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Synthetic Studies Towards Western and Eastern Macropolypeptide Subunits of Kistamycin

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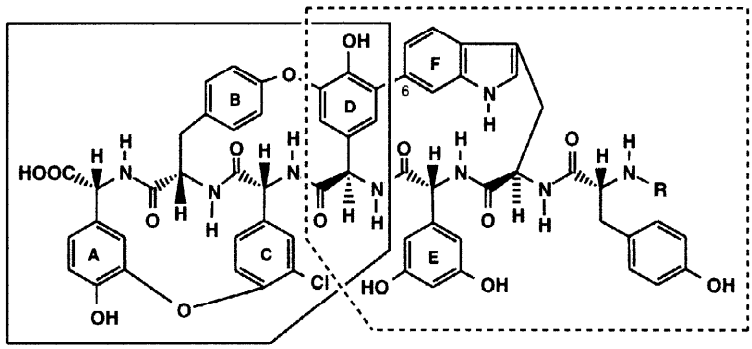
Abstract: The western subunit (fused bicyclic 16+15 membered ring) was synthesized by sequential intramolecular S_NAr reaction and the first 17-membered ring compound as model of the eastern subunit was obtained by an intramolecular Ni^0 mediated coupling reaction.

The recently isolated Kistamycins A and B[1] produced by *Microtetraspora Parvasaeta* sbsp *Kistanae*, which exhibit type A influenza virus inhibition and moderate *in vitro* reactivity against Gram positive bacteria[1] are strucurally complex molecules. Their tricyclic macropolypeptide framework can be delineated into two subunits. The western one is a bicyclic tripeptide **AOCBOD** which possesses a unique structure, *i.e.*, a 16-membered ring containing an *endo* biaryl ether bond **BOD** fused to a 15-membered ring **AOC** containing also an *endo* biaryl ether bond, while the eastern one is a 17-membered ring polypeptide characterized by an *endo* carbon-carbon bond between tryptophane **F** and the central 3,4-dihydroxyphenylglycine **D** (Fig. 1). At the beginning of our work, there was in the literature no report dealing with the synthesis of either subunit and so we were prompted to investigate the synthesis of simplified models of both.



Kistamycin A R=H
Kistamycin B R= CO-NH-CH_2-CH_2-C_6H_5

Figure 1

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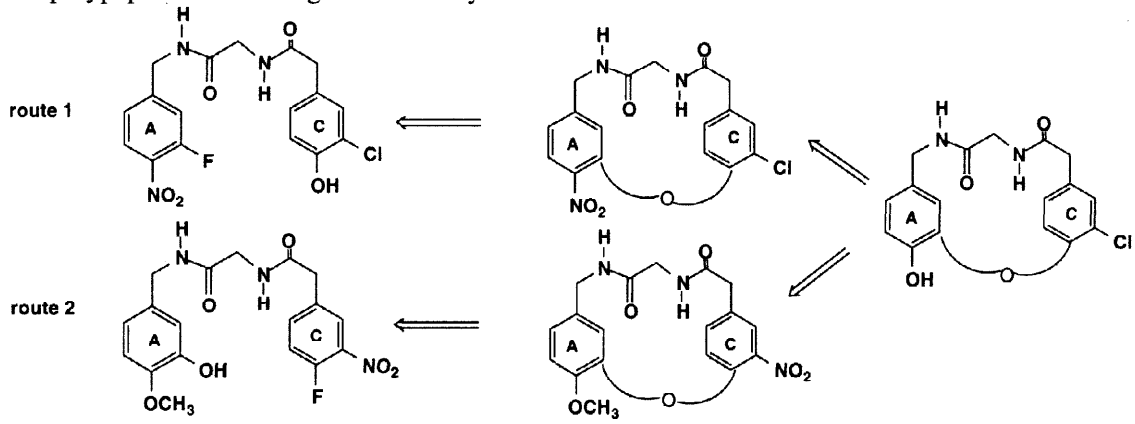
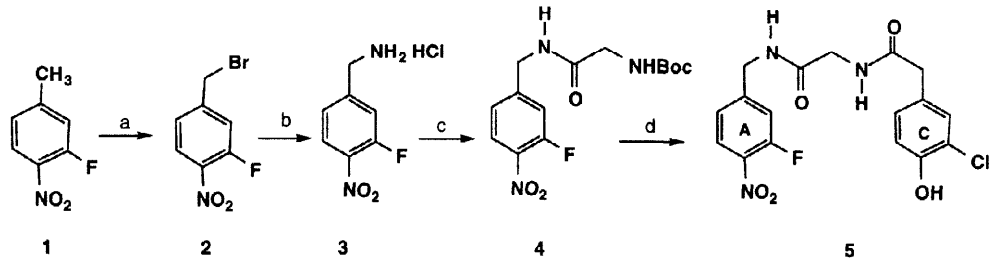
WESTERN SUBUNIT

The synthesis of 16-membered ring macropolypeptides is well documented in the field of vancomycin,[2] but that of the 15-membered ring macropolypeptide **BOD** constituting the lower part of kistamycin was unknown. Before undertaking the synthesis of the fused 16+15 membered ring macropolypeptide **AOBCOD**, the synthesis of a 15-membered ring was investigated *via* the intramolecular S_NAr based methodology developped in the course of studies toward a variety of macropolypeptides containing an *endo* biaryl ether bond.[3]



Two routes towards a simplified model of the properly substituted macropolypeptide appeared *a priori* possible from precursors differing by the substitution pattern of the terminal phenyl rings **A** and **C**. For cyclisation *via* route 1, the linear peptide had to carry the nucleophilic and the electrophilic functionalities respectively on **A** and **C** while the reverse arrangement of functional groups was needed for cyclisation *via* route 2.

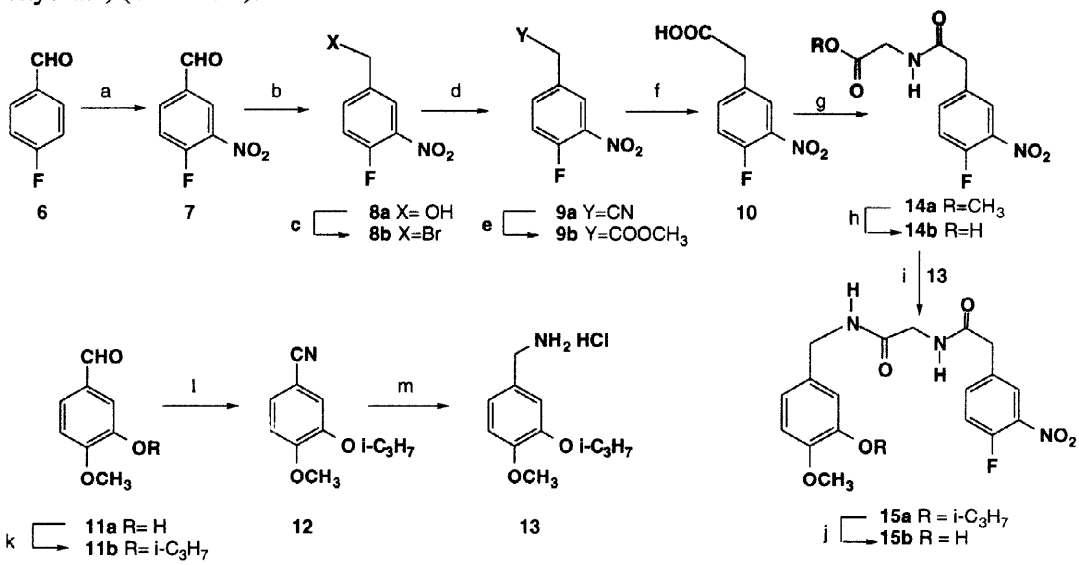


Reagents and conditions: a: NBS, CCl_4, $(C_6H_5CO)_2O_2$, 88%; b: hexamethylenetetramine, CCl_4, HCl, EtOH, 90%; c: glycine NHBoc, NEt_3, DMF, DCC, HOBT, 87%; d: TFA, CH_2Cl_2, 3-chloro-4-hydroxyphenylacetic acid, NEt_3, DCC, HOBT, DMF, 75%

Scheme 1

For macrocyclisation *via* route 1 the linear precursor **5** with terminal phenyl **C** was readily obtained by coupling 3-fluoro-4-nitrobenzylamine **3** (prepared from commercially available 3-fluoro-4-nitrotoluene **1** *via* benzylbromide **2**) with *N*-Boc-glycine to give the peptide **4**. Deprotection and coupling with 3-chloro-4-hydroxyphenylacetic acid replacing the amino acid **C**, led to **5** (Scheme 1). For macrocyclisation *via* route 2, the synthesis of the precursor **15b** possessing the reverse functionalities required 3-fluoro-4-nitrophenylacetic acid **10** (prepared in 62% overall yield from 4-fluorobenzaldehyde **6** by a five step sequence involving nitration, borohydride reduction, cyanation and

hydrolysis of the resulting nitrile) and 3-isopropoxy-4-methoxybenzylamine **13** (prepared in three steps from commercially available isovanillin **11a** *via* **11b**, the nitrile **12** finally reduced to give **13**, stable as chlorohydrate) (Scheme 2).

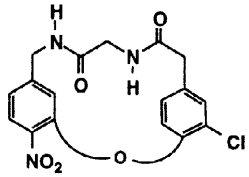


Reagents and conditions: a: H_2SO_4, HNO_3, 92%; b: $NaBH_4$, Ethanol, 0°C, 100%; c: PBr_3, Toluene, 0°C, 82%; d: Et_4NCN, Acetonitrile, 96%; e: MeOH, HCl, 85%; f: MeOH, NaOH, H_2O, 98%; g: Glycine methyl ester hydrochloride, DMF, NEt_3, DCC, HOBT, DMF, 93%; h: K_2CO_3, MeOH, H_2O, 94%; i: **13**, DCC, HOBT, NEt_3, DMF, 80%; j: BCl_3, CH_2Cl_2, 0 °C, 95%; k: i-PrBr, DMF, K_2CO_3, 80°C, 90%; l: NaN_3, THF, $AlCl_3$, 96%; m: BH_3, THF, HCl, MeOH, 58%

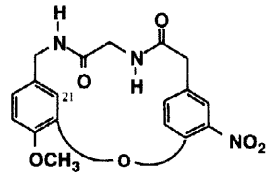
Scheme 2

Coupling of **10** with glycine methyl ester hydrochloride gave **14a** (93%) which after hydrolysis to the corresponding acid **14b** and coupling with **13** gave the peptide **15a** whose phenol function was deprotected to give **15b.** With precursors **5** and **15b** in hand, comparative macrolactamization studies were carried out (Table 1).

Table 1 Comparative cyclization studies of **5** and **15b**



5 ⟶ 16



15b ⟶ 17

entry	conditions[a]	route 1	route 2
1	K_2CO_3, DMF	14h ; 0%	20h ; 80%
2	K_2CO_3, DMF[b]	2h ; 0%	10h ; 86%
3	CsF, DMF	3h ; 0%	

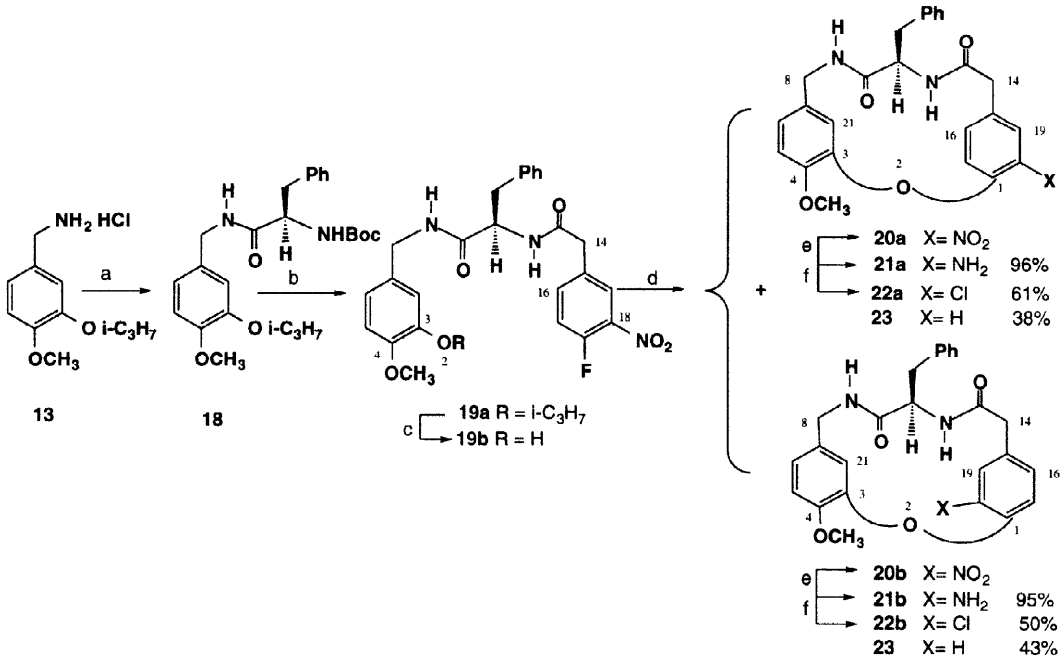
a: reaction carried out at r.t., 0.01M concentration, 3 eq. of base; b: 18-crown-6 ether 0.01M

The precursor **5** was observed to turn dark in solution. After 14 hours (entry 1), the starting material was totally consumed, but no cyclized compound **16** could be characterized in the complex

outcome of the reaction *via* route 1. In sharp contrast, *via* route 2 the precursor **15b** led to the cyclized product **17** in high yield (80%) and pure form. The addition of 18-crown-6 ether (entry 2), known in many intances to improve the reaction rate, led after 2 hours to the same failure *via* route 1 while a dramatic acceleration of route 2 was observed, **17** being then obtained in 91 % yield after only 8 hours. However, this successfull cyclisation to the 15-membered ring macrocycle was slow compared with many previously reported ring closure reactions to 16-membered ring macrocycles occuring in the range of 3 to 4 hours.

A conformational simulation revealed that the two active sites (OH and C_F) of the terminal phenyl rings involved an *endo* biaryl ether bond formation leading to the *meta-para* cyclophanes **16** and **17** lie within 4.29 Å (activation energy =-167 KJ/mol) for the linear precursor **5** (route 1) and 4.85 Å (activation energy =-187 KJ/mol) for the linear precursor **15b** (route 2). This values indicate some degree of preorganisation for both, but the experimental failure of route 1 compared to the efficiency of route 2, suggested that the substitution pattern of the respective nucleophilic termini played a role. Indeed, the *ortho*-chlorophenol of **5** could be expected to be a weaker nucleophile than the *ortho* -methoxy phenol chromophore of **15b** when opposed to the same electrophilic system. This difference, not critical for ring closure of the 16-membered ring recently reported by Rao[4] *via* route 1, became obviously crucial for the much slower closure of the more strained 15-membered ring.

Intramolecular S_NAr based cyclisation are known to give mixtures of atropisomeric 14, 16, or 17-membered ring macropolypeptides as a consequence of the creation of a chiral planar center. That this was also the case for the 15-membered ring was evidenced by cyclization of the chiral precursor **19b** (Scheme 3).



Reagents and conditions: a: NEt_3, EDC, HOBT/DMF, *(R)*-NHBoc-phenylalanine, 77%; b: TFA, CH_2Cl_2 then NEt_3, EDC, HOBT, DMF, 4-fluoro-3-nitrophenylacetic acid, 97%; c: BCl_3, CH_2Cl_2, 0°C, 80%; d: see Table 2; e: Pd/C, H_2, MeOH; f: NO_2Na, HCl, CuCl, $CuCl_2$

Scheme 3

This linear peptide was synthesized by a sequence of reactions starting from 4-methoxy-3-isopropyloxybenzylamine hydrochloride **13**. Coupling with *(S)*-phenylalanine gave **18**, which after deprotection was coupled with 4-fluoro-3-nitro phenylacetic acid to give **19a**. Isopropyl group removal gave **19b**, ready for macrocyclisation (Table 2).

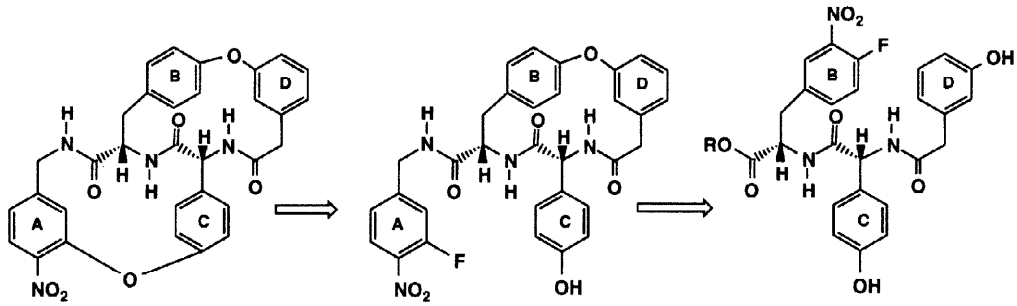
Table 2 Macrocyclisation of the chiral precursor **22**

Entry	Conditions[a]	**20a + 20b**	**20a /20b**
1	K_2CO_3, DMF, 24 h	65	5/4
2	K_2CO_3, DMF, 6 h[b]	79	5/4
3	K_2CO_3, THF, 10 h[b]	82	3/2
4	$KHCO_3$, THF, 20 h	71	4/3

a: r.t.; 0.01M concentration; 3 eq. of base; b: 18-crown-6 ether 0.01M

Under conditions identical to those used for cyclisation of the achiral precursor, **19b** led to a pair of atropisomers **20a** and **20b** (entry 1). The yield was improved and the reaction was faster in the presence of 18-crown-6 ether, but the ratio of atropisomers remained unchanged (entry 2). A slightly large excess of **20a** was observed by changing DMF for THF (entry 3), while a weaker base (entry 4) gave almost the same result as observed in entries 1 and 2. Each atropisomer obtained in pure form from silica gel column chromatography and submitted to reduction gave the compounds **21a** and **21b** in quantitative yield. Sandmeyer reaction performed on **21a** and **21b** led in each case to the atropisomeric chloro-derivatives **22a** and **22b** possessing the substitution pattern of the western kistamycin subunit. From these reactions, a minor and common product devoid of axial asymetry was isolated and identified as **23** (α_D=-100°).

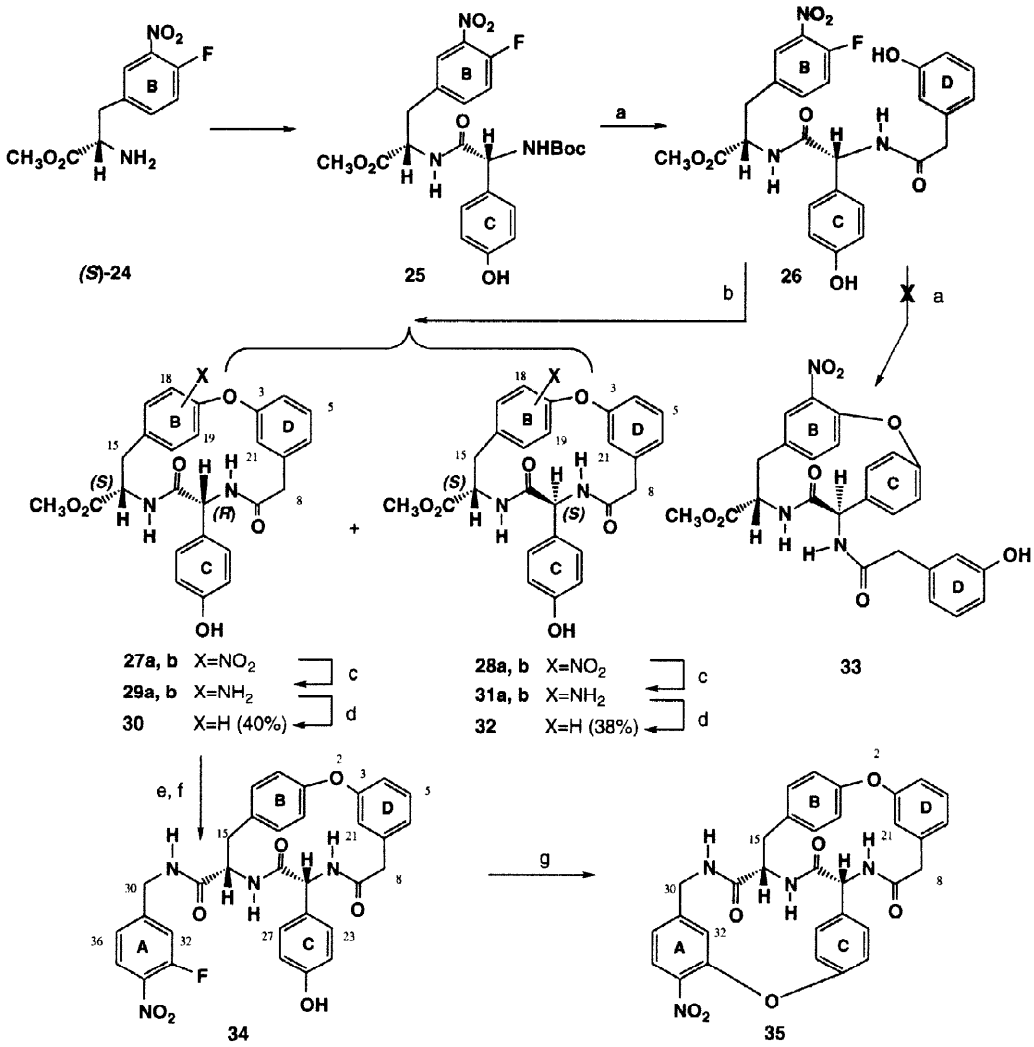
Having secured a route to 15-membered ring macropolypeptides, it became possible to plan a synthesis of the fused 16+15 bicyclic macropolypeptide **AOCBOD** by a strategy implying first the synthesis of the upper 16-membered ring system **BOD** upon which the lower fused 15-membered ring **AOC** would then be constructed (Scheme 4).



Scheme 4

The non proteinogenic *(S)*-4-fluoro-3-nitrophenylalanine **24** required as terminal electrophilic component of the tripeptide precursor to the 16-membered **BOD** ring was obtained in enantiomerically pure form as methyl ester by the method based upon enzymatic resolution of the corresponding trifluoroacetates previously reported by our group.[5] Coupling of *(S)*-**24** with NHBoc protected amino

acid **C** afforded the peptide **25**.[3e] Deprotection under mild acidic conditions followed by coupling with 3-hydroxyphenylacetic acid as a substitute to amino acid **D** provided then the diphenol precursor **26** (Scheme 5). The phenol group of **C** was not protected on the assumption that an intramolecular reaction with the electrophile would give a *para-para* 14-membered cyclophane, and would therefore not compete with the reaction designed to give the *meta-para* 16-membered cyclophane.



Reagents and conditions: a: 3-Hydroxyphenylacetic acid, HOBT, EDC, NEt3/CH2Cl2 89%; b: K_2CO_3/DMF, r.t., 6h (see Table 2); c: Pd/C/MeOH; d: t-BuONO/DMF 40 %; e: LiOH, THF, MeOH, 8h, 98%; f: **3**, DCC, HOBT/DMF, 87%; g: $KHCO_3$/DMF/18-crown-6, 4h, 80%.

Scheme 5

Under classical conditions (Table 3, entry 1), the precursor **26** had totally reacted after 4 hours, yielding a mixture of four cyclised products in 75 % isolated yield. Preparative thin layer chromatography gave pure samples of *(S,R)*-**27a**, *(S,R)*-**27b** and *(S,S)*-**28b** while *(S,S)*-**28a** could not be separated from *(S,S)*-**28b**. All were 16-membered macrocycles as evidenced by MS and ^1H NMR spectroscopy where the H-21 (bs) signal found at δ=6.81 ppm in the precursor had undergone the

characteristic upfield shift (δ=6.34 ppm) observed in the spectra of all 16-membered ring macropolypeptides.[3f]

This first result showed that, as anticipated, the *para-para* cyclophane was not formed in competitive macrocyclisation which would have led to the 14-membered ring compound **33**, but that the reaction conditions had induced racemization of the unprotected amino acid **C**, as evidenced by ^{1}H NMR spectra of *(S,R)*-**27a**, *(S,R)*-**27b**, *(S,S)*-**28b** and of the mixture of *(S,S)*-**28a** + *(S,S)*-**28b**. Several attempts were effected to find conditions under which racemization could be minimized. Replacing K_2CO_3 by a weaker base in the same solvent shortened the reaction time (entry 2) changing DMF for THF (entry 3) or using CsF as a base in place of $KHCO_3$ (entry 4) could not suppress the racemization.

Table 3 Macrocyclisation of the chiral precursor **26**

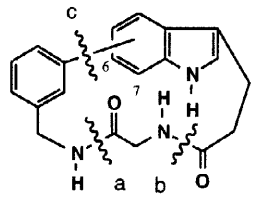
Entry	Conditions	*(S,R)*-**27a**	**27b**	*(S,S)*-**28a**	**28b**
1	K_2CO_3[b], DMF, 4 h	40	22	26	12
2	$KHCO_3$[b], DMF, 2 h	43	23	21	13
3	$KHCO_3$, THF[b], 2 h	46	24	19	11
4	CsF, DMF, 3 h	35	28	23	14

Removal of the activating nitro group was effected by reduction of *(S,R)*-**27a** or *(S,R)*-**27b** to the corresponding amino derivatives *(S,R)*-**29a** or *(S,R)*-**29b** whose reductive deamination afforded a single and identical compound *(S,R)*-**30**. The same sequence effected on the atropomeric mixture *(S,S)*-**28a,b** or on pure *(S,S)*-**28b** led to the diastereomeric compound *(S,S)*-**32**.

The formation of equal amounts of atropisomers was of no consequence upon the planned synthesis as the newly created chiral planarity had to be destroyed at the next stage of the sequence of reactions leading to the bicyclic macropolypeptide. The product of *(S,R)* natural configuration required for the the synthesis of the fused bicyclic compound could thus be obtained on a larger scale by column chromatography separation of the diastereomeric mixture *(S,R)*-**30** and *(S,S)* **32** resulting from the reduction of the crude outcome of the macrocyclisation reaction. Coupling of **30** with 3-fluoro-4-nitrobenzylamine used as substitute of amino acid **A** for the synthesis of a simplified analogue gave the 16-membered ring macropolypetide **34**, carrying terminal phenyl rings properly substituted for the second intramolecular S_NAr reaction. The optimized conditions defined in Table 1 led to the 16+15 fused bicyclic ring system **AOBOD 35** in 80% yield. Each signal of the ^{1}H NMR spectrum was split in two, revealing the presence of two conformers C_1 and C_2 whose ratio was solvant dependant (C_1/C_2= 1 in acetone-D_6 , and 4.5 in DMSO-D_6). Upfield shift of H-32 (δ= 5.51 and 5.25), characteristic of the 15-membered ring together with that of H-21 (δ= 6.02 and 5.92) characteristic of the upper 16-membered macrocycle were observed, but a definitive attribution of the axial configuration could not be made (Scheme 5).

EASTERN SUBUNIT

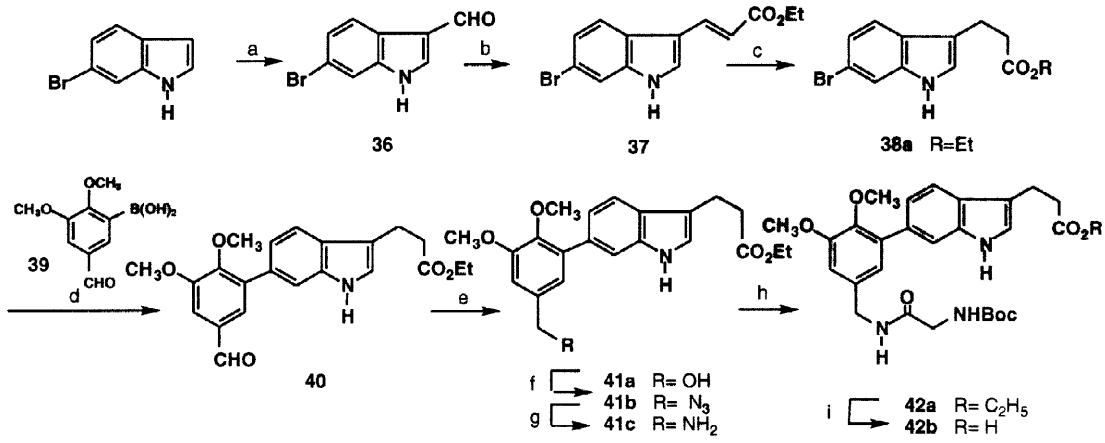
The major problem for the synthesis of macropolypeptides containing an *endo* carbon-carbon bond is the key reaction for ring closure. As far as the eastern 17-membered ring macropolypeptide of kistamycin which contains the 6-phenylindole component is concerned, only one unsuccessfull attempt by macrolactamization (disconnection a) was reported.[6] In our effort toward the synthesis of the simplified 17-membered ring macropolypeptide, we decided to investigate the macrolactamization approach (disconnection b) to supplement the above mentionned report, and simultaneously to explore the feasibility of the hitherto unprecedented macrocyclization (disconnection c).



Macrolactamization studies

The linear peptide used by Gurjar[6] as precursor for macrolactamization comprised, among other structural features, an N_1-Ts protected tryptophane. We speculated that this rather bulky protecting group might have forced the peptide in an unfavorable conformation and that a precursor devoid of protection at N_1 might behave better in the delicate cyclization process. We also wondered wether the intramolecular carboxyl activation could be performed differently, keeping in mind that the pentafluoro ester method was used by Evans[7] to synthesize OF 49 49III, a 17-membered ring macropolypeptide containing an *endo* biaryl ether bond and by Nicolaou[8] for the synthesis of a fused (16+12)-membered ring macropolypeptide (western part of vancomycin). Furthermore, the Ag^+ assisted thio ester activation, very recently reported by Zhang *et al*[9] for the synthesis of large ring macropolypeptides was thought to be relevant to out purpose.

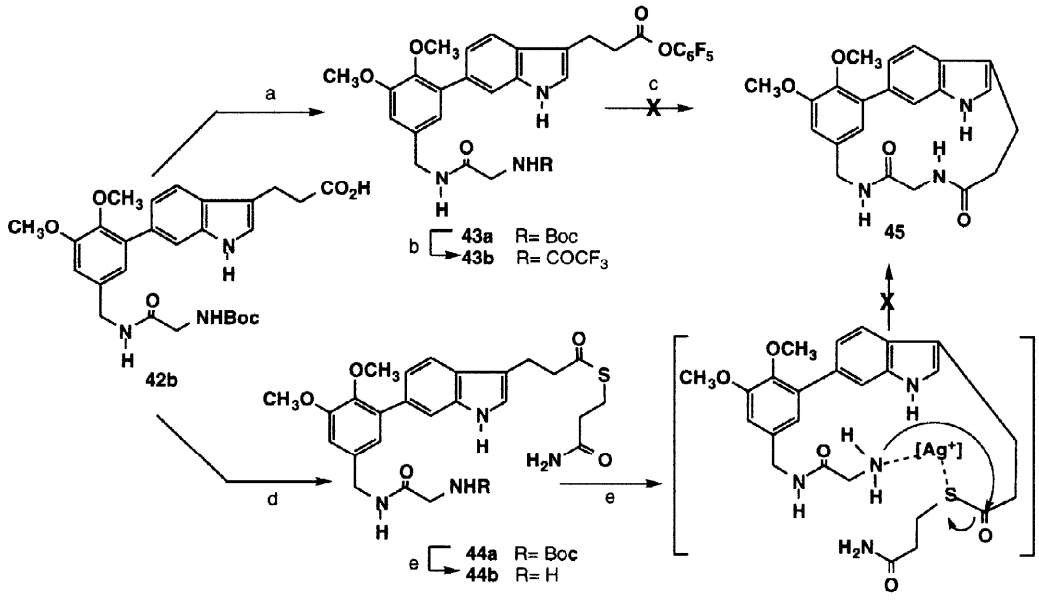
The simplified peptide **42b**, common to the linear precursors necessary to study both approaches was prepared as follows (Scheme 6). 6-Bromo-3-formylindole **36** obtained by Vilsmeier-Hack formylation[10] of 6-bromoindole[11] was treated with monoethylmalonate. Chimiospecific reduction of the intermediate acrylic compound **37**[12] gave the 6-bromo-propionic indole derivative **38** whose arylation with phenyl boronic acid **39** was realized by palladium mediated Suzuki cross coupling reaction to give the N_1-H unprotected 6-arylindole derivative **40**. Functionnal group transformation was efficiently performed *via* alcohol **41a** and azide **41b** according to a reported procedure[13] to give the benzylamine derivative **41c**.



Reagents and conditions. a: $POCl_3$, DMF à 0°C, 73%; b: $CO_2HCH_2CO_2Et$, pyridine, piperidine 50°C, 97%; c: $NaBH_4$, $BiCl_3$, ETOH 0°C, 75%; d: Na_2CO_3, $Pd(PPh_3)_4$, EtOH-DME, 71%; e: $NaBH_4$, MeOH, 94%; f: DPPA, DBU, toluène, 85%; g: $Pd/CaCO_3$, EtOH; h: glycine NH-Boc, HOBT, EDC, DMF, 67 %; i: KOH, EtOH, 97%

Scheme 6

Coupling with NHBoc protected glycine under standard conditions led to **42a**, saponified to give the linear peptide **42b** (Scheme 6), from which the precursors **43b** and **44b** required for macrolactamization studies *via* the two above mentionned procedures were easily prepared (Scheme 7). Esterification of **42b** with C_6F_5OH gave good yield of the activated ester **43a** and deprotection of the amino group led to **43b**. The intramolecular amidification attempt was carried out by heating **43b** (0.01M) in dioxane-pyridine at 90°C for 20 hours. The outcome of this reaction was an untractable mixture from which no definite compound could be isolated.



Reagents and conditions. a: HOC_6F_5, EDC, HOBT, DMF; b: TFA-CH_2Cl_2, thioanisole; c: dioxane-pyridine (5:1) 90 °C d: 3-mercaptopropionamide, DPPA, DMF, 86%; e: i) TFA, CH_2Cl_2, ii) NEt_3, CH_2Cl_2; f: Ag^+, DMSO-tampon pH=5.5 (1:1)

Scheme 7

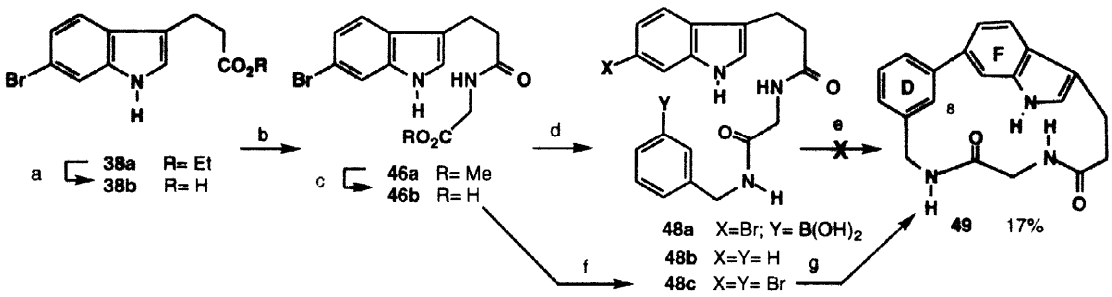
Treatment of **42b** with 3-mercaptopropionamide, separately synthesized according to a reported procedure,[14] gave good yield of the carboxyl activated compound **44a** which was deprotected to give the precursor **44b**. The macrolactamization was conducted using high dilution technique: to a DMSO silver trifluorocetate solution (10^{-3} M), a DMSO solution of **44b** (2 10^{-3} M) was added with a syringe at the rate of 1 mL/hour. After the end of addition, the extraction gave an untractable mixture looking like that obtained from **43b**.

Thus, our failure to cyclize a simplified precursor devoid of protection at N_1 (disconnection b) by two macrolactamization methods which had proven to be efficient in related cases, added to Gurjar's initial observations with a more sophisticated model, definitely establish that this strategy is unappropriate for the synthesis of 17-membered ring macropolypeptide **45** containing an *endo* carbon-carbon bond.

Macrocyclisation studies

Among a number of classical biaryl cross coupling reactions which could be adapted for C-C ring closure step, we first chose the Pd^0 catalyzed Suzuki reaction although, to the best of our knowledge, there was no precedent in the field of macropolypeptides synthesis.[15] The precursor **48a** necessary to investigate the feasibility of this approach was prepared from 6-bromoindole propionic acid **38b**. Coupling with glycine methyl ester gave **46a** and base treatment gave **46b**. 3-Methanolamine phenylboronic acid **47**, separately prepared from 3-bromo-benzylamine[16] was then coupled with **46b** to give the linear peptide **48a** ready for testing macrocyclisation *via* intramolecular Suzuki reaction (Scheme 8). After consumption of the starting material, a complex mixture of products was obtained from which the only compound isolated in pure form and identified was **48b**, resulting from reduction of the two functionalized phenyl termini. No cyclized product **49** could be detected.

For effecting the desired C-C ring closure bond between indole and phenyl ring, we then attempted a Ni^0 intramolecular cross coupling reaction pioneered by Semmelhack[17] and recently used by Nicolaou[18] for achieving ring closure of the 12-membered ring of vancomycin by biphenyl coupling. The linear precursor **48c** necessary for that purpose was readily obtained by coupling **46b** with 3-bromobenzylamine. The intramolecular Ni^0 mediated reaction was then carried out under reported conditions using separately prepared Ni^0 as recommended by Kende.[19] The outcome of this reaction was encouraging since a mixture of only two products was formed. Preparative thin layer chromatography provided pure **48b** and a more polar fraction. Careful H^1 NMR spectrum examination showed that H-8 found at 7.45 ppm for the linear precursor **48c** was shifted to 6.0 ppm, strongly indicating the presence of a cyclized product. Indeed in the spectrum of the natural product H-8 is found at 5.70 ppm and in that of chloropeptin II, whose eastern part is constituted of a closely related 17-membered ring macroplypeptide, H-8 is found at 5.81 ppm. Further purification led to a pure sample (17%) of the simplified 17-membered ring macroplypeptide **49** whose structure was fully established by spectroscopic methods.



Reagents and conditions. a: NaOH, MeOH-H_2O, 94%; b: glycine methyl ester hydrochloride, NEt_3, HOBT, EDC, DMF, 77%; c: NaOH, MeOH-H_2O, 97%; d: 3-methanolamine phenylboronic acid **47**, CH_2Cl_2, 58%; e: $(AcO)_2Pd$, $Ba(OH)_2$, EtOH-DME; f: 3-bromobenzylamine hydrochloride, NEt_3, HOBT, EDC-DMF, 96%; g: $Ni(Ph_3P)_2Cl_2$, Zn, Ph_3P, DMF

Scheme 8

Conclusion

The synthesis of the first fused bicyclic (16+15) membered ring macropolypeptide containing an *endo* biaryl ether bond in each macrocycle and that of the first 17-membered ring macropolypeptide containing an *endo* carbon-carbon between the indole and the phenyl component, which are respectively simplified models of the western and eastern subunits of kistamycin represent an advanced state toward the total synthesis of the natural product.

Experimental Section

Melting points were determined with a Richter apparatus. Infrared 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 *AC*-200 (200MHz), *AC*-250 (250MHz), *AC-300* (300MHz) and Brucker WM-400 (400MHz), spectrometers with tetramethylsilane as internal standard (δ ppm), and using $CDCl_3$, CD_3OD, CD_3COCD_3 as solvents. All reactions requiring anhydrous conditions or inert atmosphere were conducted under argon.

[(3-Fluoro-4-nitro-benzylcarbamoyl)-methyl]-carbamic acid *ter*-butyl ester (4). A solution of 3-fluoro-4-nitrobenzylamine hydrochloride 3 (300 mg, 1.45 mmol) in anhydrous DMF (5 mL) was added successively with NEt3 (305 ml, 2.18 mmol, 1.5 eq), HOBT (236 mg, 1.74 mmol, 1,2 eq), EDC (280 mg, 1.45 mmol, 1.0 eq.) and glycine-NHBoc (254 mg, 1.45 mmol) and stirred for 14 h at room temperature. Quenching by H_2O (40 mL), extraction (AcOEt) and column chromatography (SiO_2, CH_2Cl_2/MeOH, 97:3), gave **4**, (412 mg, 1.26 mmol, 87 %): mp 112-115° C (CH_2Cl_2/heptane); IR (KBr) υ 1698, 1608, 1504, 1351, 1346; ^1H NMR (250 MHz, $CDCl_3$) δ 1.42 (s, 9H), 3.86 (d, 2H, *J*= 5.8 Hz), 4.51 (d, 2H, *J*= 6.2 Hz), 5.53 (bs, 1H), 7.17 (d, 1H, *J*= 7.6 Hz), 7.21 (d, 1H, *J*= 11.7 Hz), 7.35 (bs, 1H), 7.99 (t, 1H, *J*= 8.1 Hz); ^{13}C NMR δ 28.24, 42.20, 44.44, 80.70, 116.80 (d, *J*= 21.5 Hz), 123.07, 126.30, 136.02, 148.02 (d, *J*= 7.1 Hz), 155.63 (d, *J*= 263.3 Hz), 156.44, 170.36; MS (CI) *m/z* 328 $[M+H]^+$, 272 $[M-56+H]^+$, 228 $[M-Boc+H]^+$; CIHRMS *m/z* 328.1303 ($C_{14}H_{18}FN_3O_5+H^+$ requires 328.1308).

2-(3-Chloro-4-hydroxyphenyl)-*N*-[(3-fluoro-4-nitro-benzylcarbamoyl)-methyl]-acetamide (5). Compound **4**, (380 mg 1.16 mmol) dissolved in anhydrous CH_2Cl_2 (5mL) and TFA (2 mL), was set aside at 0° for 30 mn. After removal of the solvent, the solution in anhydrous CH_2Cl_2

(50 mL) was successively added with NEt_3 (490 ml, 3.48 mmol, 3.0 eq), HOBT (188 mg, 1.40 mmol, 1.2 eq), EDC (268 mg, 1.40 mmol, 1.2 eq) and 3-chloro-4-hydroxyphenylacetic acid (217 mg, 1,16 mmol). After stirring for 18 h at room temperature, quenching with NH_4Cl, extraction (AcOEt), column chromatography (SiO_2, CH_2Cl_2/MeOH 95:5), gave **5** (345 mg, 0,87 mmol, 75 %): mp 137-140°C (MeOH/ether); IR (KBr) υ 3248, 3082, 1606, 1531, 1500, 1349; ^1H NMR (300 MHz, $CDCl_3$) δ 3.46 (s, 2H), 3.87 (s, 2H), 4.45 (s, 2H), 6.78 (d, 1H, *J*= 8.3 Hz), 7.00 (dd, 1H, J_1= 2.1, J_2= 8.3 Hz), 7.21 (d, 1H, *J*= 2.1 Hz), 7.26 (d, 1H, *J*= 8.6 Hz), 7.30 (d, 1H, *J*= 12.1 Hz), 8.03 (dd, 1H, J_1= 7.9, J_2= 8.1 Hz); ^{13}C NMR δ 41.98, 42.75, 43.56, 117.33, 117.37 (d, *J*= 20.8 Hz), 121.28, 123.99 (d, *J*= 2.8 Hz), 126.97, 128.10, 129.50, 132.32, 136.50, 149.60 (d, *J*= 7.1 Hz), 153.46, 156.41 (d, *J*= 261.0 Hz), 171.75, 174.48; MS (CI) *m/z* 398, 396 $[M+H]^+$, 245, 243; CIHRMS *m/z* 396.0726/398.0712 ($C_{17}H_{15}ClFN_3O_5+H^+$ requires 396.0762/398.0739); Anal. Calcd. for $C_{17}H_{15}ClFN_3O_5$: C, 51.59; H, 3.82; N, 10.61. Found: C, 51.61; H, 4.05; N, 10.31.

4-Fluoro-3-nitrophenylacetic acid methyl ester (9b). A solution of 4-fluoro-3-nitrophenylacetonitrile **9a**[3b] (41.2 mmol) in MeOH (100 mL), added with a saturated solution of HCl in MeOH at 0° C was stirred for 4 h. Removal of solvent and column chromatography (SiO_2, heptane/AcOEt, 8:2) gave **9b** (7.5 g, 35.0 mmol, 85 %): ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 2H), 3.72 (s, 3H), 7.27 (dd, 1H, J_1 = 8.4, J_2 = 10.7 Hz), 7.55-7.61 (m, 1H), 8.01, (dd, J_1= 2.3, J_2= 6.7 Hz).

4-Fluoro-3-nitrophenylacetic acid (10). A solution of **9b** (1.68g, 7.79 mmol) in MeOH (20 mL), added with 6M aqueous solution of NaOH (2 mL) was stirred at room temperature for 2 h. Removal of solvent, neutralization with HCl 10% and extraction (AcOEt) gave compound **10** (1.53 g, 7.68 mmol, 98 %): mp 99° C (MeOH/ether); ^1H NMR (300 MHz, acetone-D_6) δ 3.72 (s, 2H), 7.33 (dd, 1H, J_1 = 8.6, J_2 = 11.2 Hz), 7.60-7.65 (m, 1H), 8.01, (dd, J_1= 2.2, J_2= 7.0 Hz); ^{13}C NMR δ 40.14, 119.14 (d, *J*= 21.2 Hz), 127.89, 133.65, 138.04 (d, *J*= 8.2 Hz), 139.04, 155.62 (d, *J*= 226.2 Hz); MS (EI) *m/z* 199 [M]. Anal. Calcd. for $C_8H_6FNO_4$: C, 48.25; H, 3.04; N, 7.03. Found: C, 48.42; H, 3.23; N, 6.95.

3-Isopropoxy-4-methoxybenzaldehyde (11b). A solution of isovaniline **11a** (3.0 g, 19.7 mmol) in anhydrous DMF (50 mL), added with K_2CO_3 (5.4 g, 39.45 mmol, 2,0 eq) and isopropylbromide (5.1 mL, 55.20 mmol, 2.8 eq) was stirred at 80° C for 3 h. Quenching with water (50 mL) extraction (AcOEt), and by column chromatography (SiO_2, heptane/AcOEt, 7:3) gave **11b** (3.4 g , 17.5 mmol, 89 %) as a colorless oil: IR ($CHCl_3$) υ 1686, Lit..[20] 1690; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (d, 6H, *J*= 6.1 Hz), 3.93 (s, 3H), 4.44 (sept, 1H, *J*= 6.1 Hz), 6.98 (d, 1H, *J*= 8.0 Hz), 7.42 (d, 1H, *J*= 1.8 Hz), 7.46 (dd, 1H, J_1 = 1.8, J_2 = 8.0 Hz); ^{13}C NMR δ 21.81, 56.03, 71.22, 110.89, 112.69, 126.38, 128.30, 149.69, 147.77, 155.55, 190.81.

3-Isopropoxy-4-methoxybenzonitrile (12). A solution of 3-isopropoxy-4-methoxybenzaldehyde **11b** (2.0 g, 10.3 mmol) in anhydrous THF (60 mL), added with NaN_3 (4.0 g, 61.80 mmol, 6.0 eq) and aluminium trichloride (2.74 g, 20.6 mmol, 2.0 eq) was stirred at reflux for 24 h. After addition of HCl 10% (50 mL), and extraction (AcOEt), column chromatography (SiO_2, heptane/AcOEt, 9:1) gave **12** (1.9 g, 9.9 mmol, 96 %): ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (d, 6H, *J*= 6.0 Hz), 3.31 (s, 3H), 4.44 (Sept, 1H, *J*= 6.0 Hz), 6.89 (d, 1H, *J*= 8.2 Hz) 6.95-7.00 (m, 2H).

3-Isopropoxy-4-methoxybenzylamine-hydrochloride (13). A solution of compound **12** (1.4g, 7.34 mmol) in anhydrous THF (20 mL) was slowly added with 14.6 mL of BH_3 in THF (14.7 mmol, 2.0 eq.) and stirred for 10 mn at 0° C, for 20 mn at room temperature and then for 3 h at 75° C. After addition of MeOH (5 mL) the volatile was evaporated *in vacuo* and the residue was treated with concentrated HCl (770 mL, 8.8 mmol, 1.2 eq). Concentration *in vacuo* and crystallisation ($MeOH/Et_2O$)

afforded pure 13 (980 mg, 4.23 mmol, 58 %): mp 240-242° C (MeOH/ether); ^{1}H NMR (300 MHz, methanol-D4) δ 1.31 (d, 6H, *J*= 6.1 Hz), 3.82 (s, 3H), 3.97 (s, 2H), 4.56 (sept, 1H, *J*= 6.1 Hz), 6.98-7.04 (m, 3H); ^{13}C NMR δ 22.58, 44.37, 56.69, 73.37, 114.03, 118.69, 123.75, 127.21, 149.05, 152.20; MS (CI, isobutene) *m/z* 199 $[M-HCl+H]^+$; Anal. Calcd. for $C_{11}H_{18}ClNO_2$: C, 57.01; H, 7.82; N, 6.04. Found: C, 56.82; H, 7.66; N, 5.94.

[2-(4-Fluoro-3-nitrophenyl)-acetylamino]-acetic acid methyl ester (14a). A solution of glycine methyl ester hydrochloride (315 mg, 2.51 mmol) in DMF (5 mL), added with NEt_3 (530 mL, 3.76 mmol, 1.5 eq), 4-fluoro-3-nitrophenylacetic acid **10** (500 mg, 2.51 mmol) and DCC (482 mg, 2.51 mmol) was stirred at room temperature for 5 h, diluted with aqueous NH_4Cl (20 mL), and extracted with AcOEt to give **14a** (636 mg, 2.35 mmol, 93 %): mp 82-84° C (CH_2Cl_2/heptane); IR ($CHCl_3$) υ 1747, 1684, 1624, 1540, 1519, 1441, 1372, 1351; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 2H), 3.71 (s, 3H), 4.00 (d, 2H, *J*= 5.4 Hz), 7.25 (dd, 1H, J_1= 8.6, J_2= 10.8 Hz), 7.39 (t, 1H, *J*= 5.4 Hz), 7.60-7.65 (m, 1H), 8.02 (dd, 1H, J_1= 2.3, J_2= 7.0 Hz), ^{13}C NMR δ 40.84, 41.13, 52.04, 118.10, 126.44, 132.20, 136.58, 137.70, 154.25, 169.99, 170.21; MS (CI, isobutene) *m/z* 271 $[M+H]^+$; CIHRMS *m/z* 271,0736 ($C_{11}H_{11}FN_2O_5+H^+$ requires 271,0730); Anal. Calcd. for $C_{11}H_{11}FN_2O_5$: C, 48.90; H, 4.11; N, 10.36. Found: C, 49.34; H, 4.57; N, 10.45.

[2-(4-Fluoro-3-nitrophenyl)-acetylamino] acetic acid (14b). A solution of compound **14a** (450 mg, 1.67 mmol) in MeOH (40 mL), added with K_2CO_3 (345 mg, 2.51 mmol, 1.5 eq), and H_2O (10 mL) was stirred at room temperature for 5 h and extracted (AcOEt) to give **14b** (405 mg, 1.58 mmol, 94 %): mp 127-129° C (MeOH/ether); ^{1}H NMR (300 MHz, acetone-D6) δ 3.75 (s, 2H), 3.97 (d, 2H, *J*= 5.8 Hz), 7.39 (dd, 1H, J_1= 8.6, J_2= 11.2 Hz), 7.73-7.78 (m, 2H), 8.10 (dd, 1H, J_1= 2.2, J_2= 7.2 Hz); ^{13}C NMR δ 41.52, 41.75, 118.96 (d, *J*= 20.1 Hz), 127.51, 134.43 (d, *J*= 4.7 Hz), 137.87 (d, *J*= 8.5 Hz), 138.43, 155.05 (d, *J*= 260.0 Hz), 171.06, 171.43; MS (CI, isobutene) *m/z* 257 $[M+H]^+$, 227; CIHRMS *m/z* 257.0568 ($C_{10}H_9FN_2O_5+H^+$ requires 257.0573).

2-(4-Fluoro-3-nitrophenyl)-N-[(3-isopropoxy-4-methoxy-benzylcarbamoyl)-methyl]-acetamide (15a). A solution of 3-isopropoxy-4-methoxybenzylamine hydrochloride **13** (96 mg, 0.41 mmol) in anhydrous DMF (10 mL), added with NEt_3 (87 mL, 0.62 mmol, 1,5 eq) and after 15 mn with **14b** (106 mg, 0.41 mmol), HOBT (67 mg, 0.50 mmol, 1.2 eq) and EDC (80 mg, 0.41 mmol) was stirred at room temperature for 4 h, and quenched by a saturated aqueous NH_4Cl solution. Extraction (AcOEt), and preparative tlc (SiO_2, CH_2Cl_2/MeOH 9:1) yielded compound 15a (144 mg, 0.33 mmol, 80 %): mp 132° C (CH_2Cl_2/heptane); IR ($CHCl_3$) υ 1677, 1601, 1542, 1513, 1503, 1353; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, 6H, *J*= 6.0 Hz), 3.58 (s, 2H), 3.79 (s, 3H), 3.91 (d, 2H, *J*= 5.0 Hz), 4.29 (d, 2H, *J*= 5.5 Hz), 4.48 (sept, 1H, *J*= 6.0 Hz), 6.72-6.77 (m, 4H), 7.16-7.20 (m, 2H), 7.48-7.54 (m, 1H), 7.96 (dd, 1H, J_1= 2.2, J_2= 7.0 Hz); ^{13}C NMR δ 22.17, 41.51, 43.42, 43.52, 56.06, 71.82, 112.07, 113.95, 118.52 (d, *J*= 20.9 Hz), 120.65, 126.76, 129.98, 131.96, 136.53 (d, *J*= 8.1 Hz), 137.07, 147.42, 150.16, 154.76 (d, *J*= 263.3 Hz), 168.46, 170.06; MS (CI, isobutene) *m/z* 434 $[M+H]^+$, 404; CIHRMS *m/z* 434.1735 ($C_{21}H_{24}FN_3O_6+H^+$ requires 434.1727).

2-(4-Fluoro-3-nitrophenyl)-N-[(3-hydroxy-4-methoxy-benzyl-carbamoyl)-methyl] acetamide (15b). BCl_3 (460 mL, 0.46 mmol, 2.0 eq) in anhydrous CH_2Cl_2 (2 mL) was slowly added to a solution of **15a** (100 mg, 0.23 mmol) in anhydrous CH_2Cl_2 (10 mL). After 1h at 0° C, MeOH (10 mL) was added and the volatile was removed *in vacuo*. Preparative tlc (SiO_2, CH_2Cl_2/MeOH, 9:1) gave **15b** (85 mg, 0.22 mmol, 95 %): mp 130° C (CH_2Cl_2/heptane); ^{1}H NMR (300 MHz, methanol-D4) δ 3.67 (s, 2H), 3.79 (s, 3H), 3.86 (s, 2H), 4.23 (s, 2H), 6.63 (dd, 1H, J_1= 1.6, J_2= 8.2 Hz), 6.69 (d, 1H, *J*= 1.6 Hz), 6.79 (d, 1H, *J*= 8.2 Hz), 7.32 (dd, 1H, J_1= 8.6, J_2= 11.0

Hz), 7.62-7.67 (m, 1H), 8.04 (dd, 1H, J_1= 2.1, J_2= 8.1 Hz); ^{13}C NMR δ 41.73, 43.60, 43.75, 56.35, 112.54, 114.95, 119.18 (d, J= 21.1 Hz), 119.74, 127.75, 132.41, 133.99, 137.86 (d, J= 8.1 Hz), 140.01, 147.51, 150.16, 155.53 (d, J= 263.0 Hz), 171.16, 173.13; MS (CI, isobutene) *m/z* 392 $[M+H]^+$, 362. Anal. Calcd. for $C_{18}H_{18}FN_3O_6$: C, 55.24; H, 4.63; N, 10.70. Found: C, 55.78; H, 5.21; N, 9.74.

4-Methoxy-18-nitro-2-oxa-9,12-diaza-tricyclo[13.2.2.1^{3,7}]-eicosa-1(18),3,5, 7(20), 15(19),16-hexaene-10,13-dione (17). A solution of **15b** (40 mg, 010 mmol) in anhydrous DMF (10 mL) added with K_2CO_3 (28 mg, 0.20 mmol, 2.0 eq) and 18-crown-6 ether (13 mg, 0.05 mmol, 0.5 eq) was stirred at room temperature for 10 h. Dilution with H_2O (10 mL), extraction (AcOEt) and preparative tlc (SiO_2, CH_2Cl_2/MeOH, 9:1) yielded **17** (33 mg, 0.086 mmol, 86 %): mp > 230° C CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (d, 2H, J= 3.9 Hz), 3.72 (t, 2H, J= 6.3 Hz), 3.97 (s, 3H), 4.10 (dd, 1H, J_1= 5.9, J_2= 16.1 Hz), 4.33 (dd, 1H, J_1= 6.7, J_2= 16.1 Hz), 5.30 (s, 1H), 6.03 (bs, 1H), 6.21.(bs, 1H), 6.70, (dd, 1H, J_1= 1.4, J_2= 8.3 Hz), 6.86 (d, 1H, J= 8.3 Hz), 7.28 (d, 1H, J= 8.4 Hz), 7.66 (dd, 1H, J_1= 2.2, J_2= 8.4 Hz), 8.10 (d, 1H, J= 2.2 Hz); ^{13}C NMR δ 39.95, 42.95, 43.08, 55.96, 111.36, 112.82, 120.11, 126.03, 127.06, 131.34, 136.07, 142.91, 146.62, 148.22, 168.67, 170.28; FABMS (thio/Li^+) *m/z* 378 $[M+Li]^+$, 313.

[1-(3-Isopropoxy-4-methoxybenzylcarbamoyl)-*(2R)*-2-phenyl-ethyl]-carbamic acid ter-butyl ester (18). A solution of **13** (690 mg, 2.98 mmol) in DMF (20 mL), added with NEt_3 (630 mL, 4.47 mmol, 1.5 eq) and after 10 mn with *(R)*-NHBoc-phenylalanine (790 mg, 2.98 mmol), EDC (572 mg, 2.98 mmol) and HOBT (483 mg, 3.57 mmol, 1.2 eq) was stirred at room temperature for 6 h. Dilution with H_2O (40 mL), extraction (ACOEt) and column chromatography (SiO_2, heptane/AcOEt, 7:3) gave compound **18** (1.02 g, 2.3 mmol, 77 %): mp 102° C (CH_2Cl_2/heptane); $[\alpha]_D$= -6° (c= 0.12, $CHCl_3$); IR ($CHCl_3$) υ 1707, 1666, 1527, 1364; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, 6H, J= 6.1 Hz), 1.33 (s, 9H), 2.94-3.09 (m, 2H), 3.77 (s, 3H), 4.15 (dd, 1H, J_1= 4.0, J_2= 14.3 Hz), 4.26 (dd, 2H, J_1= 5.5, J_2= 14.3 Hz), 4.44 (sept, 1H, J= 6.1 Hz), 5.46 (d, 1H, J= 8.3 Hz), 6.64 (bs, 1H), 6.73 (d, 2H, J= 8.1 Hz), 6.80 (bs, 1H), 7.13-7.25 (m, 5 H); ^{13}C NMR δ 21.98, 28.13, 38.74, 43.02, 55.86, 71.29, 79.74, 111.98, 115.66, 120.36, 126.61, 128.36, 129.35, 130.25, 136.77, 147.20, 149.69, 155.41, 171.28; MS (CI, isobutene) *m/z* 443 $[M+H]^+$, 387 $[M-56+H]^+$, 343 $[M-Boc+H]^+$; CIHRMS *m/z* 443.2533 ($C_{25}H_{34}N_2O_5+H^+$ requires 443.2546); Anal. Calcd. for $C_{25}H_{34}N_2O_5$: C, 67.85; H, 7.74; N, 6.33. Found: C, 67.93; H, 7.52; N, 6.41.

2-[*(2R)*-2-(4-Fluoro-3-nitrophenyl)-acetylamino]-*N*-(3-isopropoxy-4-methoxy-benzyl)-3-phenylpropionamide (19a). Trifluoroacetic acid (4 mL) was slowly added to **18** (680 mg, 1.54 mmol) in anhydrous CH_2Cl_2 (10 mL). After 30 mn at room temperature, volatiles were removed *in vacuo* and NEt_3 (430 ml, 3.08 mmol, 2.0 eq) in CH_2Cl_2 (10 mL), HOBT (250 mg, 1.85 mmol, 1.2 eq), EDC (295 mg, 1.54 mmol) and 4-fluoro-3-nitrophenylacetic acid (306 mg, 1.54 mmol) were added and the solution was stirred at room temperature for 10 h. Dilution with saturated aqueous NH_4Cl solution, extraction (ACOEt) and column chromatography (SiO_2, CH_2Cl_2/MeOH, 98:2) gave **19a** (786 mg, 1.5 mmol, 97 %): mp 160° C (CH_2Cl_2/heptane); $[\alpha]_D$= -1° (c= 0.14, $CHCl_3$); IR ($CHCl_3$) υ 1662, 1545, 1509, 1352; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, 6H, J= 6.1 Hz), 3.04 (d, 2H, J=7.6 Hz), 3.41 (d, 2H, J= 8.6 Hz), 3.78 (s, 3H), 4.10 (dd, 1H, J_1= 5.2, J_2= 14.6 Hz), 4.24 (dd, 1H, J_1= 5.9, J_2= 14.6 Hz), 4.42 (Sept, 1H, J= 6.1 Hz), 4.77 (q, 1H, J= 7.6 Hz), 6.57 (dd, 1H, J_1= 2.0, J_2= 8.2 Hz), 6.67 (d, 1H, J= 2.0 Hz), 6.70 (d, 2H, J= 8.2 Hz), 7.08-7.18 (m, 6H), 7.30-7.35 (m, 1H), 7.42 (d, 1H, J= 8.0 Hz,), 7.83 (dd, 1H, J_1= 2.2, J_2= 7.0 Hz); ^{13}C NMR δ 21.98, 38.23, 39.18, 43.02, 54.64, 55.83, 71.55, 111.98, 115.71, 118.06 (d, J= 20.7 Hz), 120.05, 126.27, 126.80, 128.31, 129.22, 129.82, 132.44, 136.15 (d, J= 8.0 Hz), 136.36, 136.80, 147.22, 149.86, 154.24 (d, J= 262.3 Hz), 169.85, 171.68; MS (EI) *m/z* 523, 493; CIHRMS *m/z* 523.2132

($C_{28}H_{30}FN_3O_6$+H^+ requires 523.2118); Anal. Calcd. for $C_{28}H_{33}FN_3O_6$: C, 64.23; H, 5.77; N, 8.02. Found: C, 64.25; H, 5.85; N, 8.04.

2-[(*2R*)-2-(4-Fluoro-3-nitrophenyl)-acetylamino]-*N*-(3-hydroxy-4-methoxy-benzyl)-3-phenylpropionamide (19b). BCl_3 (2.4 mL, 2.4 mmol, 2.0 eq) in anhydrous CH_2Cl_2 (2 mL) was slowly added to a solution of **19a** (620 mg, 1.18 mmol) in anhydrous CH_2Cl_2 (30 mL). After 1h 30 at 0° C, MeOH (20 mL) was added and the volatile was removed *in vacuo*. Column chromatography (SiO_2, CH_2Cl_2/MeOH, 95:5) gave **19b** (450 mg, 0.93 mmol, 80 %): mp 179° C (CH_2Cl_2/heptane); $[\alpha]_D$= +14° (c= 0.10, $CHCl_3$); IR ($CHCl_3$) υ 3536, 1662, 1539, 1507, 1353; ^1H NMR (300 MHz, $CDCl_3$) δ 2.89 (dd, 1H, J_1=8.6, J_2= 13.8 Hz), 3.15 (dd, 1H, J_1=5.6, J_2= 13.8 Hz), 3,62 (d, 2H, J= 5.1 Hz), 3.80 (s, 3H), 4.24 (d, 2H, J= 5.5 Hz), 4.72 (Sex, 1H, J_1= 5.6, J_2= 8.6 Hz), 6.63 (dd, 1H, J_1= 2.0, J_2= 8.2 Hz), 6.74 (d, 1H, J= 2.0 Hz), 6.83 (d, 1H, J= 8.2 Hz), 7.18 (bs, 5H), 7.34 (dd, 1H, J_1= 8.6, J_2= 11.2 Hz), 7.54-7.58 (m, 1H), 7.60-7.64 (m, 2H), 7.97 (dd, 1H, J_1= 2.2, J_2= 7.2); ^{13}C NMR δ 37.97, 40.45, 41.66, 53.88, 55.65, 112.04, 114.79, 117.87, 118.07 (d, J= 15.7 Hz), 126.04, 127.80, 129.04, 131.62, 133.78, 136.20 (d, J= 6.7 Hz), 136.83, 137.63, 142.03, 146.42 (d, J= 7.9 Hz), 155.28 (d, J= 258.5 Hz), 168.81, 170.70; MS (CI, isobutene) *m/z* 482 $[M+H]^+$; CIHRMS *m/z* 482.1751 ($C_{25}H_{24}FN_3O_6$+H]$^+$ requires 482.1727).

11-Benzyl-4-methoxy-18-nitro-2-oxa-9,12-diaza-tricyclo[13.2.2.1^{3,7}] eicosa-1(18),3,5, 7(20),15(19),16-hexaene-10,13-dione (20a) and (20b). A solution of **19b** (150 mg, 0.31 mmol) in anhydrous THF (31 mL), added with K_2CO_3 (130 mg, 0.93 mmol, 3.0 eq) and 18-crown-6 ether (27 mg, 0.010 mmol, 0.3 eq) was stirred at room temperature for 10 h. Dilution with H_2O (50 mL) and extraction (AcOEt) gave a mixture of (**20a**) and (**20b**) (**20a/20b** = 1/4, 118 mg, 0.26 mmol, 82 %). Pure compounds were obtained by preparative tlc (SiO_2, ether).

20a: mp 210-212° C (CH_2Cl_2/heptane); $[\alpha]_D$= -57° (c= 0.10, $CHCl_3$); IR ($CHCl_3$) υ 1669, 1539, 1513, 1345; ^1H NMR (300 MHz, $CDCl_3$) δ 2.87-3.03 (m, 2H, H-22), 3.33 (dd, 1H, J_1= 4.2, J_2= 16.2 Hz, H-8'), 3.55 (d, 1H, J= 13.0 Hz, H-14), 3.73 (d, 1H, J= 13.0 Hz, H-14'), 3.94 (s, 3H, H-21), 4.20-4.27 (m, 1H, H-11), 4.53 (dd, 1H, J_1= 7.9, J_2= 16.2 Hz, H-8), 5.22 (d, 1H, J= 1.7 Hz, H-20), 5.66 (dd, J_1= 4.2, J_2= 7.9 Hz, NH-9), 5.85 (d, 1H, J= 8.1 Hz, NH-12), 6.58 (dd, 1H, J_1= 1.7, J_2= 8.3 Hz, H-6), 6.83 (d, 1H, J= 8.3 Hz, H-5), 7.18 (d, 1H, J= 8.3 Hz, H-17), 7.20-7.29 (m, 5H, H aromatics), 7.58 (dd, 1H, J_1= 2.1, J_2= 8.3 Hz, H-16), 8.08 (d, 1H, J= 2,1 Hz, H-19); ^{13}C NMR δ 40.09, 41.72, 44.58, 56.75, 57.08, 112.48, 114.46, 121.44, 126.30, 127.71, 128.98, 129.36, 130.26, 132.22, 136.93, 138.09, 138.37, 145.14, 148.79, 150.12, 151.82, 173.11, 173.32; NOESY: H-19/H-14'; H-16/H-14, NH-12, H-20; NH-12/H-22, H-14, H-11, H-20; H-11/H-22, NH-9, H-17; H-22/H-17; NH-9/H-8', H-20; H-6/H-8'; MS (EI) *m/z* 461; CIHRMS *m/z* 461.1574 ($C_{25}H_{23}N_3O_6$+H]$^+$ requires 461.1586).

20b: mp 140-142° C (CH_2Cl_2/heptane); $[\alpha]_D$= -49.0° (c= 0.11, $CHCl_3$); IR ($CHCl_3$) υ 1673, 1534, 1513, 1357; ^1H NMR (300 MHz, $CDCl_3$) δ 2.88-3.02 (m, 2H, H-22), 3.42 (dd, 1H, J_1= 4.5, J_2= 16.0 Hz, H-8'), 3.53 (d, 1H, J= 12.8 Hz, H-14), 3.70 (d, 1H, J= 12.8 Hz, H-14'), 3.94 (s, 3H, H-21), 4.18-4.26 (m, 1H, H-11), 4.62 (dd, 1H, J_1= 8.3, J_2= 16.0 Hz, H-8), 5.28 (d, 1H, J= 1.5 Hz, H-20), 5.44 (dd, 1H, J_1= 4.5, J_2= 7.9 Hz, NH-9), 6.00 (d, 1H, J= 8.3 Hz, NH-12), 6.62 (dd, 1H, J_1= 1.5, J_2= 8.3 Hz, H-6), 6.82 (d, 1H, J= 8.3 Hz, H-5), 7.13 (d, 1H, J= 8.6 Hz, H-17), 7.16-7.26 (m, 5H, H aromatics), 7.63 (dd, 1H, J_1= 2.1, J_2= 8.6 Hz, H-16), 8.07 (d, 1H, J= 2.1 Hz, H-19); ^{13}C NMR δ 40.04, 41.79, 44.70, 56.85, 57.05, 113.00, 114.22, 121.56, 127.59, 127.69, 128.25, 129.35, 130.26, 132.47, 135.99, 138.12, 138.30, 145.29, 148.80, 150.72, 151.80, 173.01, 173.20; NOESY: H-19/H-14, NH-12; H-16/H-14'; NH-12/H-22, H-14, H-11, H-20; H-11/H-22, NH-9, H-17; H-22/H-17, H-14; NH-9/H-8', H-17, H-20; H-6/H-8'; MS (IE) *m/z* 461; Anal. Calcd. for $C_{25}H_{23}N_3O_6$: C, 65.06; H, 5.03; N, 9.01. Found: C, 64.34; H, 5.26; N, 8.72.

18-Amino-11-benzyl-4-methoxy-2-oxa-9,12-diaza-tricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5, 7(20),15(19),16-hexaene-10,13-dione (21a). Compound **20a** (35 mg, 0.076 mmol) in MeOH (10 mL) was hydrogenated in the presence of Pd/C (10%). Filtration through celite and evaporation gave **21a** (31.5 mg, 0.073 mmol, 96 %):.$[\alpha]_D$= -258° (c= 0.03, $CHCl_3$); IR ($CHCl_3$) υ 3403, 1669, 1622, 1517; ^1H NMR (250 MHz, $CDCl_3$) δ 2.96 (ddd, 2H, J_1= 5.9, J_2= 9.1, J_3= 13.0, Hz, H-22), 3.33 (d, 1H, J= 13.2 Hz, H-14), 3.42 (d, 1H, J= 13.2 Hz, H-14'), 3.46 (dd, 1H, J_1= 4.5, J_2= 16.0 Hz, H-8'), 3.92 (s, 3H, H-21), 4.22 (ddd, 1H, J_1= 5.9, J_2= 7.7, J_3= 9.1, Hz, H-11), 4.64 (dd, 1H, J_1= 8.3, J_2= 16.0 Hz, H-8), 5.53, (d, 1H, J= 1.9 Hz, H-20), 5.87 (d, 1H, J= 7.7 Hz, NH-12), 6.00 (dd, J_1= 4.5, J_2= 8.3 Hz, NH-9), 6.60 (dd, 1H, J_1= 1.9, J_2= 8.3 Hz, H-6), 6.63-6.67 (m, 2H, H-16, H-19), 6.80 (d, 1H, J= 8.3 Hz, H-5), 6.98 (d, 1H, J= 8.6 Hz, H-17), 7.15-7.25 (m, 5H, H aromatics); ^{13}C NMR δ 39.62, 41.35, 43.13, 44.99, 56.24, 57.00, 111.52, 111.81, 115.89, 118.77, 119.68, 125.22, 126.85, 128.53, 129.36, 130.48, 135.82, 136.85, 141.00, 142.21, 147.64, 149.13, 171.64, 172.21; MS (CI, isobutane) *m/z* 432 $[M+H]^+$; CIHRMS *m/z* 432.1914 ($C_{25}H_{25}N_3O_4+H]^+$ requires 432.1923).

18-Amino-11-benzyl-4-methoxy-2-oxa-9,12-diaza-tricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5, 7(20),15(19),16-hexaene-10,13-dione (21b). Compound **20b** (30 mg, 0.065 mmol) in MeOH (10 mL) was hydrogenated in the presence of Pd/C (10%). Filtration through celite and evaporation gave **21b** (26.6 mg, 0.06 mmol., 95 %): mp 122-125° C (CH_2Cl_2/heptane); $[\alpha]_D$= -162 ° (c= 0.15, $CHCl_3$); IR ($CHCl_3$) υ 3405, 1666, 1625, 1516; ^1H NMR (300 MHz, $CDCl_3$) δ 2.99 (ddd, 2H, J_1= 5.5, J_2= 9.4, J_3= 13.1, Hz, H-22), 3.32 (d, 1H, J= 13.0 Hz, H-14), 3,47 (d, 1H, J= 13.0 Hz, H-14'), 3.50 (dd, 1H, J_1= 4.3, J_2= 16.1 Hz, H-8'), 3.91, (s, 3H, H-21), 4.32 (ddd, 1H, J_1= 5.5, J_2= 7.8, J_3= 9.4, Hz, H-11), 4.66 (dd, 1H, J_1= 8.2, J_2= 16.1 Hz, H-8), 5.53 (d, 1H, J= 1.7 Hz, H-20), 5.99 (d, 1H, J= 7.8 Hz, NH-12), 6.20 (dd, 1H, J_1= 4.3, J_2= 7.2 Hz, NH-9), 6.43 (dd, 1H, J_1= 1.8, J_2= 8.3 Hz, H-16), 6.59 (dd, 1H, J_1= 1.9, J_2= 8.3 Hz, H-6), 6.63 (d, 1H, J= 8.3 Hz, H-17), 6.69 (d, 1H, J= 1.9 Hz, H-19), 6.79 (d, 1H, J= 8.3 Hz, H-5), 7.15-7.27 (m, 5H, H aromatics); ^{13}C NMR δ 39.68, 41.42, 45.10, 56.17, 56.61, 111.78, 116.55, 118.80, 119.54, 124.71, 126.84, 128.51, 129.33, 130.47, 135.69, 136.77, 141.70, 147.45, 149.07, 171.59, 172.07; MS (IC, isobutane) *m/z* 432 $[M+H]^+$.

11-Benzyl-18-chloro-4-methoxy-2-oxa-9,12-diaza-tricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5, 7(20),15(19),16-hexaene-10,13-dione (22a). A solution of $NaNO_2$ (9.6 mg, 0.14 mmol, 2,0 eq) in degassed concentrated HCl (1 mL) was added with **21a** (30 mg, 0.070 mmol) in degassed HOAc at 0° C. and stirring was continued for 20 mn. The reaction mixture transferred into a solution of CuCl (20.7 mg, 0.21 mmol) and $CuCl_2$ (0.21 mmol, 3.0 eq) in concentrated degassed HCl at 0° C. was stirred for 3 h at room temperature, and quenched by addition of NH_4OH in saturated aqueous NH_4Cl untill the blue color persisted. Extraction (CH_2Cl_2) gave a mixture of **22a**, and **23** which were separated by preparative tlc (SiO_2, CH_2Cl_2/MeOH, 95:5).

22a (19.2 mg, 0.042 mmol, 61%): mp 130° C (MeOH/ether); $[\alpha]_D$= -66 ° (c= 0.19, $CHCl_3$); IR ($CHCl_3$) υ 1669, 1512; ^1H NMR (300 MHz, $CDCl_3$) δ 2.96 (ddd, 2H, J_1= 5.5, J_2= 9.8 J_3= 13.0, Hz, H-22), 3.43 (dd, 1H, J_1= 4.4, J_2= 16.1 Hz, H-8'), 3.46 (d, 1H, J= 13.2 Hz, H-14), 3.62 (d, 1H, J= 13.2 Hz, H-14'), 3.94 (s, 3H, H-21), 4.19 (ddd, 1H, J_1= 5.5, J_2= 7.9, J_3= 9.8, Hz, H-11), 4.64 (dd, 1H, J_1= 8.5, J_2= 16.1 Hz, H-8), 5.28 (d, 1H, J= 1.9 Hz, H-20), 5.53 (dd, 1H, J_1= 4,4, J_2= 8.5 Hz, NH-9), 5.76 (d, 1H, J= 7.9 Hz, NH-12), 6.59 (dd, 1H, J_1= 1.6, J_2= 8.2 Hz, H-6), 6.83 (d, 1H, J= 8.2 Hz, H-5), 7.16-7.26 (m, H-16, H-17 and 5H aromatics); ^{13}C NMR δ 39.88, 41.37, 44.70, 56.52, 57.23, 111.43, 112.32, 119.90, 126.55, 127.04, 128.45, 128.66, 129.32, 129.75, 130.14, 130.81, 136.43, 136.60, 147.69, 149.54, 151.69, 171.17, 171.35; NOESY: H-19/H-14'; H-16/H-14, NH-12, H-20; NH-12/H-22, H-14, H-11, H-20; H-11/H-22, NH-9, H-17; H-22/H-17, H-14'; NH-

9/H-8', H-8, H-20; H-6/H-8'; MS (CI, isobutane) *m/z* 451 $[M+H]^+$; Anal. Calcd. for $C_{25}H_{23}ClN_2O_4$: C, 66.59; H, 5.14; N, 6.21. Found: C, 65.81; H, 5.82; N, 6.05.

11-Benzyl-4-methoxy-2-oxa-9,12-diaza-tricyclo[13.2.2.1^{3,7}]-eicosa-1(18),3,5,7(20), 15(19), 16-hexaene-10,13-dione (23) (11 mg, 0.026 mmol, 38 %): fusion: 100° C turns brown, 195° C clears, mp 202° C; $[\alpha]_D$= -100° (c= 0.11, $CHCl_3$); IR ($CHCl_3$) υ 1662, 1512, 1506; ^1H NMR (300 MHz, $CDCl_3$) δ, 2.97 (ddd, 2H, J_1= 5.5, J_2= 9.6, J_3= 13.0, Hz, H-22), 3.43-3.49 (m, 2H, H-8' et H-14), 3.63 (d, 1H, *J*= 13.2 Hz, H-14'), 3.93 (s, 3H, H-21), 4.21 (ddd, 1H, J_1= 5.5, J_2= 7.8, J_3= 9.6, Hz, H-11), 4.64 (dd, 1H, J_1= 8.2, J_2= 16.1 Hz, H-8), 5.23 (d, 1H, *J*= 1.6 Hz, H-20), 5.61 (dd, 1H, J_1= 4.3, J_2= 8.2 Hz, NH-9), 5.73 (d, 1H, *J*= 7.8 Hz, NH-12), 6.56 (dd, 1H, J_1= 1.6, J_2= 8.2 Hz, H-6), 6.79 (d, 1H, *J*= 8.2 Hz, H-5), 6.92 (dd, 1H, J_1= 2.4, J_2= 8.8 Hz, Ar-H), 7.14 (dd, 1H, J_1= 1.7, J_2= 8.1 Hz, Ar-H), 7.18 (d, 1H, *J*= 2.0 Hz, Ar-H), 7.20-7.34 (m, 6H aromatiques); ^{13}C NMR δ 39.86, 41.38, 44.99, 56.34, 57.21, 111.89, 112.64, 119.16, 125.01, 125.09, 127.01, 128.45, 128.65, 129.38, 130.08, 130.29, 134.95, 136.43, 136.76, 147.45, 149.54, 151.59, 156.13, 171.36, 171.87; FABMS (thio) *m/z* 417 $[M+H]^+$; Anal. Calcd. for $C_{25}H_{24}N_2O_4$: C, 72.09; H, 5.14; N, 6.72. Found: C, 71.57; H, 6.29; N, 6.34.

11-Benzyl-18-chloro-4-methoxy-2-oxa-9,12-diaza-tricyclo[13.2.2.1^{3,7}]eicosa-1(18),3,5, 7(20),15(19),16-hexaene-10,13-dione (22b). A solution of $NaNO_2$ (11.2 mg, 0.16 mmol, 2,0 eq) in degassed concentrated HCl (1 mL), added with a solution of **21b** (35 mg, 0.081 mmol) in degassed HOAc at 0° C was stirred for 20 mn and transferred into a solution of CuCl (24.2 mg, 0.24 mmol) and $CuCl_2$ (33 mg, 0.24 mmol, 3.0 eq) in concentrated degassed HCl at 0° C. After stirring for 3 h at room temperature and quenching by NH_4OH saturated aqueous solution untill the blue color persisted. Extraction with CH_2Cl_2 and preparative tlc (SiO_2, CH_2Cl_2/MeOH, 95:5) gave a mixture of **22b** and **23**.

22b (18.0 mg, 0.040 mmol, 50%): mp 112-114° C (CH_2Cl_2/heptane); $[\alpha]_D$= -248 ° (c= 0.06, $CHCl_3$); IR ($CHCl_3$) υ 1662, 1581, 1518; ^1H NMR (250 MHz, $CDCl_3$) δ 2.88-3.02 (m, 2H, H-22), 3.40 (d, 1H, *J*= 12.9 Hz, H-14), 3.45 (dd, 1H, J_1= 4.5, J_2= 16.0 Hz, H-8'), 3.59 (d, 1H, *J*= 12.9 Hz, H-14'), 3.93 (s, 3H, H-21), 4.18-4.28 (m, 1H, H-11), 4.68 (dd, 1H, J_1= 8.3, J_2= 16.0 Hz, H-8), 5.28 (d, 1H, *J*= 1.6 Hz, H-20), 5.69 (dd, 1H, J_1= 4.4, J_2= 8.3 Hz, NH-9), 5.88 (d, 1H, *J*= 8.0 Hz, NH-12), 6.60 (dd, 1H, J_1= 1.6, J_2= 8.2 Hz, H-6), 6.82 (d, 1H, *J*= 8.2 Hz, H-5), 6.94 (d, 1H, *J*= 8.4 Hz, H-17), 7.16 (dd, 1H, J_1= 2.1, J_2= 8.4 Hz, H-16), 7.18-7.28 (m, 5H, H aromatics), 7.43 (d, 1H, *J*= 2.1 Hz, H-19); ^{13}C NMR δ, 39.93, 41.47, 44.80, 56.49, 57.04, 111.88, 112.31, 119.92, 126.23, 127.03, 128.46, 128.64, 129.32, 130.03, 130.39, 130.82, 136.27, 136.59, 147.55, 149.50, 151.83, 171.17, 171.29; NOESY: H-19/H-14, NH-12; H-16/H-14', H-20; NH-12/H-22, H-14, H-11, H-20; H-11/H-22, NH-9, H-17; H-22/H-17, H-14; NH-9/H-8', H-17, H-20; H-6/H-8'; MS (CI) *m/z* 451 $[M+H]^+$; CIHRMS *m/z* 451.1401/453.1357 ($C_{25}H_{23}ClN_2O_4+H^+$ requires 451.1424/453.1394).

23 (14.5 mg, 0.034 mmol, 43 %): fusion: 100° C turns brown, 190° C clears, mp 201° C; $[\alpha]_D$= -87° (c= 0.14, $CHCl_3$); IR ($CHCl_3$) υ 1662, 1512, 1506; ^1H NMR (300 MHz, $CDCl_3$) δ 2.98 (ddd, 2H, J_1= 5.5, J_2= 9.6, J_3= 13.2, Hz, H-22); 3.42-3.50 (m, 2H, H-8' et H-14), 3.64 (d, 1H, *J*= 13.2 Hz, H-14'), 3.93 (s, 3H, H-21), 4.21 (ddd, 1H, J_1= 5.5, J_2= 7.8, J_3= 9.6, Hz, H-11), 4.64 (dd, 1H, J_1= 8.3, J_2= 16.1 Hz, H-8), 5.23 (d, 1H, *J*= 1.8 Hz, H-20), 5.64 (dd, 1H, J_1= 4.4, J_2= 8.3 Hz, NH-9), 5.75 (d, 1H, *J*= 7.8 Hz, NH-12), 6.55 (dd, 1H, J_1= 1.8, J_2= 8.2 Hz, H-6), 6.79 (d, 1H, *J*= 8.2 Hz, H-5), 6.92 (dd, 1H, J_1= 2.4, J_2= 8.8 Hz, Ar-H), 7.14 (dd, 1H, J_1= 2.0, J_2= 8.6 Hz, Ar-H), 7.18 (d, 1H, *J*= 2.0 Hz, Ar-H), 7.20-7.35 (m, 6H, H aromatics); ^{13}C NMR δ 39.86, 41.38, 44.99, 56.34, 57.21, 111.89, 112.64, 119.16, 125.01, 125.09, 127.01, 128.45, 128.65, 129.38, 130.08, 130.29, 134.95, 136.43, 136.76, 147.45, 149.54, 151.59, 156.13, 171.36, 171.87; FABMS (thio) *m/z* 417 $[M+H]^+$.

***(3S)*-3-(4-Fluoro-3-nitrophenyl)-2-{*(2R)*-2-(4-hydroxy-phenyl)-2-[2-(3-hydroxy-phenyl)-acetylamino]-acetylamino}-propionic acid methyl ester (26).** Compound **25** (460 mg 0.936 mmol) dissolved in anhydrous CH_2Cl_2 (10 mL) and TFA (2 mL) was set aside at 0° for 30 mn. The solvent was removed *in vacuo*. NEt_3 (200 ml, 1.42 mmol, 1.5 eq) in anhydrous CH_2Cl_2 (10 mL) was added. After 10 mn at 0° C, the solvent was removed and the resulting solid was dissolved in CH_2Cl_2 (10 mL). 3-Hydroxyphenylacetic acid (142 mg, 0.94 mmol, 1.0 eq), HOBT (190 mg, 1.4 mmol, 1.5 eq) and EDC (180 mg, 0.94 mmol, 1.0 eq) were successively added. After stirring for 5 h at room temperature, quenching (NH_4Cl) and extraction (AcOEt) column chromatography (SiO_2, CH_2Cl_2/MeOH, 99:1) gave **26** (440 mg, 0.84 mmol 89 %): $[\alpha]_D$= - 77° (c = 0.16, MeOH); IR (KBr) υ 3346, 1734, 1651, 1543, 1511, 1448, 1352; ^1H NMR (250 MHz, acetone-D_6) δ 2.98 (dd, 1H, J_1=8.4, J_2= 14.0 Hz), 3.19 (dd, 1H, J_1= 4.9, J_2= 14.0 Hz), 3.48 (s, 2H), 3.67 (s, 3H), 4.78 (ddd, 1H, J_1= 4.9, J_2= 8.4 Hz), 5.39 (d, 1H, J= 7.4 Hz), 6.69 (d, 2H, J= 8.6 Hz, in a m, 3H), 6.81 (d, 1H, J=1.8 Hz), 7.08 (d, 2H, J= 8.6 Hz, in a m, 1H), 7.27-7.31 (m, 1H), 7.59 (d, 1H, J= 7.4 Hz), 7.80 (d, 1H, J= 8.4 Hz), 7.87 (dd, 1H, J_1= 2.2, J_2= 7.2 Hz); ^{13}C NMR δ 36.01, 42.58, 51.85, 52.89, 56.41, 113.75, 115.21, 116.35, 117.98 (d, J= 20.6 Hz), 120.44, 126.53, 128.60, 128.83, 129.40, 134.43, 135.64 (d J= 8.4 Hz), 137.42, 154.07 (d, J= 259.5 Hz), 157.24, 157.52, 170.07 , 170.49, 171.10; m p 92° C (CH_2Cl_2/heptane); MS (CI, isobutane) *m/z* 526 $[M+H]^+$; CIHRMS *m/z* 526.1628 ($C_{26}H_{24}FN_3O_8$+H^+ requires 526.1626).

11-(4-hydroxyphenyl)-18-nitro-9,12-dioxo-2-oxa-10,13-diaza-tricyclo-[14.2.2.1^{3,7}]-heneicosa-1(19),3(21),4,6(20),17-hexaene-*(14S)*-14-carboxylic acid methyl ester (27a and 27b). A solution of **26** (126 mg, 0.24 mmol) in anhydrous DMF (24 mL), added with $KHCO_3$ (72 mg, 0.72 mmol, 3.0 eq) and 18-crown-6 ether (19 mg, 0.076 mmol, 0.3 eq) was stirred at room temperature for 10 h and diluted with H_2O (50 mL). Extraction (AcOEt) gave a mixture of **27a,b** (**27a/27b**=1.7) and **28a,b** (**28a/28b**= 1.3) and column chromatography (SiO_2, AcOEt/Heptane 1:1) led to pure samples of **27a**, **27b**, **28b** and **28a** (19 mg, 0.037 mmol, 15 %) containing 40% of **27b**.

27a (44 mg, 0.087 mmol, 36%): mp 144-146° C (CH_2Cl_2/heptane); $[\alpha]_D$= -144° (c= 0.31, MeOH); IR (KBr) υ 3346, 1743, 1651, 1539, 1440, 1342; ^1H NMR (300 MHz, Acetone-D_6) δ 2.93 (dd, 1H, J_1=6.8, J_2= 13.8 Hz, H-15), 3.17 (d, 1H, J= 13.7 Hz, H-8), 3.63 (dd, 1H, J_1=2.7, J_2= 13.8 Hz, H-15'), 3.64 (s, 3H, H-29), 3.76 (d, 1H, J= 13.7 Hz, H-8'), 4.30 (ddd, 1H, J_1= 2.7, J_2= 6.8, Hz, H-14), 5.35 (d, 1H. J= 8.4 Hz, H-11), 6.48 (bs, 1H, H-21), 6.79 (d, 2H, J= 8.5 Hz, H-24 et H-26), 6.92 (d, 1H, J= 4.7 Hz, H-6), 6.96 (d, 1H, J= 8.4 Hz, H-19), 7.09 (dd, 1H, J_1=2.4, J_2= 8.2 Hz, H-4), 7.13 (d, 2H, J= 8.5 Hz, H-23 et H-27), 7.30 (t, 1H, J= 7.9 Hz, H-5), 7.47 (dd, 1H, J_1=2.0, J_2= 8.4 Hz, H-20), 7.51 (d, 1H, J= 8.4 Hz, NH-10), 7.76 (d, 1H, J= 6.8 Hz, NH-13), 8.25 (d, 1H, J= 2.0 Hz, H-17), 8.42 (bs, 1H, OH); NOESY: H-21/H-8'NH-10; H-17/H-15'; H-20/H-15; H-14/H-15, H-15', NH-13; H-8/H-11, H-6; H-8'/NH-10; H-11/ H-20; ^{13}C NMR δ 36.21, 43.49, 52.21, 53.98, 56.01, 115.53, 116.10, 116.89, 124.68, 124.74, 128.96, 129.87, 130.65, 131.11, 136.12, 137.54, 139.75, 143.57, 149.22, 158.07, 160.83, 169.68, 170.44, 171.47; FABMS (thio) *m/z* 506 $[M+H]^+$.

27b (18 mg, 0.035 mmol, 15 %): mp 160-162° C (CH_2Cl_2/heptane); $[\alpha]_D$= -24° (c= 0.40, MeOH); IR (KBr) υ 3346, 1743, 1651, 1532, 1433, 1342; ^1H NMR (300 MHz, acetone-D_6) δ 3.10 (dd, 1H, J_1=6.9, J_2= 13.8 Hz, H-15), 3.26 (d, 1H, J= 14.7 Hz, H-8), 3.49 (dd, 1H, J_1=5.1, J_2= 13.8 Hz, H-15'), 3.61 (s, 3H, H-29), 3.68 (d, 1H, J= 14.7 Hz, H-8'), 4.40 (q, 1H, J= 6.9 Hz, H-14), 5.44 (d, 1H, J= 8.5 Hz, H-11), 6.34 (bs, 1H, H-21), 6.77 (d, 2H, J= 8.5 Hz, H-24 et H-26), 6.87 (d, 1H, J= 7.7 Hz, H-6), 7.08 (dd, 1H, J_1=2.3, J_2= 8.2 Hz, H-4), 7.13 (d, 1H, J= 8.3 Hz, H-19), 7.16 (d, 2H, J= 8.5 Hz, H-23 et H-27), 7.27 (d, 1H, J= 7.7 Hz, H-5), 7.34 (t, 1H, J= 8.5 Hz, NH-10), 7.65 (d, 1H, J= 6.8 Hz, NH-13), 7.80 (dd, 1H, J_1=2.0, J_2= 8.3 Hz, H-20), 7.91 (d, 1H, J= 2.0 Hz, H-17), 8.45 (bs, 1H, OH); NOESY: H-21/NH-10; H-17/H-15; H-20/H-15'; H-14/H-15', H-15, NH-13; H-8/H-6; H-8'/NH-10; H-11/NH-10, NH-13, H-19; ^{13}C NMR δ 35.82, 42.98, 51.77,

53.42, 55.89, 113.41, 115.66, 116.26, 124.02, 125.07, 127.72, 129.34, 129.76, 130.12, 136.08, 138.40, 138.80, 142.36, 148.13, 157.52, 160.07, 168.95, 169.92, 171.02; FABMS (thio) *m/z* 506 $[M+H]^+$; Anal. Calcd. for $C_{26}H_{23}N_3O_8$: C, 61.78; H, 4.58; N, 8.31. Found: C, 61.23; H, 4.75; N, 8.51.

28b (8 mg, 0.016 mmol, 7 %): ^1H NMR (300 MHz, acetone-D_6 + MeOD) δ 2.88 (t, 1H, *J*= 13.1 Hz, H-15), 3.27 (d, 1H, J= 14.6 Hz, H-8), 3.54 (dd, 1H, J_1=4.6, J_2= 13.1 Hz, H-15'), 3.70 (s, 3H, H-29), 3.87 (d, 1H, *J*= 14.6, Hz, H-8'), 5.16 (dd, 1H, J_1=4.6, J_2= 13.1 Hz, H-14), 5.46 (bs, 1H, H-11), 6.08 (bs, 1H, H-21), 6.72 (d, 2H, *J*= 8.6 Hz, H-24 et H-26), 6.90 (d, 1H, *J*= 7.3 Hz, H-6), 7.07 (dd, 1H, J_1=2.3, J_2= 8.1 Hz, H-4), 7.16 (d, 1H, *J*= 8.3 Hz, H-19), 7.18 (d, 2H, *J*= 8.6 Hz, H-23 et H-27), 7.30 (d, 1H, *J*= 7.8 Hz, H-5), 7.81 (dd, 1H, J_1=2.0, J_2= 8.3 Hz, H-20), 7.91 (d, 1H, *J*= 2.0 Hz, H-17); ^{13}C NMR δ 37.80, 43.11, 52.60, 52.85, 55.84, 112.34, 116.19, 116.40, 124.47, 126.59, 128.80, 129.01, 130.59, 130.77, 136.79, 136.99, 139.89, 142.81, 148.02, 158.00, 160.43, 169.31, 170.88, 171.86.

***(11R)*-11-(4-hydroxyphenyl)-9,12-dioxo-2-oxa-10,13-diaza-tricyclo-[14.2.2.1^{3,7}]-heneicosa-1(19),3(21),4,6(20),17-hexaene-*(14S)*-14-carboxylic acid methyl ester (30)**. Compound **27b** (30 mg, 0.06 mmol) in MeOH (3 mL), was hydrogenated in the presence of Pd/C (5 %). After filtration through celite, and evaporation, the residue dissolved in anhydrous DMF was added dropwise *via* syringe to a stirred solution of t-BuONO (40 ml, 0,30 mmol, 5,0 eq) in anhydrous and degased DMF (1 mL) heated to 65° C. After stirrring for 15 mn, cooling to room temperature and dilution with Et_2O. the resulting solution was poured into 20% aqueous HCl and extracted (AcOEt). Preparative tlc (SiO_2, AcOEt/heptane, 1:1) gave **30** (10.5 mg, 0.023 mmol, 38 %): mp 159-160° C ($CHCl_3$/heptane); $[\alpha]_D$= - 46 ° (c= 0.22, MeOH); IR (KBr) υ 3416, 1747, 1663, 1508, 1448, 1347; ^1H NMR (300 MHz, acetone-D_6) δ 3.03 (dd, 1H, J_1=6.9, J_2= 13.9 Hz), 3.21 (d, 1H, *J*= 14.1 Hz), 3.37 (dd, 1H, J_1=5.2, J_2= 13.9 Hz), 3.61 (d, 1H, *J*= 14.1 Hz), 3.65 (s, 3H), 4.42 (ddd, 1H, J_1= 5.2, J_2= 6.9 Hz), 5.39 (d, 1H, *J*= 8.4 Hz), 6.25 (bs, 1H), 6.76 (d, 2H, *J*= 8.5 Hz in m, 1H), 6.81 (dd, 1H, J_1=2.2, J_2= 8.3 Hz), 6.93 (dd, 1H, J_1=2.4, J_2= 8.1 Hz), 7.01 (dd, 1H, J_1=2.4, J_2= 8.1 Hz), 7.16 (d, 2H, *J*= 8.5 Hz), 7.21 (dd, 1H, J_1=2.2, J_2= 8.3 Hz, Ar-H), 7.24 (t, 1H, *J*= 7.9 Hz), 7.37 (d, 1H, *J*= 6.9 Hz), 7.43 (dd, 1H, J_1=2.2, J_2= 8.3 Hz), 7.48 (d, 1H, *J*= 8.4 Hz), 8.41 (bs, 1H, OH); ^{13}C NMR δ 36.62, 43.76, 52.33, 54.16, 56.89, 115.80, 116.16, 116.43, 122.58, 122.71, 123.59, 129.82, 130.43, 130.93, 132.66, 133.41, 134.56, 139.18, 156.35, 158.06, 162.34, 170.01, 170.27, 172.12; FABMS (thio) *m/z* 461 $[M+H]^+$.

The same experiment carried out on **27a** (157 mg, 0.31 mmol), gave 30 (55 mg, 0.12 mmol, 40%): mp 161-162° C ($CHCl_3$/heptane); FABMS (thio) *m/z* 461 $[M+H]^+$; $[\alpha]_D$= -38° (c= 0.34, MeOH).

***(11R)*-11-(4-Hydroxy-phenyl)-9,12-dioxo-2-oxa-10,13-diaza-tricyclo-[14.2.2.1^{3,7}]-heneicosa-1(19),3(21),4,6,16(20),17-hexaene-*(14S)*-14-carboxylic-3-fluoro-4-nitro-benzylamine (34)**. An aqueous 0.4 M solution of LiOH (1 mL, 4.0 eq) was added to compound **30** (45 mg, 0.097 mmol) disssolved in THF/MeOH (1:2) (4 mL) and stirred for 8 h, after removal of solvent anhydrous DMF (1 mL), HOBT (20 mg, 0.14 mmol, 1.5 eq), EDC (18.5 mg, 0.097 mmol, 1 eq) give a solution whichwas added to a solution in anhydrous DMF (1 mL) of 3-fluoro-4-nitro-benzylamine hydrochlorhyde[20] (20 mg , 0.096 mmol, 1 eq) and NEt_3 (20 ml). Hydrolysis and extraction (ACOEt) afforded a crude mixture and preparative tlc (SiO_2, AcOEt/heptane, 3:1) gave **34** (57 mg, 0.095mmol, 98%): mp 228° C (acetone/ether); $[\alpha]_D$= -52 ° (c= 0.1, MeOH); ^1H NMR (300 MHz, acetone-D_6) δ 3.05, (dd, 1H, J_1=9.8, J_2= 13.9 Hz, H-15), 3.34 (d, 1H, *J*= 15.1 Hz, H-8), 3.37 (dd, 1H, J_1=5.7, J_2= 13.9 Hz, H-15'), 3.55 (d, 1H, *J*= 14.2 Hz, H-8'), 4.51 (dd, 1H, J_1=6.1, J_2= 11.0 Hz, H-30), 4.76 (ddd, 1H, J_1=5.7, J_2= 9.8 Hz, H-14), 5.45 (d, 1H, *J*= 8.7 Hz, H-11), 6.24 (d, 1H, *J*= 1.7 Hz, H-21), 6.72 (d, 2H, *J*= 8.7 Hz, H-24 et H-26), 6.81 (d ,1H, *J*= 7.5 Hz, H-6), 6.93 (d,

1H, *J*= 7.6 Hz, NH-13), 6.94-7.01 (m, 2 H aromatics), 7.05 (dd, 1H, J_1=2.3, J_2= 8.0 Hz, H-4), 7.16 (d, 2H, *J*= 8.7 Hz, H-23 et H-27), 7.19 (d, 1H, *J*= 1.6 Hz, H-32), 7.24 (d ,1H, *J*= 8.0 Hz, H-36), 7.28-7.36 (m, 3H, H aromatics), 7.45 (d, 1H, *J*= 8.7 Hz, NH-10), 7.96 (d, 1H, *J*= 6.1 Hz, NH-29), 8.01 (t, 1H, *J*= 8.0 Hz, H-35), 8.43 (bs, 1H, OH); ^{13}C NMR δ 37.34, 43.27, 43.54, 55.58, 58.60, 115.53, 116.54, 117.82 (d, *J*=21.5 Hz), 123.64, 123.94, 124.03, 124.34, 127.35, 129.31, 129.82, 130.27, 130.80, 131.74, 133.25, 134.82, 138.23, 149.45 (d, *J*=7.5 Hz), 156.68, 158.77, 161.21 (d, *J*=169.2 Hz), 163.19, 172.43, 173.15, 173.76; FABMS (thio) *m/z* 599 $[M+H]^+$; Anal. Calcd. for $C_{32}H_{27}FN_4O_7$: C, 64.21; H, 4.55; N, 9.36. Found: C, 61.55; H, 5.12; N, 8.16.

Bicyclic compound (35). A solution of **34** (11 mg, 0.018 mmol) in anhydrous DMF (1.8 mL), added with $KHCO_3$ (9.2 mg, 0.092 mmol, 5.0 eq) and 18-crown-6 ether (14.5 mg, 0.056 mmol, 3.0 eq) was stirred at room temperature for 4 h and diluted with H_2O (20 mL). Extraction (AcOEt), and preparative tlc (SiO_2, AcOEt/heptane, 3:1) gave **35** (8.5 mg, 0.014 mmol, 80%): mp > 300° C (MeOH/ether); ^{1}H NMR (300 MHz, acetone-D_6) δ 2.99 (d, 1H, *J*= 11.6 Hz, H-15/C_2), 3.04 (d, 1H, *J*= 11.6 Hz, H-15/C_1), 3.21, (d, 1H, *J*=12.7 Hz, H-8/C_2), 3.27 (d, 1H, *J*= 14.8 Hz, H-8/C_1), 3.29 (dd, 1H, J_1=3.0, J_2= 11.6 Hz, H-15'/C_2), 3.39 (dd, 1H, J_1=3.2, J_2= 11.6 Hz, H-15'/C_1), 3.65 (d, 1H, *J*= 12.7 Hz, H-8'/C_2), 3.87 (d, 1H, *J*= 14.8 Hz, H-8'/C_1), 4.13-4.20 (m, 2H, H-30/C_2), 4.38-4.45 (m, 1H, H-14/C_2), 4.71-4.74 (m, 2H, H-30/C_1), 4.92-5.02 (m, 1H, H-14/C_1), 5.25 (bs, 1H, H-32/C_2), 5.51 (bs, 1H, H-32/C_1), 5.82 (d, 2H, *J*= 10.0 Hz, H-11/C_2 and C_1), 5.92 (bs, 1H, H-21/C_2), 6.02 (bs, 1H, H-21/C_1), 6.82 (d, 2H, *J*= 7.0 Hz, H aromatics), 6.89 (dd, 2H, J_1=2.7, J_2= 8.3 Hz, H aromatics), 6.97-7.30 (m, 16H), 7.42 (dd, 1H, J_1=2.3, J_2= 8.3 Hz, H aromatic/C_2), 7.47 (dd, 1H, J_1=2.3, J_2= 8.6 Hz, H aromatic/C_1), 7.66 (dd, 1H, J_1=2.3, J_2= 8.4 Hz, H aromatic/C_2), 7.73 (bs, 1H, NH), 7.75 (bs, 1H, NH), 7.88 (dd, 1H, J_1=2.3, J_2= 8.8 Hz, H aromatic/C_1), 7.92 (d, 1H, *J*= 8.3 Hz, H aromatic/C_2), 7.97 (d, 1H, *J*= 8.3 Hz, H aromatics/C_1), 8.25 (bs ,1H, NH), 9.15 (bs, 1H, NH); FABMS (thio+Na) *m/z* 601 $[M+Na]^+$, 579 $[M+H]^+$.

3-(6-Bromo-3H-indol-3-yl)-acrylic acid methyl ester (37). 6-Bromoindole-3-carboxaldehyde **36**[21] (1.35 g, 6.03 mmol), monoethylmalonate (1.2 g, 9.04 mmol), dry pyridine (50 mL) and dry piperidine (3 drops) were heated on a oil-bath at 50° C for 24 h. Evaporation of the volatile, dilution with water (50 mL), extraction (AcOEt) and flash chromatography (SiO_2, CH_2Cl_2/heptane, 10:1) gave **37** (1.72 g, 5.85 mmol): mp 147-149° C (acetone/ether); 97%. IR ($CHCl_3$) υ 1696, 1631, 1527, 1451, 1408, 1370, 1337; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, 3H, *J*= 7.1 Hz), 4.28 (q, 2H, *J*= 7.1 Hz), 6.41 (d, 1H, *J*= 16.0 Hz), 7.33 (dd, 1H, J_1= 1.6, J_2= 8.6 Hz), 7.44 (d, 1H, *J*= 2.3 Hz), 7.56 (d, 1H, *J*= 1.6 Hz), 7.74 (d, 1H, *J*= 8.6 Hz), 7.86 (d, 1H, *J*= 16.0 Hz), 8.82 (bs, 1H); ^{13}C NMR δ 14.52, 60.48, 113.61, 114.02, 114.96, 116.82, 121.63, 124.32, 124.74, 129.37, 137.89, 138.04, 168.48; MS (EI) *m/z* 295, 293.

3-(6-Bromo-3H-indol-3-yl)-propionic acid methyl ester (38a). To an ice cooled solution of **37** (1.72 g, 5.85 mmol) in 95% ethanol (50 mL) were added $BiCl_3$ (776 ml, 11.67mmol) and portionwise $NaBH_4$ (890 mg, 23.41mmol). After stirrring for 24 h at 0°C, filtration and evaporation, the residue was partitioned between AcOEt/H_2O. The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography (SiO_2, CH_2Cl_2/heptane 10:1) gave **38a** (1.3 g, 4.40 mmol, 75%): mp 96-97° C (CH_2Cl_2/heptane); IR ($CHCl_3$) υ 1729, 1617, 1456, 1376, 1328; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (t, 3H, *J*= 7.2 Hz), 2.60 (t, 2H, *J*= 7.6 Hz), 2.97 (t, 2H, *J*= 7.6 Hz), 4.04 (q, 2H, *J*= 7.2 Hz), 6.85 (d, 1H, *J*= 2.2 Hz), 7.12 (dd, 1H, J_1= 1.6, J_2= 8.3 Hz), 7.33 (d, 1H, *J*= 8.3 Hz), 7.36 (d, 1H, *J*= 1.6 Hz), 8.03 (bs, 1H); ^{13}C NMR δ 14.28, 20.55, 34.99, 60.56, 114.14, 115.22, 115.62, 120.02, 122.15, 122.62, 126.21, 137.13, 173.45; MS (EI) *m/z* 297, 295.

3-(6-Bromo-3H-indol-3-yl)-propionic acid (38b). Compound **38a** (200 mg, 0.68 mmol) in MeOH (10 mL), was treated at room temperature for 4 h, an aqueous solution of NaOH (40 mg, 1.01 mmol). Acid-base extraction gave **38b** (171 mg, 0.64 mmol, 94 %): mp 115-116° C (MeOH/ether); IR ($CHCl_3$) υ 3481, 1712, 1456, 1331; ^1H NMR (300 MHz, acetone-D_6) δ 2.69 (t, 2H, *J*= 7.7 Hz), 3.04 (t, 2H, *J*= 7.7 Hz), 7.15 (dd, 1H, J_1= 1.7, J_2= 8.4 Hz), 7.19 (d, 1H, *J*= 2.3 Hz), 7.53 (d, 1H, *J*= 8.4 Hz), 7.58 (d, 1H, *J*= 1.7 Hz), 10.14 (bs, 1H); ^{13}C NMR δ 21.03, 35.10, 114.49, 115.30, 115.35, 120.77, 122.48, 123.89, 127.19, 138.33, 175.53; MS (EI) *m/z* 269, 267.

3-[6-(5-Formyl-2,3-dimethoxyphenyl)-3H-indol-3-yl]-propionic acid ethyl ester (40). A solution of **38a** (660 mg, 2.23 mmol) in carefully degassed EtOH/DME (1/1, 40 mL), was introduced *via* a syringe in a two-necked round bottomed flask containing Na_2CO_3 (710 mg, 6.69 mmol, 3 eq), $Pd(PPh_3)_4$ (10 mg, 0.044 mmol, 0.02 eq) and 5-formyl-2,3-dimethoxyphenylboronic acid[6] **39** (1.4 g, 6.69 mmol, 3 eq). After stirring at reflux for 24 h., filtration over celite and column chromatography purification (SiO_2, ether/heptane, 1:4) gave **40** (600 mg, 1.57 mmol, 71 %): mp 99-100° C (CH_2Cl_2/heptane); IR ($CHCl_3$) υ 1725, 1693, 1581, 1462, 1456, 1387; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, 3H, *J*= 7.2 Hz), 2.74 (t, 2H, *J*= 7.7 Hz), 3.14 (t, 2H, *J*= 7.7 Hz), 3.65 (s, 3H), 3.98 (s, 3H), 4.15 (q, 2H, *J*= 7.2 Hz), 7.08 (d, 1H, *J*= 1.6 Hz), 7.31 (dd, 1H, J_1= 1.2, J_2= 8.2 Hz), 7.43 (d, 1H, *J*= 1.6 Hz), 7.54 (d, 1H, *J*= 1.8 Hz), 7.57 (bs, 1H), 7.67 (d, 1H, *J*= 8.2 Hz), 8.09 (bs, 1H), 9.93 (s, 1H); ^{13}C NMR δ 14.28, 20.71, 35.08, 56.15, 60.49, 60.79, 108.89, 112.01, 114.97, 118.62, 120.77, 122.56, 126.86, 128.14, 130.80, 132.38, 136.41, 137.11, 152.15, 153.85, 173.50, 179.32, 191.57; MS (EI) *m/z*: 381 [M]; Anal. Calcd. for $C_{22}H_{23}NO_5$: C, 69.27; H, 6.07; N, 3.67. Found: C, 69.38, H, 5.87, N, 3.45.

3-[6-(5-Hydroxy-methyl-2,3-dimethoxyphenyl)-3H-indol-3-yl]-propionic acid ethyl ester (41a). To compound **40** (620 mg, 1.36 mmol) in MeOH (5 mL), was added $NaBH_4$ (56 mg, 1.49 mmol, 1.1 eq). After stirring for 15 mn, acidification and extraction (AcOEt) gave **41a** (492 mg, 1.28 mmol, 94 %): mp 114-116° C (CH_2Cl_2/heptane); IR ($CHCl_3$) υ 3478, 1727, 1586, 1454, 1424, 1375, 1339; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3H, *J*= 7.2 Hz), 2.75 (t, 2H, *J*= 7.3 Hz), 3.12 (t, 2H, *J*= 7.3 Hz), 3.53 (s, 3H), 3.93 (s, 3H), 4.14 (q, 2H, *J*= 7.2 Hz), 4.68 (s, 2H), 6.95 (d, 1H, *J*= 1.8 Hz), 6.99 (d, 1H, *J*= 1.8 Hz), 7.03 (d, 1H, *J*= 2.2 Hz), 7.30 (dd, 1H, J_1= 1.4, J_2= 8.2 Hz), 7.56 (bs, 1H), 7.63 (d, 1H, *J*= 8.2 Hz), 8.14 (bs, 1H); ^{13}C NMR δ 14.25, 20.73, 35.11, 55.97, 60.49, 60.55, 65.16, 109.59, 112.08, 114.55, 118.22, 120.80, 122.35, 126.41, 131.71, 136.44, 136.69, 136.93, 145.75, 153.09; MS (EI) *m/z* 383 [M]; Anal. Calcd. for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.36, H, 6.61, N, 3.57.

3-[6-(5-Azido-methyl-2,3-dimethoxyphenyl)-3H-indol-3-yl]-propionic acid ethyl ester (41b). A mixture of 41a (210 mg, 0.55 mmol) and DPPA (146 ml, 0.82 mmol, 1.5 eq) in toluene (560 ml) and DBU (123 ml) was kept for 2 h at 0° C, and extracted (AcOEt). Column chromatography (SiO_2, ether/heptane, 1:1) gave **41b** (191 mg, 0.47 mmol, 85 %): mp 118° C ($CHCl_3$/heptane); IR ($CHCl_3$) υ 2104, 1723, 1584, 1486, 1455, 1424, 1352; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3H, *J*= 7.1 Hz), 2.73 (t, 2H, *J*= 7.7 Hz), 3.13 (t, 2H, *J*= 7.7 Hz), 3.55 (s, 3H), 3.93 (s, 3H), 4.14 (q, 2H, *J*= 7.1 Hz), 4.33 (s, 2H), 6.85 (d, 1H, *J*= 1.8 Hz), 6.95 (d, 1H, *J*= 1.8 Hz), 7.05 (d, 1H, *J*= 2.2 Hz), 7.30 (dd, 1H, J_1= 1.4, J_2= 8.2 Hz), 7.57 (bs, 1H), 7.63 (d, 1H, *J*= 8.2 Hz), 8.10 (bs, 1H); ^{13}C NMR δ 14.35, 20.79, 35.17, 55.03, 56.18, 60.49, 60.67, 110.74, 112.07, 115.08, 118.47, 121.05, 122.27, 123.14, 126.66, 131.21, 131.72, 136.43, 137.06, 146.67, 153.48, 173.54; MS (EI) *m/z* 408 [M].

3-(6-{5-[(2-*tert*-Butoxycarbonylamino-acetylamino)-methyl]-2,3-dimethoxy-phenyl}-3H-indol-3-yl)-propionic acid ethyl ester (42a). Compound **41b** (18.0 mg, 4.4 10^{-2} mmol) in absolute EtOH (3 mL) was hydrogenated in the presence of $Pd/CaCO_3$. After filtration over celite a

solution of HOBT (9.2 mg, 0.68 mmol, 1.5 eq) and EDC (9.6 mg, 0.05 mmol, 1.1 eq) in freshly distilled DMF (1mL) was added. Extraction (ACOEt) andpreparative tlc (SiO_2, CH_2Cl_2/MeOH, 95:5) gave **42a** (16 mg, 0.029 mmol. 67 %): IR ($CHCl_3$) υ 1727, 1681, 1502, 1451, 1426, 1370; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24, (t, 3H, *J*= 7.1 Hz), 1.39 (s, 9H), 2.73 (t, 2H, *J*= 7.7 Hz), 3.12, (t, 2H, *J*= 7.7 Hz), 3.35, (s, 3H), 3.83 (d, 2H, *J*= 5.8 Hz), 3.90 (s, 3H), 4.15 (q, 2H, *J*= 7.1 Hz), 4.45 (d, 2H, *J*= 5.8 Hz), 5.10 (bs), 6.40, (bs, 1H), 6.82 (d, 1H, *J*= 1.9 Hz), 6.88 (d, 1H, *J*= 1.9 Hz), 7.04 (d, 1H, *J*= 2.1 Hz), 7.29 (dd, 1H, J_1= 1.3, J_2= 8.3 Hz), 7.54 (bs, 1H), 7.62 (d, 1H, *J*= 8.3 Hz), 8.10 (bs); ^{13}C NMR δ 14.33, 20.79, 28.34, 35.17, 43.53, 56.12, 60.49, 60.64, 80.50, 110.52, 112.05, 114.92, 118.37, 120.98, 122.26, 122.38, 126.55, 131.78, 133.78, 136.48, 136.91, 145.98, 153.35, 169.50, 173.55; MS (CI, isobutane) *m/z* 540 $[M+H]^+$, 484 $[M-56+H]^+$, 440 $[M-Boc+H]^+$; CIHRMS *m/z* 540.2693 ($C_{29}H_{37}N_3O_7+H^+$ requires 540.2709).

3-(6-{5-[(2-*tert*-Butoxycarbonylamino-acetylamino)-methyl]-2,3-dimethoxy-phenyl}-3H-indol-3-yl)-propionic acid (42b). A solution of **42a** (87 mg, 0.16 mmol) in EtOH (5 mL), added with aqueous of KOH 0.25 M (2 mL, 0.5 mmol, 3.0 eq) was kept for 22 h at room temperature. Evaporation, addition of aqueous HCl 5% (10 mL) and extraction (AcOEt) gave **42b** (80 mg, 0.15 mmol, 97 %): mp 84-86° C (MeOH/ether); IR ($CHCl_3$) υ 3344, 1709, 1673, 1585, 1502, 1456, 1425, 1368; ^1H NMR (300 MHz, acetone-D_6) δ 1.37 (s, 9H), 2.73 (t, 2H, *J*= 7.6 Hz), 3.12 (t, 2H, *J*= 7.6 Hz), 3.35 (s, 3H), 3.83 (d, 2H, *J*= 5.6 Hz), 3.90 (s, 3H), 4.42 (d, 2H, *J*= 5.8 Hz), 6.30 (bs, 1H), 6.93 (s, 1H), 6.97 (s, 1H), 7.19 (d, 1H, *J*= 1.5 Hz), 7.21 (dd, 1H, J_1= 1.3, J_2= 8.2 Hz), 7.55 (bs, 1H), 7.60 (d, 1H, *J*= 8.2 Hz), 7.71 (bs, 1H), 10.06 (bs, 1H); ^{13}C NMR δ 21.48, 28.62, 35.37, 43.49, 44.87, 56.35, 60.51, 79.50, 111.60, 113.01, 115.14, 118.71, 121.40, 122.72, 123.62, 127.52, 132.66, 137.82, 146.66, 154.15, 170.74, 174.87; MS (EI) *m/z* 567 [M+56], 511[M], 411 [M-Boc].

3-(6-{5-[(2-*tert*-Butoxycarbonylamino-acetylamino)-methyl]-2,3-dimethoxy-phenyl}-3H-indol-3-yl)-thiopropionic acid *S*-(2-carbamoyl-ethyl)-ester (44a). A solution of **42b** (30 mg, 0.058 mmole) in DMF (6 mL), added with DPPA (15.5 mL, 0.070 mmole, 1.2 eq), NEt_3 (10.0 mL, 0.070 mmole, 1.2 eq) and 3-mercapto-propionamide[14] (9.25 mg, 0.088 mmole, 1.5 eq) was kept for 24 h at room temperature. Quenching by H_2O (10 mL), extraction (ACOEt) and preparative tlc (SiO_2, CH_2Cl_2/MeOH, 95:5) gave **44a** (30 mg, 0.050 mmole, 86%): mp 90-92° C ($CHCl_3$/ether); IR ($CHCl_3$): υ 1686, 1589, 1507, 1456, 1425, 1369; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9H), 2.32 (t, 2H, *J*= 6.7 Hz), 2.89 (t, 2H, *J*= 7.6 Hz), 3.02 (t, 2H, *J*= 6.7 Hz), 3.10 (t, 2H, *J*= 7.6 Hz), 3.50 (s, 3H), 3.80 (bs, 2H), 3.85 (s, 3H), 4.56 (d, 2H, *J*= 5.6 Hz), 5.51 (bs, 1H, exchanged with D_2O), 5.67 (bs, 1H, exchanged with D_2O), 5.75 (bs, 1H, exchanged with D_2O), 6.78 (s, 1H), 6.82 (s, 1H), 6.93 (s, 1H, exchanged with D_2O), 6.96 (d, 1H, *J*= 1.6 Hz), 7.23 (d, 1H, *J*= 8.3 Hz), 7.44 (bs, 1H), 7.54 (d, 1H, *J*= 8.3 Hz), 8.76 (bs, 1H); ^{13}C NMR δ 21.42, 24.52, 28.36, 35.49, 43.41, 44.49, 44.88, 56.09, 60.68, 80.40, 110.59, 112.13, 113.95, 118.38, 120.90, 122.28, 122.81, 126.50, 131.78, 133.99, 136.47, 136.81, 145.79, 153.22, 169.79, 173.46, 199.82; FABMS (thio/Li^+) *m/z* 605 $[M+Li]^+$, 505$[M-Boc+Li]^+$.

[3-(6-Bromo-3H-indol-3-yl)-propionylamino]-acetic acid methyl ester (46a). A solution of glycine methyl ester hydrochloride (140 mg, 1.12 mmol) in DMF (10 mL), added with NEt_3 (230 ml, 1.65 mmol) was stirred at room temperature for 15 min. EDC (143 mg, 0.75 mmol), HOBt (151 mg, 1.12 mmol) and **38b** (200 mg, 0.75 mmol) were then added, and stirring was continued for 15 h. Dilution (aqueous NH_4Cl), extraction (AcOEt) and preparative tlc (CH_2Cl_2/MeOH 9:1) gave **46a** (197 mg, 0.58 mmol, 77%): mp 146-147° C (acetone/ether); IR ($CHCl_3$) υ 1749, 1677, 1516, 1456, 1436, 1377; ^1H NMR (300 MHz, acetone-D_6) δ 2.60 (t, 2H, *J*= 7.6 Hz), 3.04 (t, 2H, *J*= 7.6 Hz), 3.65 (s, 3H), 3.93 (d, 2H, *J*= 5.9 Hz), 7.13 (dd, 1H, J_1= 1.7, J_2= 8.5 Hz), 7.18 (d, 1H, *J*= 2.3 Hz), 7.45

(bs, 1H), 7.52 (d, 1H, *J*= 8.5 Hz), 7.57 (d, 1H, *J*= 1.7 Hz), 10.15 (bs, 1H); ^{13}C NMR δ 21.78, 37.24, 41.60, 52.13, 115.03, 115.28, 115.90, 121.01, 122.45, 124.19, 127.53, 138.60, 171.29, 173.31; MS (IE) *m/z* 340, 338.

[3-(6-Bromo-3H-indol-3-yl)-propionylamino]-acetic acid (46b). Compound **46a** (42 mg, 0.123 mmol) in MeOH (10 mL), was treated at room temperature for 15 h, with aqueous NaOH (7 mg, 0.185 mmol). Evaporation of the volatile, acid-base extraction (AcOE) gave **46b** (39 mg, 0.123 mmol, 97 %): mp 152° C (acetone/ether); IR ($CHCl_3$) υ 3475, 1722, 1669, 1516, 1457; ^{1}H NMR (300 MHz, acetone-D_6) δ 2.64 (t, 2H, *J*= 7.6 Hz), 3.05 (t, 2H, *J*= 7.6 Hz), 3.97 (d, 2H, *J*= 5.7 Hz), 7.12 (dd, 1H, J_1= 1.7, J_2= 8.4 Hz), 7.18 (d, 1H, *J*= 2.2 Hz), 7.49 (bs, 1H), 7.51 (d, 1H, *J*= 8.4 Hz), 7.56 (d, 1H, *J*= 1.7 Hz), 10.17 (br, 1H); ^{13}C NMR δ 21.78, 37.29, 41.67, 115.03, 115.27, 115.80, 120.98, 122.42, 124.21, 127.49, 138.56, 171.76, 173.82; MS (CI, Isobutene) *m/z* 327, 325.

***N*-[(3-Bromo-benzylcarbamoyl)-methyl]-3-(6-Bromo-3H-indol-3-yl)-propion-amide (48c).** A solution of 3-bromobenzylamine hydrochloride (33 mg, 0.147 mmol) in DMF (2 mL), added with NEt_3 (26 ml, 0.184 mmol) was stirred at room temperature for 10 min. After addition of EDC (24 mg, 0.123 mmol), HOBt (25 mg, 0.184mmol) and **46b** (40 mg, 0.123 mmol), stirring was continued for 15 h. Quenching with water (10 mL), extraction (AcOEt), evaporation and preparative tlc (CH_2Cl_2/MeOH 9:1) gave **48c** (58 mg, 0.117 mmol, 96%): mp 170° C (MeOH/ether); IR (KBr) υ 1649, 1612, 1553, 1451, 1425, 1334; ^{1}H NMR (300 MHz, acetone-D_6) δ 2.64 (t, 2H, *J*= 7.6 Hz), 3.05 (t, 2H, *J*= 7.6 Hz), 3.87 (d, 2H, *J*= 5.8 Hz), 4.35 (d, 2H, *J*= 6.2 Hz), 7.12 (dd, 1H, J_1= 1.7, J_2= 8.4 Hz), 7.18 (d, 1H, *J*= 2.3 Hz), 7.23-7.25 (m, 1H), 7.38-7.41 (m, 1H), 7.45 (bs, 2H), 7.51 (d, 1H, *J*= 8.4 Hz), 7.55 (d, 1H, *J*= 1.7 Hz), 7.60 (bs, 1H), 10.14 (bs, 1H); ^{13}C NMR δ 20.49, 35.80, 41.26, 42.00, 113.48, 113.70, 114.07, 119.97, 120.83, 121.46, 123.14, 125.92, 126.04, 129.41, 129.65, 130.23, 136.90, 142.16, 169.11, 172.14; MS (EI) *m/z* 495, 493; HRMS *m/z* 490.9837/492.9825/494.9794 ($C_{18}H_{19}Cl_2N_2O_4$ requires 490.9844/492.9822/494.9801).

Compound (49). Into a flamed 25 mL bottom flask were placed $(TPP)_2NiCl_2$ (93 mg, 0.14 mmole), triphenylphosphine (74 mg, 0.28 mmole), and zinc powder (9.3 mg, 0.14 mmole). A septum cap was placed on the flask, and dry O_2-free DMF (2 mL) was added through a septum cap. The flask was evacuated and filled with N_2 three times by means of a syringe needle connected with tyflon tubing to a vacuum line and another syringe needle connected to nitrogen line.[19] After 1 h **48c** (35 mg, 0.07 mmole) in dry O_2-free DMF (2 mL) was added *via* a syringe with careful exclusion of air and the reaction mixture was stirred under nitrogen at 50° C for 2 hrs. It was then cooled, poured into 5 % HCl (10 mL), extracted with AcOEt (20 mL), washed with distilled water and brine, then dried over Na_2SO_4. Filtration and removal of solvents yielded a residue which was purified by tlc on silica to yield **49** (4 mg, 0.012 mmole, 17%) as a yellow solid: mp 225-228° C (MeOH/ether); IR (KBr) υ 1649, 1612, 1553, 1451, 1425, 1334, 1425, 1334, 1104, 1067; ^{1}H NMR (300 MHz, acetone-D_6) δ 1.95 (ddd, 1H, J_1= 2.8, J_2= 10.6, J_3= 13.7 Hz, H-20), 2.54 (ddd, 1H, J_1= 2.1, J_2= 7.2, J_3= 13.7 Hz, H-20'), 2.87 (ddd, 1H, J_1= 2.8, J_2= 7.2, J_3= 14.2 Hz, H-21), 3.33 (ddd, 1H, J_1= 2.1, J_2= 10.6, J_3= 14.2 Hz, H-21'), 3.42 (dd, 1H, J_1= 2.0, J_2= 16.5 Hz, H-17), 4.10 (dd, 1H, J_1= 5.0, J_2= 16.4 Hz, H-14), 4.25 (dd, 1H, J_1= 6.6, J_2= 16.5 Hz, H-17'), 4.51 (dd, 1H, J_1= 8.3, J_2= 16.4 Hz, H-14'), 6.00 (bs, 1H, H-8), 6.09 (d, 1H, *J*= 5.0 Hz H-18), 6.90 (dd, 1H, J_1= 1.3, J_2= 8.5 Hz, H-5), 6.98 (dd, 1H, J_1= 0.7, J_2= 7.5 Hz, H-12), 7.04 (d, 1H, *J*= 2.3 Hz, H-2), 7.08 (d, 1H, *J*= 0.9 Hz, H-7), 7.28 (d, 1H, *J*= 7.5 Hz, H-11), 7.42 (dd, 1H, J_1= 0.7, J_2= 7.5 Hz, H-10), 7.46 (bs, 1H, H-15), 7.64 (d, 1H, *J*= 8.5 Hz, H-4), 9.58 (bs, 1H H-1); ^{13}C NMR δ 22.31, 40.96, 43.21, 43.97, 115.23, 118.23, 120.93, 121.30, 122.51, 122.69, 123.24, 123.54, 129.27, 132.82, 136.49, 137.58, 139.01, 145.83, 171.18, 172.79; MS (EI) *m/z* 333 [M]; HRMS m/z 333.1484 ($C_{20}H_{19}N_3O_2$ requires 333.1477).

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