightly faster than that of **17a** gave two major diastereomeric products in almost equal amounts, namely (*(S,S,R)* -**18c**) and *(S,S,S)* -**18d** (whose atropisomers could not be detected by ^{1}H NMR) along with very minor amounts of *(R,S,R)* -**18a** and *(R,S,S)* -**18b**. It became then possible to establish (^{1}H-NMR) that **18c** and **18d** were the two minor components present in the mixture of six products resulting from the reactions of the linear peptide *(R,S,R)* -**17a**.

EASTERN SUBUNIT

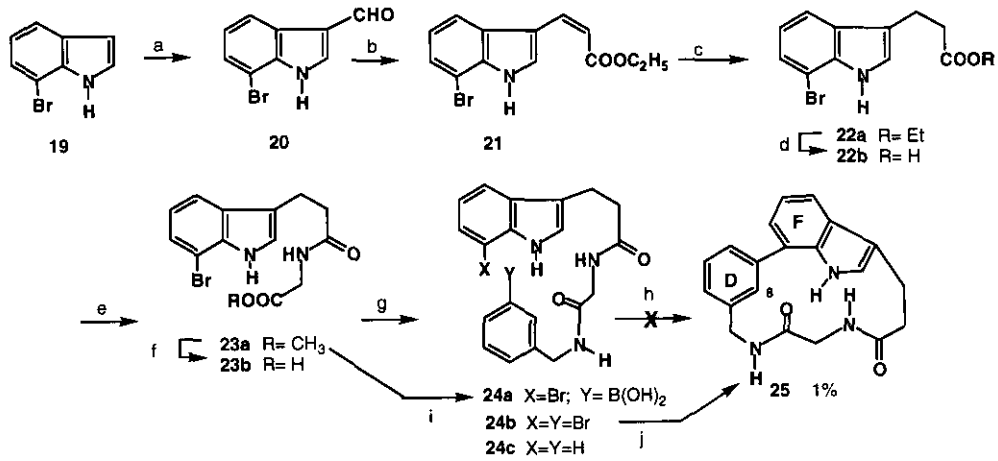
The eastern subunit of chloropeptine I differs from chloropeptine II by the position of the *endo* carbon-carbon linkage between the central hydroxyphenylglycine **D** with the indole component. Indeed, the former (at position C-7) results in a 16-membered ring macropolypeptide, while the latter (at position C-6) gives a 17-membered ring macropolypeptide. In a previous paper,[13] we have reported the synthesis of a simplified 17-membered ring macropolypeptide of kistamycin which is distinct of that of chloropeptin I by amino acid **E** only. Therefore only the synthesis of a simplified 16-membered macropolypeptide **DFE** encountered in chloropeptin II eastern subunit is here reported.

The macrolactamisation approach requires a linear precursor containing the 7-phenylindole subunit which turned to be hardly available due to the very poor yield[13] or the failure[14] reported for arylation of the indole at position C-7, and we focused our efforts on the macrocyclisation approach.

Reactions selected to effect ring closure by carbon-carbon linkage were those already reported in a preliminary study,[14] namely the intramolecular versions of cross-coupling Pd catalysed Suzuki reaction[15] and Ni^0 catalysed reaction according to Semmelhack.[16]

The simplified precursors needed for performing the key intramolecular biaryl cross coupling reaction at position C-7 were easily prepared from 7-bromoindolepropionic acid (**22b**), itself synthesized from 7-bromoindole (**17**).[17] Formylation under Vilsmeier-Hack conditions led to 3-formylindole (**20**)[18] which was treated with ethyl monomalonate[19] to give ethyl indoleacrylate (**21**) whose selective reduction[20] gave the 7-bromo-3-indolepropionic acid ethyl ester (**22a**). The acid (**22b**) resulting from saponification was

then coupled with glycine methyl ester in place of amino acid **E** to give the peptide (**23a**), readily saponified to **23b** (Scheme 6).



Reagents and conditions. a: $POCl_3$, DMF at 0°C; b: $HOOCCH_2COOC_2H_5$, pyridine, piperidine, 50°C, 60%; c: $NaBH_4$, $BiCl_3$, C_2H_5OH, 0°C, 40%; d: NaOH, CH_3OH-H_2O, 98%; e: glycine methyl ester hydrochloride, $N(C_2H_5)_2$, HOBT, EDC, DMF, 58%; f: NaOH, C_2H_5OH-H_2O, 84%; g: 3-aminomethylphenylboronic acid, CH_2Cl_2; h: $Pd(OAc)_2$, $Ba(OH)_2$, C_2H_5OH, DME; i: 3-bromobenzylamine hydrochloride, $N(C_2H_5)_3$, HOBT, EDC, DMF, 38%; j: $Ni(Ph_3P)_2Cl_2$, *Zn*, Ph_3P, DMF, 1%.

Scheme 6

The linear precursor required for the Suzuki reaction was easily obtained by coupling (**23b**) with 3-aminomethylphenylboronic acid[14] to give **24a**. When a 0.01M solution of **24a** in degassed C_2H_5OH/DME was treated with $Pd(OAc)_2$ and $Ba(OH)_2$, the only product which could be isolated and characterized was **24c**.

The linear precursor (**24b**) carrying bromine instead of boronic acid on the benzylamine component needed for carrying out intramolecular Semmelhack type reaction was prepared by coupling the peptide (**23b**) with 3-bromobenzylamine under standard conditions. Treatment of a 0.01M solution of **24b** with Ni^0 (prepared apart according to the procedure described by Kende[21]) at 50° C lead after consumption of the starting material to a mixture of several products which were separated by preparative thin layer chromatography. The major product was once again **24c**, but in the ^1H NMR spectrum of a more polar and minor fraction the H-8 signal of **24b** was shifted from 7.35 to 5.85 ppm, a value close to that of chloropeptin I (5.81).[12] Further purification led finally to pure **25** whose structure was established by physical methods.

The yield was very poor (1%), but no efforts were made to increase it since chloropeptin I is probably an

artefact. Indeed, it has been very recently reported[22] that chloropeptin II (also called complestatin) was quantitatively converted to chloropeptin I under acidic conditions (CF_3COOH), so that, the synthesis of the fully functionalized 17-membered ring eastern part, provides an acces to the 16-membered ring compound. We are therefore now focusing our efforts on chloropeptin II which is more interesting than chloropeptin I from a biological point of view.

CONCLUSION

We have described an access to a 16-membered **ABOD** ring model of the western subunit of chloropeptins I, II *via* an S_NAr cyclisation reaction and the first synthesis of a 16-membered ring macropolypeptide **DFE** containing an *endo* C-C bond, as model of the eastern subunit of chloropeptin I. These results represent an important step towards the total synthesis of chloropeptin I and chloropeptin II.

EXPERIMENTAL SECTION

Melting points were determined with a Richter apparatus. IR spectra were recorded on a Nicolet-205 spectrometer. $[\alpha]_D$ were recorded on a Perkin-Elmer 141 polarimeter. ^1H NMR spectra were recorded on Brucker WP 200 SY (200MHz), AC-250 (200MHz), AC-300 (300MHz) and Brucker WM-400 (400MHz) spectrometers with tetramethylsilane as internal standard (δ ppm), using $CDCl_3$, CD_3OD, CD_3COCD_3 as solvents. All reactions requiring anhydrous conditions or inert atmosphere were conducted under argon. Analytical and preparative TLC were performed on SiO_2 plates.

***(R)-N-tert*-Butoxycarbonyl-4-methoxyphenylglycine methyl ester (1a)[23]:** To a solution of *(R)-N-tert*-Butoxycarbonyl-4-hydroxyphenylglycine (0.50 g, 1.87 mmol) in acetone (25 mL) were added K_2CO_3 (0.77 g, 5.61 mmol), TBAI (50 mg, 0.19 mmol) and $(CH_3)_2SO_4$ (0.39 mL) and the mixture was stirred at reflux. After 6 h, hydrolysis, extraction (AcOEt) and flash chromatography (SiO_2, heptane/AcOEt=9/1) gave **1a** as an oil (0.50 g, 90%): ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 9H, Boc), 3.70 (s, 3H), 3.78(s,3H), 5.25 (d,1H, J =7.3 Hz), 5.54 (d,1H, J =7.3 Hz), 6.86 (d, 2H, J =8.7 Hz), 7.26 (d, 2H, J =8.7 Hz); ^{13}C NMR δ 28.31, 52.59, 55.27, 57.06, 80.50, 114.51, 128.41, 131.35, 155.01, 159.70, 171.95.

***N*-[*(R)*-(4-Methoxyphenylacetic acid methyl ester)-*(2S)*-2-*tert*-butyloxycarbonylamino]-propionamide (3a):** To a solution of **1a** (0.55 g, 1.80 mmol) in CH_3CN (4 mL), was added HCl (0.60 mL) and the mixture was kept at rt for 2 h. Evaporation of volatiles gave the hydrochloride salt (**2b**) (0.38 g, 89%). **2b** (50 mg, 0.22 mmol) dissolved in anhydrous CH_2Cl_2 (5 mL) in the presence of $N(C_2H_5)_3$ (45 mL, 0.32 mmol) was kept for 15 min at rt and concentrated under vacuum. A solution of *(S)*-*N*-Boc-alanine (41 mg, 0.22 mmol), EDC (46 mg, 0.24 mmol) and HOBT (30 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) was then added and stirred at rt for 4 h. Hydrolysis followed by extraction ($AcOC_2H_5$) and flash chromatography (heptane/$AcOC_2H_5$, 1:1) yielded **3a** as an oil (74 mg, 93%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, 3H, J = 7.0 Hz), 1.44 (s, 9H), 3.71 (s, 3H,), 3.87 (s, 3H), 4.18-4.26 (m, 1H), 5.25 (br s, 1H, NH), 5.47 (d, 1H, J = 7.0 Hz), 6.87 (d, 2H, J = 8.6 Hz), 7.22 (br s, 1H, NH), 7.27 (d, 2H, J = 8.6 Hz); ^{13}C NMR δ 17.98, 28.34, 49.91, 52.72, 55.35, 55.91, 80.51, 114.41, 128.02, 128.51, 155.01, 159.80, 171.41, 172.16.

***N*-(*tert*-Butoxycarbonyl)-*(S)*-(4-fluoro-3-nitro)-phenylalanine methyl ester (5b):** To a solution of compound **5a** (261 mg, 1.08 mmol) in anhydrous THF (10 mL) were added Boc_2O (258 mg, 1.18 mmol) and $N(C_2H_5)_3$ (302 mL, 2.15 mmol) and the mixture was stirred at rt for 16 h. Solvent evaporation, extraction ($AcOC_2H_5$) and flash chromatography (SiO_2, heptane/$AcOC_2H_5$, 9:1) gave **5b** (198 mg, 0.58 mmol, 54 %) : mp 89-90° C (CH_2Cl_2/heptane); $[\alpha]_D$ = +39° (c= 0.1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$,) δ 1.42 (s, 9H), 3.05 (dd, 1H, J_1= 6.5, J_2= 13.9 Hz), 3.26 (dd, 1H, J_1= 5.4, J_2= 13.9 Hz), 3.77 (s, 3H), 4.59 (ddd, 1H, J_1 = 6.5, J_2 = 5.4 Hz), 5.13 (d, 1H, J =6.5 Hz), 7.22 (dd, J_1= 8.6, J_2= 10.4 Hz), 7.39-7.47 (m, 1H), 7.84 (dd, 1H, J_1 = 2.0, J_2 = 6.9 Hz); ^{13}C NMR δ 27.97, 37.04, 52.33, 54.07, 79.96, 118.22 (d, J = 21.2 Hz), 126.56 (d, J = 2.4 Hz), 133.73 (d, J = 5.5 Hz), 136.40 (d, J = 7.9 Hz), 136.78(d, J = 6.9 Hz), 154.35 (d, J = 262.3 Hz), 154.88, 171.50; MS (CI, isobutene) *m/z* 287 $[M-57]^+$, 243.

***(S)*-*N*-(*tert*-Butoxycarbonyl)-*N*-methyl-*(S)*-(4-fluoro-3-nitro)phenylalanine methyl ester (6a):** A mixture of **5b** (0.30 g, 0.89 mmol), CH_3I (4.5 mL, 71.3 mmol) and Ag_2O (2.0 g, 8.92 mmol) in DMF (6 mL), was heated (60° C) in a sealed tube for 60 h. Usual work up and preparative TLC (heptane/$AcOC_2H_5$, 9:1) gave **6a** (0.260 g, 83%) as a colorless oil: $[\alpha]_D$ = -16° (c= 0.24, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.74 (s, 3H), 3.08 (dd, 1H, J_1 = 10.6, J_2 = 14.5 Hz), 3.36 (dd, 1H, J_1 = 5.3, J_2 = 14,5 Hz), 3.76 (s, 3H), 4.53 and 4.88 (2 dd, 1H, J_1 = 5.3, J_2 = 10.6 Hz), 7.17-7.22 (m, 1H), 7.40-7.46 (m, 1H), 7.88 (dd, 1H, J_1 = 2.0, J_2 = 7.0 Hz); ^{13}C NMR δ 28.26, 34.05, 34.65, 52.52,

59.43, 80.77, 118.47 (d, J = 20.4 Hz), 126.38, 134.92, 136.23 (d, J = 8.7 Hz), 136.80, 154.47 (d, J = 263.3 Hz), 154.54, 171.04; MS (CI, isobutene) *m/z* 357 $[M+H]^+$, 301, 257; Anal. Calcd for $C_{16}H_{21}N_2O_6F$: C, 53.92; H, 5.94; N, 7.86. Found: C, 54.09; H, 5.84; N, 7.72.

***(S)*-*N*-(*tert*-Butoxycarbonyl)-*N*-methyl-*(S)*-(4-fluoro-3-nitro)phenylalanine (6b):** Compound (**6a**) (230 mg, 0.65 mmol) in CH_3OH (16 mL) was treated at rt for 6 h with H_2O (2 mL) and K_2CO_3 (133 mg, 0.97 mmol). Acid-base workup gave **6b** (199 mg, 90%): mp 176-178° C (acetone/heptane); $[\alpha]_D$ = -12° (c=0.1, CH_3OH); ^1H NMR (200 MHz, $CDCl_3$), δ 1.32 (s, 9H), 2.73 and 2.75 (2s, 3H), 3.23 (dd, 1H, J_1 = 10.9, J_2 = 14.4 Hz), 3.39 (dd, 1H, J_1 = 5.0, J_2 = 14.4 Hz), 4.81 and 4.96 (2dd, 1H, J_1 = 5.0, J_2 = 10.9 Hz), 7.42 (dd, 1H, J_1 = 8.7, J_2 = 10.8 Hz), 7.71-7.74 (m, 1H), 8.04 (dd, 1H, J_1 =1.6, J_2 =7,0 Hz); ^{13}C NMR δ 28.20, 33.78, 34.35, 59.76, 81.20, 118.48 (d, J = 20.5 Hz), 126.05, 134.77 (d, J = 4.2 Hz), 136.23 (d, J = 8.7 Hz), 137.15 (d, J = 6.9 Hz), 154.44 (d, J = 262.5 Hz), 155.10, 174.58; MS (CI, isobutene) *m/z* 343 $[M+H]^+$, 287, 243.

3,5-Dichloro-4-methoxybenzyl alcohol (7): To a solution of methyl 3,5-dichloro-4-methoxybenzoate (5 g, 21.3 mmol) in anhydrous THF (50 mL) was slowly added $LiAlH_4$ (1.0 g, 26.3 mmol) in anhydrous THF (20 mL) and the solution was stirred at rt for 4 h. Hydrolysis by succesive addition of H_2O (2 mL), 15% NaOH (2 mL) and H_2O (8 mL), filtration, evaporation and extraction (CH_2Cl_2) gave **7** (3.87 g, 88%) : mp 40°C (MeOH/$(C_2H_5)_2O$) lit.,[24] 42-44°C; ^1H NMR (200 MHz, $CDCl_3$) δ2.39 (br s 1H), 3.87 (s, 3H), 4.58 (s, 2H), 7.26 (s, 2H); ^{13}C NMR δ 60.82, 63.64, 127.14, 129.35, 138.51, 151.30.

3,5-Dichloro-4-methoxybenzaldehyde (8): To a suspension of PCC (6.0 g, 28.0 mmol) in CH_2Cl_2 (20 mL) was added **7** (2.9 g, 14.0 mmol) in CH_2Cl_2 (30 mL) and the reaction mixture was stirred at rt for 4 h. The liquid phase was removed and the solid residue washed thoroughly with CH_2Cl_2. Evaporation and chromatography (SiO_2, CH_2Cl_2/ether, 9:1) gave **8** (2.61 g, 91%): mp 55-56° C (CH_2Cl_2/heptane); lit.,[25] 58° C; ^1H NMR (200 MHz, $CDCl_3$) δ 4.00 (s, 3H), 7.85 (s, 2H), 9.83 (s, 1H,); ^{13}C NMR δ 61.13, 130.15, 131.33, 133.24, 157.37, 188.77.

[*(R)*-(3,5-Dichloro-4-methoxyphenyl)-*(S)*-(2-hydroxy-1-phenylethylamino)]acetonitrile (9a): A solution of **8** (8.34 g, 40.66 mmol) in $CHCl_3$ (47 mL) added with *(S)*-phenylglycinol (5.57 g, 40.66

mmol) was stirred at rt for 5 h, cooled to 0°C and then successively added with dry MeOH (2 mL) and TMSCN (8.1 mL, 61.0 mmol). After stirring for 15 h at rt, concentration and flash chromatography (SiO_2, heptane/$AcOC_2H_5$, 9:1) gave two compounds, *(R,S)*-**9a** and *(S,S)*-**9b**.

(R,S)-**9a** (9.22 g, 64%) colorless oil: $[\alpha]_D$ = -15° (c = 0.13, $CHCl_3$); IR ($CHCl_3$) υ 3331, 1560, 1486, 1457, 1421; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (br s, OH exchange with D_2O), 2.60 (d, 1H, J =10.6 Hz), 3.67 (dd, 1H, J_1 = 9.5, J_2 = 10.6 Hz), 3.85 (dd, 1H, J_1 = 3.9, J_2 = 10.6 Hz), 3.90 (s, 3H), 4.22 (dd, 1H, J_1 = 3.9, J_2 = 9.5 Hz), 4.42 (d, 1H, J =10.6 Hz), 7.35-7.43 (m, 5H), 7.48 (s, 2H); ^{13}C NMR δ 50.79, 60.92, 63.37, 67.34, 117.86, 127.47, 127.77, 127.83, 128.71, 128.83, 129.29, 130.05, 132.35, 137.57, 152.91; MS (CI, isobutene) m/z 382, 380 $[M\text{-}HCN+57]^+$, 326, 324 $[M\text{-}HCN+H]^+$; CIHRMS *m/z* 324.0539/326.0537 ($C_{17}H_{16}N_2O_2Cl_2$-HCN+H^+ requires 324.0558/326.0551).

(S,S)-**9b** (3.71g, 26%) colorless oil: $[\alpha]_D$ = +35° (c = 0.16, $CHCl_3$); IR ($CHCl_3$) υ 3331, 1708 1560, 1483, 1456, 1428; ^1H NMR (300 MHz, $CDCl_3$) δ 1.97 (br s, OH), 2.51 (br s, 1H), 3.65-3.85 (m, 2H), 3.89 (s, 3H), 3.90-3.95 (m, 1H), 4.76 (br s, 1H), 7.25-7.35 (m, 5H), 7.36 (s, 2H); ^{13}C NMR δ 50.14, 60.79, 62.27, 66.91, 118.35, 127.66, 127.71, 128.08, 128.45, 128.90, 129. 20, 129.96, 132.33, 138.48, 152.80; MS (CI, isobutene) *m/z* 382, 380 $[M\text{-}HCN+57]^+$, 326, 324 $[M\text{-}HCN+H]^+$.

[*(R)*-(3,5-Dichloro-4-methoxyphenyl)-(*S*)-(2-hydroxy-1-phenylethylamino)]acetic acid methyl ester (10a): A solution of aminonitrile (**9a**) (0.60 g, 1.71 mmol) in saturated solution of gaseous hydrochloric acid in dry methanol (10 mL) was stirred at rt for 15 h. Evaporation of solvent, neutralization (buffer phosphate solution), extraction (CH_2Cl_2) and column chromatography (SiO_2, heptane/$AcOC_2H_5$, 3:1) gave a mixture of **10a** and **10b** (10%). A furher purification on TLC afforded a pure sample of **10a** (0.442 g, 76%) as a colorless oil: $[\alpha]_D$ = -21° (c= 0.13, $CHCl_3$); IR ($CHCl_3$) υ 1741, 1557, 1475, 1450, 1421, 1402; ^1H NMR (300 MHz, $CDCl_3$) δ 3.57-3.69 (m, 1H), 3.70 (s, 3H), 3.75-3.80 (m, 1H), 3.70 (s, 3H), 4.20 (br s, 1H), 7.21-7.33 (m, 8H); ^{13}C NMR δ, 52.6, 60.66, 61.68, 63.56, 67.31, 127.58, 127.76, 128.29, 128.72, 129.47, 135.78, 139.41, 151.94, 173.17; MS (CI, isobutene) *m/z* 442, 440 $[M+57]^+$, 386, 384 $[M+H]^+$; CIHRMS *m/z* 384.0761/386.0717 ($C_{18}H_{19}N_2O_4Cl_2$ + H^+ requires 384.0769/386.0739).

***(R)*-(3,5-Dichloro-4-methoxy)phenylglycine methyl ester hydrochloride (11a):** To a solution of **10a**

(0.500 g, 1.3 mmol) in CH_2Cl_2 (10 mL) and CH_3OH (5 mL) was added $Pb(OAc)_4$ (0.634 g, 1.43 mmol) and the solution was stirred at 0° C for 10 min, diluted with phosphate buffer (pH 7) and then stirred for another 30 min. After filtration through Celite and water addition, extraction (CH_2Cl_2) gave crude aldimine which was dissolved in ether (10 mL) and 1N HCl and stirred at rt for 3 h. Ether extraction of the aqueous phase to remove the neutral material, and evaporation gave the pure hydrochloride salt of **11a** (0.323 g, 82%): mp 175° C ($CH_3OH/(C_2H_5)_2O$); $[\alpha]_D$= +104.3° (c= 0.25,, 0.1 N, HCl); ^1H NMR (200 MHz, D_2O) δ 3.83 (s, 3H), 3.95 (s, 3H), 5.28 (s, 1H), 7.52 (s, 2H); ^{13}C NMR δ 53.26, 57.94, 61.22, 127.95, 130.09, 137.99, 152.52, 173.85 ; MS (CI, isobutene) *m/z* 322, 320 $[M+57]^+$, 266, 264 $[M+H]^+$; CIHRMS *m/z* 264.0160/266.0145 ($C_{10}H_{11}NO_3Cl_2 + H^+$ requires 264.0194/266.0164); Anal. Calcd for $C_{10}H_{11}NO_3Cl_2$: C, 39.96; H, 4.02; N, 4.66. Found: C, 39.76; H, 3.99; N, 4.56.

***N*-(*tert*-Butoxycarbonyl)-(*R*)-(3,5-dichloro-4-methoxy)phenylglycine methyl ester (12a):** To A solution of compound (**11a**) (0.200 g, 0.66 mmol) in anhydrous THF (10 mL) were added Boc_2O (0.159 g, 0.73 mmol) and $N(C_2H_5)_3$ (186 mL, 1.33 mmol) and the solution was stirred at rt for 5 h. Solvent evaporation and extraction ($AcOC_2H_5$) gave pure **12a** (0.223 g, 92 %) oil : $[\alpha]_D$ = -54° (c= 0.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$,) δ 1.43 (s, 9H), 3.74 (s, 3H), 3.88 (s, 3H), 5.25 (d, 1H, *J* = 6.7 Hz), 5.80 (d, 1H, *J* = 6.7 Hz), 7.32 (s, 2H); ^{13}C NMR δ 28.25, 53.08, 56.39, 60.63, 80.55, 127.55, 129.70, 134.65, 152.29, 154.63, 170.49; MS (CI, isobutene) *m/z* 366, 364 $[M+H]^+$, 310, 308, 266, 264; CIHRMS *m/z* 364.0693/366.0667 ($C_{15}H_{19}NO_5Cl_2 + H^+$ requires 364.0718/366.0688).

***N*-(*ter*-Butoxycarbonyl)-(*R*)-(3,5-dichloro-4-methoxy)phenylglycine (13a):** Compound (**12a**) (200 mg, 0.55 mmol) in CH_3OH (7 mL), was treated at rt for 2 h with an aqueous solution of K_2CO_3 (115 mg, 0.82 mmol). Acid-base workup gave **13a** (129 mg, 67 %): mp 66-68°C ($CHCl_3$/heptane); $[\alpha]_D$ = +4° (c= 0.1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (s, 9H), 3.89 (s, 3H), 5.03 (d, 1H, *J* = 4.2 Hz), 7.36 (s, 2H), 8.06 (d, 1H, *J* = 4.2 Hz); ^{13}C NMR δ 28.11, 57.80, 60.83, 82.68, 127.71, 129.47, 135.77, 152.09, 156.91, 172.62; MS (CI, isobutene) *m/z* 352, 350 $[M+H]^+$, 296, 294, 252, 250; CIHRMS *m/z* 350.0573/352.0510 ($C_{14}H_{17}NO_5Cl_2 + H^+$ requires 350.0562/352.0532).

[(*2S*)-2-(*tert*-Butoxycarbonylmethylamino)-3-(4-fluoro-3-nitrophenyl)propionylamino]-(*R*)-(4-methoxyphenyl)methyl ester (14a): To a solution of **2a** (145 mg, 0.63 mmol) in CH_2Cl_2 (4 mL), were

added successively $N(C_2H_5)_3$ (132 mL, 0.94 mmol), **6b** (211 mg, 0.62 mmol), EDC (118 mg, 0.62 mmol), HOBT (125 mg, 0.92 mmol) and the solution was stirred for 2 h at rt and extracted (C_2H_5OAc). The organic phase was washed with brine, dried (Na_2SO_4) and evaporated. Purification by preparative TLC (heptane/$AcOC_2H_5$, 99:1) gave **14a** (295 mg, 92 %): mp 40-42°C ($CHCl_3$/heptane); $[\alpha]_D$ = -113.0° (c= 0.1/$CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.84 (s, 3H), 2.96 (dd, 1H, J_1 = 8.9, J_2 = 14.2 Hz), 3.33-3.41 (m, 1H), 3.71 (s, 3H), 3.79 (s, 3H), 4.91-4.97 (m, 1H), 5.40 (d, 1H, J = 6.7 Hz), 6.85 (d, 2H, J = 8.6 Hz), 7.12-7.16 (m, 1H), 7.18-7.22 (d, 2H, J = 8.6 Hz in m, 1H), 7.43-7.51 (m, 1H), 7.88 (dd, 1H, J_1 = 2.2, J_2 = 7.0 Hz); ^{13}C NMR δ 28.25, 30.79, 32.94, 52.79, 55.36, 56.12, 58.90, 81.28, 114.50, 118.41 (d, J = 25.5 Hz), 126.43, 128.39, 128.57, 134.96, 136.33 (d, J = 8.0 Hz), 136.46, 154.36 (d, J = 261.7 Hz), 155.06, 159.96, 169.38, 171.23; MS (CI, isobutene) *m/z* 520 $[M+H]^+$, 464, 420; CIHRMS *m/z* 520.2070 ($C_{25}H_{30}N_3O_8F$ + H^+ requires 520.2095).

[3-(4-Fluoro-3-nitrophenyl)-*(2S)*-2-methylaminopropionylamino]-*(R)*-(4-methoxyphenyl)acetic acid methyl ester (14b): To a solution of **14a** (300 mg, 0.58 mmol) in $CHCl_3$, (5 mL) were added NaI (105 mg, 0.69 mmol) and TMSCl (90 mL, 0.69 mmol). The reaction mixture was stirred for 10 min at rt, then quenched by CH_3OH (5 mL) and neutralized with $KHCO_3$. Extraction (C_2H_5OAc) and preparative TLC (CH_2Cl_2/CH_3OH, 99:1) gave **14b** (230 mg, 94%): mp 82° C ($CHCl_3$/heptane); $[\alpha]_D$ = -89° (c= 0.11/$CHCl_3$); IR ($CHCl_3$) υ 1774, 1672, 1542, 1513, 1441, 1354; ^1H NMR (250 MHz, $CDCl_3$) δ 1.18-1.28 (m, 1H), 2.33 (d, 3H, J = 6.0 Hz), 2.99 (dd, 1H, J_1 = 7.5, J_2 = 14.0 Hz), 3.13 (dd, 1H, J_1 = 5.3 Hz, J_2 = 14.0 Hz), 3.25-3.27 (m, 1H), 3.71 (s, 3H), 3.80 (s, 3H), 5.48 (d, 1H, J = 7.6 Hz), 6.87 (d, 2H, J = 8.6 Hz), 7.19 (dd , 1 H, J_1 = 8.8, J_2 = 10.4 Hz), 7.22 (d, 2H, J = 8.6 Hz), 7.43-7.46 (m, 1H), 7.74 (d, 1H, J = 7.6 Hz), 7.88 (dd, 1H, J_1 = 2.1, J_2 = 6.9 Hz); ^{13}C NMR δ 35.11, 37.51, 52.76, 55.33, 55.50, 65.12, 114.43, 118.55 (d, J = 20.3 Hz), 126.54, 128.31, 128.53, 134.63 (d, J = 3.2 Hz), 136.48 (d, J = 7.9 Hz), 137.13 (d, J = 6.9 Hz), 154.55 (d, J = 262.7 Hz), 159.79, 171.38, 172.07; MS (CI, isobutene) *m/z* 420 $[M+H]^+$, 390; CIHRMS *m/z* 420.1548 ($C_{20}H_{22}N_3O_6F$ H^+ requires 420.1570); Anal. Calcd for $C_{20}H_{22}N_3O_6F$: C, 57.27; H, 5.28; N, 10.01. Found: C, 57.19; H, 5.54; N, 9.37.

[2-{*(R)*-[*tert*-Butoxycarbonylamino-(3,5-dichloro-4-methoxyphenyl)acetyl]methylamino}-*(3S)*-3-(4-fluoro-3-nitrophenyl)propionylamino]-*(R)*-(4-methoxyphenyl)acetic acid methyl ester (15a): To a solution of **14b** (126 mg, 0.30 mmol) in CH_2Cl_2 (2 mL) were added **13a** (105 mg, 0.30 mmol) and

PyBrOP (186 mg, 0.41 mmol). The reaction mixture was stirred for 2 h at 0° C and then for 4 h at rt. Extraction ($AcOC_2H_5$) and preparative TLC (CH_2Cl_2/CH_3OH, 99:1) gave a mixture of **15a**, containing **16a** (less than 10%).

15a Oil (146 mg, 65 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 9H), 2.08-2.97 (m, 1H), 3.03 (s, 3H), 3.33-3.40 (m, 1H), 3.72 (s, 3H), 3.79 (s, 3H), 3.88 (s, 3H), 5.35 (d, 1H, J = 6.8 Hz), 5.43 (d, 1H, J = 6.8 Hz), 5.59 (d, 1H, J = 7.2 Hz), 5.82 (d, 1H, J = 7.2 Hz), 6.85 (d, 2H, J = 8.6 Hz), 7.03-7.16 (m, 3H), 7.25 (d, 2H, J = 8.6 Hz), 7.35 (br s, 2H), 7.40-7.44 (m, 1 H), 7.76 (dd, 1H, J_1 = 1.9, J_2 = 5.0 Hz); ^{13}C NMR δ 28.22, 30.98, 32.74, 52.78, 54.49, 55.33, 56.45, 56.92, 60.81, 80.55, 114.52, 118.44 (d, J = 21.7 Hz), 126.29, 128.14, 128.23, 128.42, 128.96, 133.81, 134.26, 135.85 (d, J = 7.4 Hz), 136.26 (d, J = 8.6 Hz), 152.74, 154.34 (d, J = 262.5 Hz), 155.28, 159.95, 167.63, 168.40, 171.34; FABMS (thio/Na^+) *m/z* 775, 773 $[M+Na]^+$, 753, 751 $[M+H]^+$ 697, 695, 653, 651.

[2-{*(R)*-[Amino-(3,5-dichloro-4-methoxyphenyl)acetyl]methylamino}-*(3S)*-3-(4-fluoro-3-nitro-phenyl)propionylamino]-*(R)*-(4-methoxyphenyl)acetic acid methyl ester (15b): To a solution of **15a** (145 mg, 0.193 mmol) in $CHCl_3$, (5 mL), were added NaI (35 mg, 0.23 mmol) and TMSCl (44 μL, 0.35 mmol) and the solution was stirred for 6 h at rt and then quenched by CH_3OH (5 mL). Neutralization with $KHCO_3$, extraction (C_2H_5OAc) and preparative TLC (CH_2Cl_2/CH_3OH, 99:1) gave **15b** (103 mg, 82%): mp 60-62° C ($CHCl_3$/heptane); $[\alpha]_D$ = -136° (c=0.16, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (br s, 4H), 3.26 (dd, 1H, J_1 = 6.9, J_2 = 14.5 Hz), 3.71 (s, 3H), 3.80 (s, 3H), 3.87 (s, 3H), 4.70 (br s, 1H), 5.43 (d, 1H, J = 7.3 Hz), 5.54 (dd, 1H, J_1 = 7.3, J_2 = 8.5 Hz), 6.86 (d, 2H, J = 8.6 Hz), 7.06 (br s, 3H), 7.24 (d, 3H, J = 8.6 Hz), 7.32-7.38 (m, 1 H), 7.76 (dd, 1H, J_1 = 2.1, J_2 = 6.9 Hz); ^{13}C NMR δ 30.93, 32.73, 52.91, 55.42, 55.93, 56.16, 57.00, 60.82, 114.61, 118.58 (d, J = 21.7 Hz), 126.42, 127.35, 128.03, 128.70, 130.03, 133.66, 135.94 (d, J = 7.8 Hz), 139.90, 137.96 (d, J = 8.6 Hz), 152.40, 154.43 (d, J = 262.5 Hz), 160.04, 168.44, 171.51, 174.43; MS (CI, isobutene) *m/z* 652, 650 $[M+H]^+$.

[2-({*(R)*-(3,5-Dichloro-4-methoxyphenyl)-[2-(3-hydroxyphenyl)acetylamino]acetyl}methylamino)-*(3S)*-3-(4-fluoro-3-nitrophenyl)propionylamino]-*(R)*-(4-methoxyphenyl)acetic acid methyl ester (17a): To a solution of **16b** (24.0 mg, 0.037 mmol) in CH_2Cl_2 (0.5 mL) were added 3-hydroxy-phenylacetic acid (5.6 mg, 0.037 mmol), EDC (7.1 mg, 0.037 mmol), HOBT (7.5 mg, 0.055 mmol) and

the solution was stirred for 30 min at rt and then extracted (C_2H_5OAc). Purification by preparative TLC (CH_3OH/CH_2Cl_2, 99:1) gave **17a** (23.9 mg, 83 %): mp 89-91°C (CH_2Cl_2/heptane); $[\alpha]_D$ = +96° (c=0.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.84 (dd, 1H, J_1 = 5.3, J_2 = 14.7 Hz, H-15), 2.98 (s, 3H, H-34), 3.28 (dd, 1H, J_1 = 7.2, J_2 = 14.7 Hz, H-15'), 3.34 (s, 2H, H-8), 3.71 (s, 3H, H-26), 3.76 (s, 3H, H-33), 3.86 (s, 3H, H-41), 5.46 (d, 1H, J = 6.7 Hz, H-24), 5.49 (d, 1H, J = 7.2 Hz, H-14), 5.62 (d, 1H, J = 6.6 Hz, H-11), 6.58-6.62 (m, 2H, H_4, H-6), 6.74 (d, 2H, J = 8.6 Hz, H-29, H_{31}, 1H, H-21), 6.92 (d, 1H, J = 6.6 Hz, H-10), 7.03 (dd, 1H, J_1= 8.6, J_2= 10.4 Hz, H-19), 7.05 (s, 2H, H-36, H-40), 7.12 (t, 1H, J =7.7 Hz, H-5), 7.15 (d, 2H, J = 8.6 Hz, H-28, H-32), 7.26-7.31 (m, 1H, H-20), 7.55 (d, 1H, J = 6.7 Hz, H-23), 7.74 (dd, 1H, J_1 = 2.2, J_2 = 6.9 Hz, H-17); ^{13}C NMR δ 31.33, 33.04, 42.83, 53.12, 53.49, 55.43, 56.36, 57.33, 60.88, 114.40, 114.99, 116.21, 118.52 (d, J = 21.6 Hz), 121.26, 126.25 (d, J = 2.8 Hz), 127.45, 128.20, 129.06, 130.05, 130.30, 133.17, 133.65 (d, J = 4.6 Hz), 135.44, 135.92, (d, J = 7.8 Hz), 137.02 (d, J = 8.6 Hz), 152.76, 154.40 (d, J = 263.8 Hz), 156.84, 159.90, 168.26, 170.84, 171.05, 171.95; FABMS (thio/Na^+) *m/z* 788, 786 $[M+H]^+$, 592, 590.

[2-({*(S)*-(3,5-Dichloro-4-methoxyphenyl)-[2-(3-hydroxyphenyl)acetylamino]acetyl}methylamino)-*(3S)*-3-(4-fluoro-3-nitrophenyl)propionylamino]-*(R)*-(4-methoxyphenyl)acetic acid methyl ester (17b): To a solution of **16b** (21.5 mg, 0.033 mmol) in CH_2Cl_2 (0.5 mL) were added 3-hydroxyphenylacetic acid (5 mg, 0.03 mmol), EDC (6.4 mg, 0.03 mmol) and HOBT (6.7 mg, 0.049 mmol) and the solution was stirred for 45 min at rt. Extraction (C_2H_5OAc) and preparative TLC (CH_3OH/CH_2Cl_2, 99:1) gave **17b** as an oil (21 mg, 81 %):^1H NMR (300 MHz, $CDCl_3$) δ 2.86-2.90 (m, 1H, H-15), 2.93 (s, 3H, H-34), 3.63 (dd, 1H, J_1 = 7.9, J_2 = 14.6 Hz, H-15'), 3.47 (s, 2H, H-8), 3.60 (s, 3H, H-26), 3.79 (s, 3H, H-33), 3.87 (s, 3H, H-41), 5.24 (d, 1H, J = 7.5 Hz, H-14), 5.29 (d, 1H, J = 7.0 Hz, H-24), 5.68 (d, 1H, J = 7.0 Hz, H-11), 6.62 (br s, 1H, H-23), 6.70-6.73 (m, 2H, H-4, H-6), 6.81 (d, 2H, J = 8.6 Hz, H-29, H-31, 1H, H-21), 6.94 (br s, 1H, H-10), 7.03 (d, 2H, J = 8.6 Hz, H-28, H-32), 7.07 (dd, 1H, J_1 = 8.8, J_2 = 10.5 Hz, H-19), 7.17 (t, 1H, J = 7.7 Hz, H-5), 7.29 (s, 2H, H-36, H-40), 7.33-7.38 (m, 1H, H-20), 7.81 (dd, 1H, J_1 =2.0, J_2 = 7.2 Hz, H-17).

[2-({*(S)*-(3,5-Dichloro-4-methoxyphenyl)-[2-(3-hydroxyphenyl)acetylamino]acetyl}methylamino)-*(3S)*-3-(4-fluoro-3-nitrophenyl)propionylamino]-*(S)*-(4-methoxyphenyl)acetic acid methyl ester (17c): To a solution of **16c** (2.0 mg, 3 μmol) in CH_2Cl_2 (0.2 mL) were added 3-hydroxyphenylacetic acid

(0.5 mg, 3 μmol), EDC (0.6 mg, 3 μmol) and HOBT (0.7 mg, 4 μmol) and the solution was stirred for 20 min at rt. Extraction (C_2H_5OAc) and preparative TLC (CH_3OH/CH_2Cl_2, 99:1) gave **17c** as an oil (1.5 mg, 66 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74 (s, 3H, H-34), 2.87 (dd, 1H, J_1 = 10.1, J_2= 14.7 Hz, H-15), 3.29 (dd, 1H, J_1 = 5.9, J_2= 14.7 Hz, H-15'), 3.51 (d, 2H, J = 5.3 Hz, H-8), 3.74 (s, 3H, H-26), 3.79 (s, 3H, H-34), 3.86 (s, 3H, H-41), 5.48 (br s, 1H, H-14), 5.60 (d, 1H, J = 7.0 Hz, H-24 and 1H, H-11), 6.67-6.72 (m, 1H, H-4 and 1H, H-6), 6.76 (br s, 1H, H-21), 6.79 (br s, 1H, H-10), 6.87 (d, 2H, J = 8.8 Hz, H-29, H-31), 7.01 (s, 2H, H-36, H-40), 7.08 (t, 1H, J = 9.4 Hz, H-19), 7.18 (t, 1H, J = 7.7 Hz, H-5), 7.23 (d, 2H, J = 8.8 Hz, H-28, H-32), 7.26 (br s, 1H, H-23), 7.30-7.36 (m, 1 H, H-20), 7.72 (dd, 1H, J_1=2.1, J_2= 7.1 Hz, H-17).

Compound (18): Compound(**17b**)(2.0 mg) in anhydrous THF (0.5 mL) was stirred at rt for 2 h in the presence of $KHCO_3$ (0.5 mg) and 18-crown-6. After filtration and solvent evaporation, purification by preparative TLC (CH_2Cl_2/MeOH, 99:1) gave a mixture of four products (1.2 mg), **18a** 30%, **18a'** 15%, **18b** 37%, **18b'** 18% (^{1}H NMR). Pure samples were obtained by preparative HPLC of the pooled outcomes of several experiments.

(R,S,R)-**18a**: mp 86-88°C (CH_3OH / CH_2Cl_2); $[\alpha]_D$ = + 4°, (c=0.13, $CHCl_3$); IR ($CHCl_3$) υ 1738, 1673, 1647, 1609, 1493, 1351; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.59 (s, 3H, H_{34}), 2.99 (dd, 1H, J_1 = 12.5, J_2 = 14.3 Hz, H-15), 3.27 (dd, 1H, J_1 = 3.9, J_2 = 14.3 Hz, H-15'), 3.31 (d, 1H, J = 14.0 Hz, H-8), 3.46 (d, 1H, J = 14.0 Hz, H-8'), 3.72 (s, 3H, H-26), 3.76 (s, 3H, H-33), 3.89 (s, 3H, H-41), 5.40 (d, 1H, J = 7.2 Hz, H-24), 5.47 (d, 1H, J = 7.5 Hz, H-11), 5.57 (dd, 1H, J_1 = 3.9, J_2 = 12.4 Hz, H-14), 6.08 (br s, 1H, H-21), 6.45 (d, 1H, J = 7.2 Hz, H-23), 6.70 (d, 2H, J = 8.7 Hz, H-29, H-31), 6.87 (d, 2H, J = 8.7 Hz, H-28, H-32), 6.89 (d, 1H, J = 7.9 Hz, H-6), 6.96 (d, 1H, J =7.5 Hz, H-10), 6.99 (d, 1H, J = 8.3 Hz, H-19), 7.15 (2dd, 2H, J_1 = 2.0, J_2 = 8.3 Hz, H-4, H-20), 7.29 (t, 1 H, J = 7.9 Hz, H-5), 7.36 (s, 2H, H-36, H-40), 8.03 (d, 1H, J =2.0 Hz, H-17); NOESY : H-21/H-19, H-10, H-8'; H-17/H-14, H-15'; H-20/H-15; H-14/H-15',H-23; H-23/H-24; H-8/H-6; H-10/H-11, H-8'; H-11/H-14; MS (CI, isobutene) *m/z* 767, 765 $[M+H]^+$; CIHRMS *m/z* 765.1711/767.1689 ($C_{37}H_{34}N_4O_{10}Cl$ H^+ requires 765.1730/767.1703).

(R,S,R)-**18a'**: Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 (s, 3H, H-34), 3.03 (dd, 1H, J_1 = 12.5, J_2 = 14.5 Hz, H-15), 3.32 (dd, 1H, J_1 = 4.3, J_2 = 14.5 Hz, H-15'), 3.41 (br s, 2H, H-8), 3.71 (s, 3H, H-26), 3.77

(s, 3H, H-33), 3.88 (s, 3H, H-41), 5.40 (d, 1H, J = 7.1 Hz, H-24), 5.49 (d, 1H, J = 7.1 Hz, H-11), 5.67 (dd, 1H, J_1 = 4.3, J_2 = 12.5 Hz, H-14), 5.91 (br s, 1H, H-21), 6.43 (d, 1H, J = 7.1 Hz, H-23), 6.71 (d, 2H, J = 8.7 Hz, H-29, H-31), 6.82 (d, 1H, J = 8.1 Hz, H-6), 6.86 (d, 1H, J = 7.1 Hz, H-10), 6.89 (d, 2H, J = 8.7 Hz, H-28, H-32), 7.13 (2dd, 2H, J_1 = 2.1, J_2 = 8.3 Hz, H-4, H-20), 7.23 (d, 1H, J = 8.3 Hz, H-19), 7.28 (t, 1H, J = 8.1 Hz, H-5), 7.39 (s, 2H, H-36, H-40), 7.63 (d, 1H, J_1 =2.1 Hz, H-17); FABMS (thio/Na^+) *m/z* 789, 787 $[M+Na]^+$, 767, 765 $[M+H]^+$.

(R,S,S)-**18b**: mp 76-78°C (CH_3OH/CH_2Cl_2); $[\alpha]_D$ = +2 ° (c= 0.33, $CHCl_3$); IR ($CHCl_3$) υ 1731, 1679, 1654, 1609, 1538, 1493, 1351; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.97 (s, 3H, H-34), 2.99 (dd, 1H, J_1 = 12.5, J_2 = 14.4 Hz, H-15), 3.33 (d, 1H, J = 14.1 Hz, H-8), 3.39 (dd, 1H, J_1 = 3.9, J_2 = 14.4 Hz, H-15'), 3.45 (d, 1H, J = 14.1 Hz, H-8'), 3.60 (s, 3H, H-26), 3.83 (s, 3H, H-33), 3.89 (s, 3H, H-41), 5.33 (d, 1H, J = 6.8 Hz, H-24), 5.56 (dd, 1H, J_1 = 3.9, J_2 = 12.5 Hz, H-14), 5.59 (d, 1H, J = 7.5 Hz, H-11), 6.05 (d, 1H, J = 6.8 Hz, H-23), 6.07 (br s, 1H, H-21), 6.87 (d, 2H, J = 8.7 Hz, H-29, H-31), 6.88 (dd, 1H, J_1 = 2.3, J_2 = 8.2 Hz, H-6), 6.98 (d, 1H, J =7.5 Hz, H-10), 7.02 (d, 1H, J = 8.3 Hz, H-19), 7.06 (d, 2H, J = 8.7 Hz, H-28, H-32), 7.15 (dd, 1H, J_1 = 2.3, J_2 = 8.2 Hz, H-4), 7.23 (dd, 1H, J_1 = 2.1, J_2 = 8.3 Hz, H-20), 7.29 (t, 1 H, J = 8.2 Hz, H-5), 7.35 (s, 2H, H-36, H-40), 7.99 (d, 1H, J =2.1 Hz, H-17); NOESY: H-21/H-19, H-10, H-11, H-8'; H-17/H-14, H-15'; H-20/H-15; H-14/H-15', H-24; H-23/H-15, H-24; H-8/H-6; H-10/H-8', H-11; FABMS (thio/Na^+) *m/z* 789, 787 $[M+Na]^+$, 767, 765 $[M+H]^+$.

(R,S,S)-**18b'**: mp 64-66° C; $[\alpha]_D$ = -1 ° (c= 0,13, $CHCl_3$); IR ($CHCl_3$) υ 1731, 1679, 1647, 1602, 1493, 1351; ^1H NMR ($CDCl_3$, 300 MHz); δ 3.00 (s, 3H, H-34), 3.04 (dd, 1H, J_1 = 12.5, J_2 = 14.4 Hz, H-15), 3.42 (s, 2H, H-8, dd, 1H, J_1 = 4.3, J_2 = 14.4 Hz, H-15'), 3.62 (s, 3H, H-26), 3.83 (s, 3H, H-33), 3.89 (s, 3H, H-41), 5.34 (d, 1H, J = 6.9 Hz, H-24), 5.59 (d, 1H, J = 7.3 Hz, H-11), 5.64 (dd, 1H, J_1 = 4.3, J_2 = 12.5 Hz, H-14), 5.91 (br s, 1H, H-21), 6.07 (d, 1H, J = 6.9 Hz, H-23), 6.82-6.84 (m, 2H, H-10, H-6), 6.87 (d, 2H, J = 8.7 Hz, H-29, H-39), 7.07 (d, 2H, J = 8.7 Hz, H-28, H-32), 7.14 (dd, 1H, J_1 = 2.4, J_2 = 8.2 Hz, H-4), 7.21 (d, 1H, J = 8.4 Hz, H-19), 7.29 (t, 1 H, J = 8.0 Hz, H-5), 7.39 (s, 2H, H-36, H-40), 7.60 (dd, 1H, J_1 = 2.1, J_2 = 8.4 Hz, H-20), 7.74 (d, 1H, J =2.1 Hz, H-17); NOESY: H-21/H-19, H-10, H-11; H-17/H-15; H-20/H-15'; H-14/H-15, H-15', H-23, H-10; H-23/H-15, H-24, H-14; H-8/H-6; FABMS (thio/Na^+) *m/z* 789, 787 $[M+Na]^+$, 767, 765 $[M+H]^+$.

3-(7-Bromo-3*H*-indol-3-yl)acrylic acid methyl ester (21): Compound (**20**), (90 mg, 0.408 mmol), monoethyl malonate (64 mg, 0.48 mmol), dry pyridine (1 mL) and dry piperidine (2 drops) were heated on an oil-bath at 50 °C for 24 h. Evaporation of the volatile and preparative TLC (CH_2Cl_2/heptane 10:1) gave **21** (70 mg, 60%): mp 146-147 °C (ether/pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, 3H, *J* = 7.1 Hz), 4.27 (q, 2H, *J* = 7.1 Hz), 6.43 (d, 1H, *J* = 16.0 Hz), 7.09 (d, 1H, *J* = 7.9 Hz), 7.39 (d, 1H, *J* = 7.9 Hz), 7.50 (d, 1H, *J* = 2.7 Hz), 7.71 (d, 1H, *J* = 7.9 Hz), 7.87 (d, 1H, *J* = 16.0 Hz), 8.82 (br s, 1H); ^{13}C NMR δ 14.38, 60.29, 105.28, 114.59, 119.60, 122.57, 125.68, 126.55, 128.59, 135.77, 137.60, 167.98; MS (CI, isobutene) *m/z* 296, 294.

3-(7-Bromo-3*H*-indol-3-yl)propionic acid methyl ester (22a): To an ice water cooled solution of **21** (632 mg, 2.14 mmol) in 95% ethanol (25 mL) and $BiCl_3$ (336 mg, 1.07 mmol) was added portionwise $NaBH_4$ (316 mg, 8.03 mmol) and the solution was stirred for 4 h at 0°C. Evaporation of the volatile and preparative TLC (CH_2Cl_2) gave **22a** (253 mg, 40%): mp 80°C (CH_3OH/pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, 3H, *J* = 7.1 Hz), 2.69 (t, 2H, *J* = 7.6 Hz), 3.07 (t, 2H, *J* = 7.6 Hz), 4.13 (q, 2H, *J* = 7.1 Hz), 6.99 (t, 1H, *J* = 7.6 Hz), 7.02 (s, 1H), 7.33 (d, 1H, *J* = 7.6 Hz), 7.54 (d, 1H, *J* = 7.6 Hz), 8.17 (br s, 1H); ^{13}C NMR δ 14.30, 20.83, 34.99, 60.53, 104.87, 116.43, 118.09, 120.60, 122.16, 124.46, 128.53, 135.05, 173.31; MS (CI, isobutene) *m/z* 298, 296.

3-(7-Bromo-3*H*-indol-3-yl)propionic acid (22b): Compound (**22a**) (170 mg, 0.57 mmol) in CH_3OH/H_2O 1:1 (10 mL), was treated with H_2O (2 mL) and NaOH (120 mg, 3 mmol) at rt for 4 h. Evaporation of the volatile and acid-base workup gave **22b** (150 mg, 98 %): mp 129-130°C (CH_3OH/ CH_2Cl_2); ^{1}H NMR (300 MHz, acetone-D_6) δ 2.81 (t, 2H, *J* = 7.5 Hz), 3.15 (t, 2H, *J* = 7.5 Hz), 7.01 (t, 1H, *J* = 7.8 Hz), 7.23 (s, 1H), 7.38 (d, 1H, *J* = 7.8 Hz), 7.60 (d, 1H, *J* = 7.8 Hz), 10.40 (br s, 1H); ^{13}C NMR δ 21.95, 35.65, 105.76, 117.30, 119.49, 121.81, 125.35, 130.59, 136.50, 174.88; MS (CI, isobutene) *m/z* 269, 267.

[3-(7-Bromo-3*H*-indol-3-yl)propionylamino]acetic acid methyl ester (23a): A solution of glycine methyl ester hydrochloride (37 mg, 0.30 mmol) in DMF (5 mL), containing $N(C_2H_5)_3$ (42 μL, 0.30 mmol) was stirred at rt for 15 min and was successively added with EDC (68 mg, 0.36 mmol), HOBT (40 mg, 0.30 mmol) and **22b** (80 mg, 0.30 mmol). After 8 h, dilution with aqueous 1N HCl (pH=3),

extraction ($AcOC_2H_5$) and preparative TLC (CH_2Cl_2/CH_3OH, 8:2) gave **23a** (58 mg, 58%): mp 124 °C (CH_3OH-ether/pentane); ^1H NMR (300 MHz, acetone-d_6) δ 2.72 (t, 2H, *J* = 7.6 Hz), 3.16 (t, 2H, *J* = 7.6 Hz), 3.74 (s, 3H), 4.04 (d, 2H, *J* = 5.8 Hz), 7.01 (t, 1H, *J* = 7.8 Hz), 7.26 (d, 1H, *J* = 2.4 Hz), 7.35 (d, 1H, *J* = 7.8 Hz), 7.45 (br s, 1H), 7.63 (d, 1H, *J* = 7.8 Hz), 9.96 (br s, 1H); ^{13}C NMR δ 21.74, 37.02, 41.45, 51.95, 105.04, 117.10, 118.85, 120.69, 124.17, 124.56, 130.01, 136.50, 171.50, 173.30; MS (CI, isobutene) *m/z* 341, 339. Anal. Calcd for $C_{14}H_{15}N_2O_5Br$: C, 49.57; H, 4.46; N, 8.25. Found: C, 50.33; H, 4.81; N, 7.71.

[3-(7-Bromo-3*H*-indol-3-yl)propionylamino]acetic acid (23b): Compound (**23a**) (1.5 g, 4.4 mmol) in CH_3OH (80 mL), was treated with H_2O (20 mL) and NaOH (0.44 g, 11 mmol) at rt for 5 h. Evaporation of the volatile and acid-base workup ($AcOC_2H_5$) gave **23b** (1.2 g, 84 %): mp 118-120°C (CH_2Cl_2); ^1H NMR (300 MHz, acetone-d_6) δ 2.61 (t, 2H, *J* = 7.6 Hz), 3.05 (t, 2H, *J* = 7.6 Hz), 3.93 (d, 2H, *J* = 4.9 Hz), 6.96 (t, 1H, *J* = 7.7 Hz), 7.25 (s, 1H), 7.30 (d, 1H, *J* = 7.7 Hz), 7.34 (br s, 1H), 7.61 (d, 1H, *J* = 7.7 Hz), 10.11 (br s, 1H); ^{13}C NMR δ 21.92, 37.14, 41.60, 104.90, 118.02, 119.02, 120.84, 124.10, 124.80, 130.06, 137.10, 171.73, 173.09; MS (CI, Isobutene) *m/z* 327, 325.

***N*-[(3-Bromobenzylcarbamoyl)methyl]-3-(7-bromo-3*H*-indol-3-yl)propionamide (24b):** A solution of 3-bromobenzylamine hydrochloride (71 mg, 0.326 mmol) and $N(C_2H_5)_3$ (45 μL, 0.326 mmol) in DMF (2 mL) was stirred at rt for 10 min. To this mixture were added EDC (68 mg, 0.391 mmol), HOBT (42 mg, 0.326 mmol) and **23b** (106 mg, 0.326 mmol) and the solution was stirred at rt for 10 min. After 15 h the reaction was quenched with water (10 mL) and extracted ($AcOC_2H_5$). Preparative TLC (CH_2Cl_2/CH_3OH 9:1) gave **24b** (60 mg, 38%): mp 159 °C (CH_3OH-ether/pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 2.57 (t, 2H, *J* = 7.2 Hz), 3.01 (t, 2H, *J* = 7.2 Hz), 3.84 (d, 2H, *J* = 5.2 Hz), 4.24 (d, 2H, *J* = 6.0 Hz), 6.74 (br s, 1H), 6.94 (t, 2H, *J* = 7.8 Hz), 7.08-7.13 (m, 3H), 7.29-7.35 (m, 3H), 7.46 (d, 1H, *J* = 7.8 Hz), 10.14 (br s, 1H); ^{13}C NMR δ 22.31, 37.70, 43.28, 43.61, 105.53, 116.34, 118.82, 120.85, 123.36, 124.23, 124.91, 127.10, 130.03, 131.17, 131.21, 136.37, 142.37, 171.78, 176.28; MS (CI, isobutene) *m/z* 495, 493, 491.

Compound (25): Into a flamed dried 25 mL round bottom flask were introduced $(TPP)_2NiCl_2$ (40 mg, 0.061 mmol), triphenylphosphine (32 mg, 0.12 mmol), and zinc powder (4.0 mg, 0.061mmol). A septum

cap was placed on the flask and of dry, O_2-free DMF (1 mL) was added. The flask was evacuated and filled with N_2 three times by means of a syringe needle connected with tygon tubing to a vacuum line and another syringe needle connected to nitrogen line. After 1 h compound (**24b**) (30 mg, 0.061 mmol) in 1 mL of dry, O_2-free DMF was added *via* syringe with careful exclusion of air and the reaction mixture was stirred under nitrogen at 50°C for 2 h. It was then cooled, poured into aqueous 5 % HCl (100 mL), extracted with $AcOC_2H_5$(20 mLx3) and the extract was washed with distilled water and brine, dried over Na_2SO_4. Removal of solvents and TLC chromatography (CH_2Cl_2/CH_3OH 9:1) gave **25** (0.2 mg, 1%) as a yellow solid; MS (EI) *m/z* 333; CIHRMS m/z 334.1562 ($C_{20}H_{19}N_3O_2 + H^+$ requires 334.1555).

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