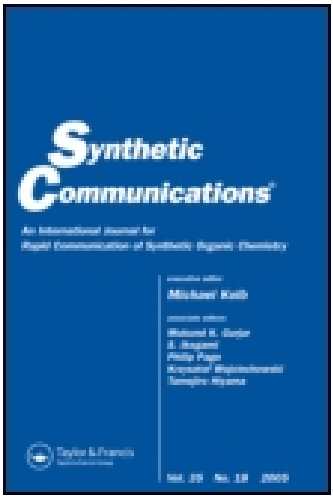

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Conformationally Restricted Analogues of Tryptophan: Synthesis of Chiral 3-Amino-4-indolyl-2-piperidones

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CONFORMATIONALLY RESTRICTED ANALOGUES OF TRYPTOPHAN: SYNTHESIS OF CHIRAL 3-AMINO-4-INDOLYL-2-PIPERIDONES

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Abstract: The {Trp-phenylglycinol} pseudodipeptide *(αR,3R*,4R*)-N-*(2-acetoxy-1-phenylethyl)-3-amino-4-indolyl-2-piperidone **33** has been synthezised by condensation of the 3-amino-substituted anhydride **30** with *(R)*-(-)-phenylglycinol followed by reduction of the resulting imide.

INTRODUCTION

The substitution of natural L-amino acids in biologically active peptides by conformationally restricted analogues and/or by their D-counterparts are two modifications used successfully in the search for peptidomimetics with good bioavailability and increased activity.[1] The incorporation of non-natural dipeptides in larger peptide chains is also a useful tool for the study of structure-activity relationships, and, consequently, for the rational design of new drugs from lead compounds.[2] Well studied examples include endogenous peptides such as somatostatin,[3] cholecystokinin

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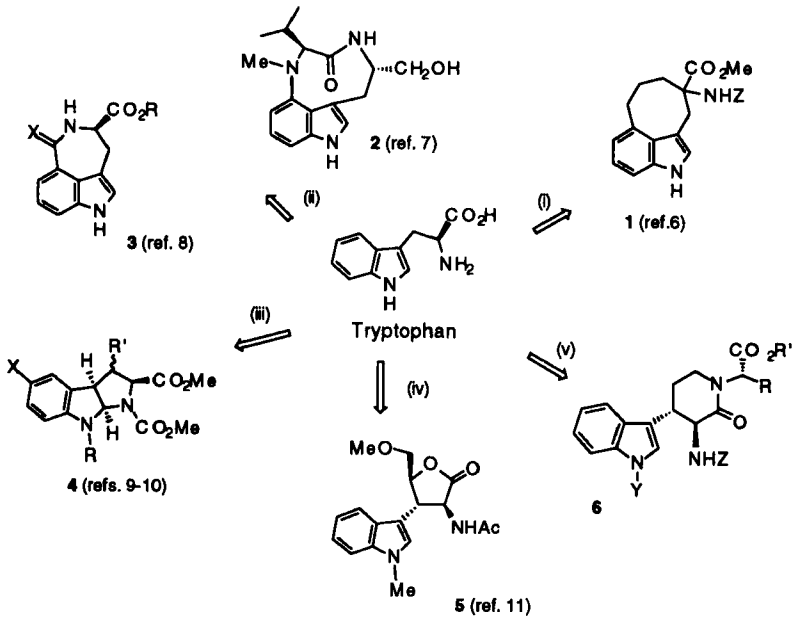
(CCK),[4] and the luteinizing hormone-releasing hormone (LH-RH),[5] in which modifications of the tryptophan residue result in changes to the conformation of the peptide and of its biological activity.

So far, four main modifications of tryptophan have been used to obtain conformationally restricted analogues: i) cyclisation between the tryptophan α-carbon and the indole 4-position;[6] ii) closure of the amino group upon the indole 4-position, by building a dipeptide such as **2**[7] or to give compounds type **3** ;[8] iii) cyclisation of the amino group upon the indole 2-position, with[9]or without[10] substitution on the β-position; iv) cyclization between the carboxy group and β-position (Scheme 1).[11]



Scheme 1

In the present paper we describe the synthesis of 4-indolyl-3-amino-2-piperidones type **6** as a fifth modification, based on the inclusion of tryptophan α and β carbons in a

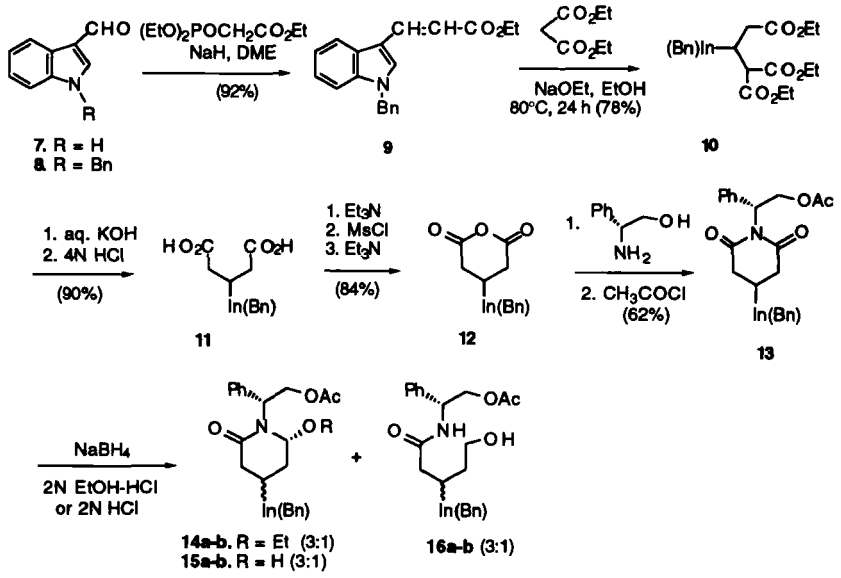
2-piperidone ring. A similar approach has been described in the preparation of phenylalanine analogs used in a study of renin inhibitors.[12]

We thus designed compound **33** (see scheme 5) which includes the desired modification on tryptophan, and a stereocenter α with respect to the lactam nitrogen. Two different approaches were taken to the synthesis of compound **33**. One was to prepare lactam **18** and introduce the 3-amino group in the last step of the synthesis. The other was to introduce the amino substituent on the starting substrate. In both, the lactam would be prepared by reduction of a conveniently substituted imide, obtained by condensation of *(R)*-(-)-phenylglycinol with the appropriate anhydride.[13] This condensation should allow the introduction of a variety of asymmetric substituents on the lactam nitrogen atom, and render possible the easy preparation of conformationally restricted tryptophan-derived dipeptides.

RESULTS AND DISCUSSION

Our first aim was to prepare anhydride **12**, which was obtained in four steps and 54% total yield (Scheme 2). Thus, 1-benzylindole-3-carbaldehyde, prepared by *N*-alkylation of indole-3-carbaldehyde, was submitted to a Wadsworth-Emmons reaction with triethylphosphonoacetate to obtain acrylate **9**. A Michael addition of diethyl malonate monosodium salt upon **9** yielded the corresponding triester **10**, which, after hydrolisis and decarboxylation, led to the desired diacid **11**. The formation of anhydride **12** was carried out by mesylation of **11** followed by Et_3N addition. The condensation of **12** with *(R)*-phenylglycinol as described previously[13] gave imide **13** in 62% yield. The reduction of the imide with $NaBH_4$[14] and 2N EtOH-HClgas at low temperature led to a mixture of ethoxylactams **14** (26% yield, **a:b** = 3:1) and hydroxyamides **16** (**a:b** = 3:1), the latter resulting from the reduction of the open-chained aldehyde present in the equilibrium mixture of the reaction.[15] When the $NaBH_4$ reduction of imide **13** was carried out using

2N aqueous HCl, hydroxylactams **15** were obtained in 50% yield, together with hydroxyamides **16** (22%), in the same diastereomeric proportions (3:1). The fact that the two diastereomers of **16**, isolated in pure form after column chromatography, were obtained indicated that the reduction takes place on both carbonyl groups but that one of them is favored probably due to the effect of the bulky α-phenyl substituent. This also implied that lactams **14** and **15** are C-4 epimeric mixtures. Furthermore, the fact that only two diastereomers of lactams **14** and **15** were obtained probably indicates that the intermediate aldehydes present at equilibrium[16] cyclize, giving the most stable hemiaminals as a result of an anomeric effect.[17]



Scheme 2

Substituted lactams**14** and **15** were reduced by treatment with Et_3SiH-TFA to the expected lactam **17**, from which only one diastereomer was isolated after SiO_2 column chromatography. The hydroxy group was subsequently deprotected with 5% aqueous

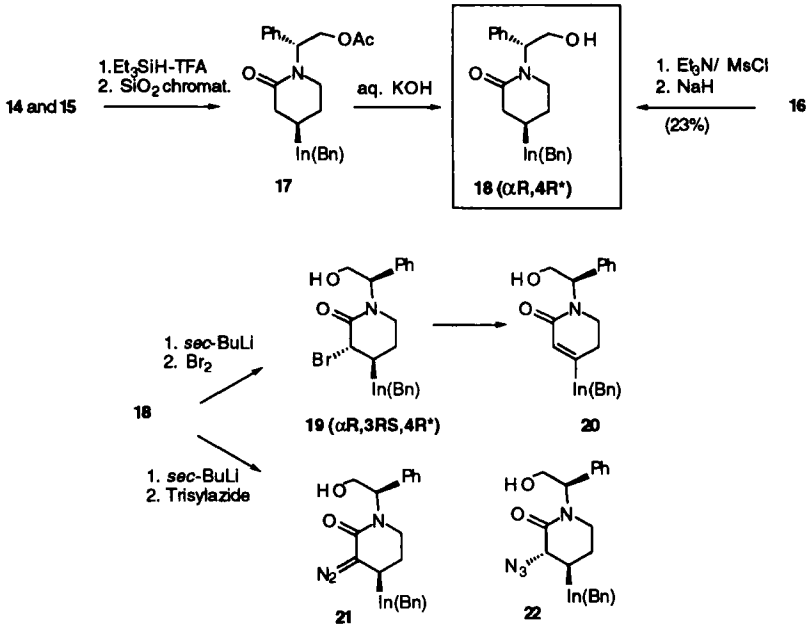
KOH at rt to obtain 4-indolyl-2-piperidone **18**. Alternatively, lactam **18** was obtained from hydroxyamide **16a** by mesylation and cyclization in the presence of NaH. In this case, the spectral data and optical rotation were identical to those obtained previously, indicating that we had the same diastereomer of lactam **18**.

The introduction of the 3-amino substituent on lactam **17** was first assayed by treatment with KHMDS and trisylazide.[18] No reaction was observed, but since the examples described in the literature had an electron withdrawing group on the amide nitrogen atom it appeared likely that the nitrogen lone pair was responsible for the lack of reactivity. We then assayed the bromination of compound **17** by treatment with LDA and NBS,[19] but this was also unsuccesful. We then carried out the bromination of hydroxylactam **18**, since the lithium alcoxyde has been reported to help stabilize the intermediate enolate by chelation with the nitrogen atom.[20] Treatment of compound **18** with *sec*-BuLi (2 equivalents) and Br_2 led to the expected 3-bromolactam **19** as a C-3 epimeric mixture (1:1.3). However, the minor 3,4-*cis* isomer readily epimerized to give the thermodynamically more stable 3,4-*trans* isomer on SiO_2 column chromatography. The most characteristic differences between *cis*- and *trans*-**19** were the ^{13}C NMR chemical shift of C-5 and the ^1H NMR chemical shift of 4-H, both more shielded in the minor *cis*-isomer ($\Delta\delta_{C\text{-}5}$ = 3 ppm, $\Delta\delta_{4\text{-}H}$ = 0.78 ppm) in which the bromine atom is pseudoaxially disposed.

Subsequent attempts to replace the bromine atom by a latent primary amine through treatment of *trans*-**19** with potassium phthalimide, benzylamine, or NaN_3 under a variety of experimental conditions always led to the unsaturated lactam **20**. Such elimination is not observed in the absence of the C-4 substituent,[21] which indicates that the indole acidifies the proton on C-4 to favor the elimination over the substitution.

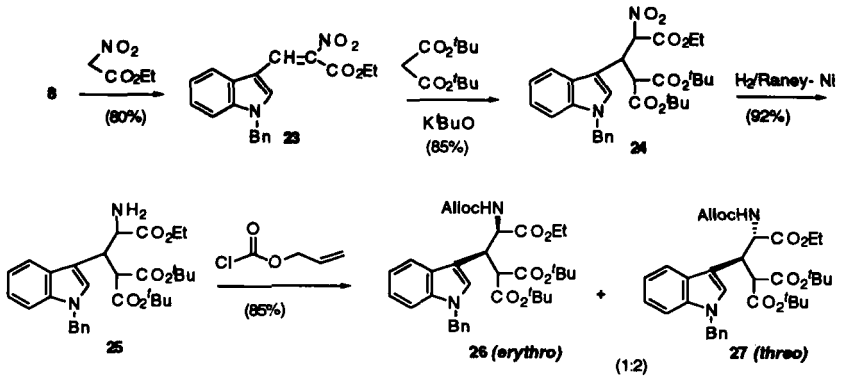
When azidation of lactam **18** was assayed using *sec*-BuLi and trisylazide, 3-diazoderivative **21** was obtained, whilst 3-azidolactam **22** was only isolated once making

the reaction useless from the synthetic viewpoint. This result derives from the preferential formation of diazo derivatives in the presence of lithium bases, whilst potassium bases tend to promote the azido transfer.[18]



Scheme 3

In view of this result we turned our attention to the synthesis of aminotriester **25** and our second approach to lactam **33**. Thus, condensation of indole-3-carbaldehyde **8** with sodium ethyl nitroacetate gave nitroacrylate **23**, which was converted into nitrotriester **24** by conjugate addition of the di-*tert*-butyl-malonate monopotassium salt (Scheme 4). At this point, the nitro group was reduced by hydrogenation in the presence of Raney-Ni.[22] The resulting primary amines **25** were protected as the allylcarbamate, and aminotriesters *erythro*-**26** and *threo*-**27** were isolated by flash column chromatography in the proportion 1:2.



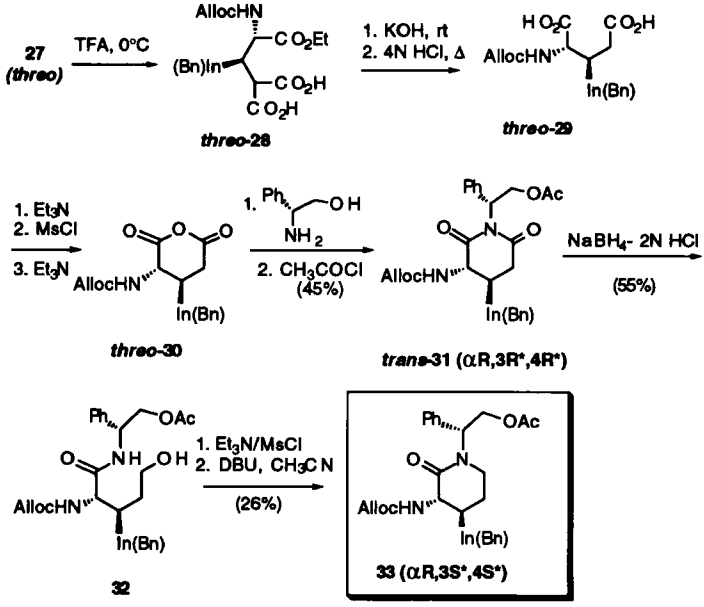
Scheme 4

Pure aminotriester **27** was subjected to a TFA treatment at 0°C, in which the *tert*-Bu esters were selectively hydrolyzed to give compound **28** (Scheme 5). The ethyl ester was cleaved subsequently with aqueous 5% KOH at rt., and final 4N HCl decarboxylation was carried out to yield diacid *threo* -**29** (97%). In contrast, when the direct saponification of triester **27** in 5% aqueous KOH followed by acid decarboxylation was carried out, a mixture of diacids *erythro*- and *threo*-**29** was obtained, due to the heating necessary in the saponification step (Scheme 6).

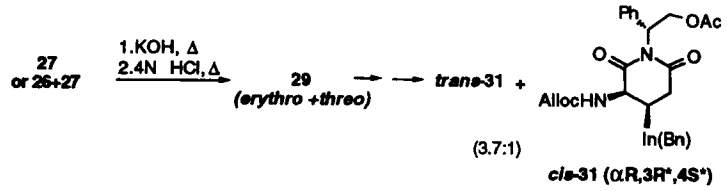
As in the previous series, anhydride *trans*-**30** was obtained from *threo*-**29**, and was transformed into imide *trans*-**31** by condensation with *(R)*-(-)-phenylglycinol.[23] The same reaction sequence was carried out from the mixture to obtain imides *cis*- and *trans*-**31**,[23] which were separated by column chromatography. The stereochemistry of imides **31** was inferred from their NMR data. Thus, the ^{1}H NMR spectrum of *trans*-**31** showed 3-H as a doublet at δ 4.59 with a coupling constant of 3 Hz. Imide *cis*-**31** showed 3-H as a larger doublet at δ 5.04 (J = 8.5 Hz). However, 2D NOE experiments showed that neither isomer presented a NOE correlation between 3-H and any 5-H. This implied that the carbamate substituent on C-3 had a pseudoaxial disposition in both cases. Furthermore, *trans*-**31** showed a strong NOE correlation between 4-H and the pseudoaxial 5-H,

indicating that the indolyl substituent was in a pseudoaxial disposition, *trans* with respect to the carbamate. Consistently, in imide *cis*-**31** 4-H showed strong NOE correlation with the pseudoequatorial 5-H, and therefore the indolyl substituent adopts a pseudoequatorial disposition, *cis* with respect to the carbamate.

The stereochemical assignment of imides **31** also allowed the stereochemical identification of the starting triesters **26** and **27**.



Scheme 5



Scheme 6

As expected for glutarimides, the subsequent $NaBH_4$-2N HCl reduction of imide *trans*-**31** occured in a regioselective manner upon the less hindered carbonyl group. However, although the reaction was carried out at -40°C to avoid the ring opening,[26] only hydroxyamide **32** was obtained. The cyclization to obtain the target lactam **33** was carried out by mesylation of **32**, followed by DBU treatment. Formation of lactam **33** was shown by the loss of the hydroxy group observed in the IR record and the loss of the amide NH proton in the ^1H NMR spectrum. Other outstanding ^1H NMR features of compound **33** were the chemical shift and signal multiplicity of 5-H and 6-H, characteristic of a piperidine stucture.

EXPERIMENTAL

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 instrument (200 MHz) and 2D NMR COSY experiments were performed on a Varian XL-500 instrument (500 MHz). Unless otherwise noted, NMR spectra were registered in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer. Flash column chromatography was carried out on SiO_2 (silica gel 60, 40-63 mm, Macherey-Nagel). TLC was performed on SiO_2 (silica gel 60 F_{254}, Merck) and developed with the solvent described in each case for flash chromatography. The spots were located by UV light and Draggendorff, phosphomolibdic acid or hexachloroplatinate reagent. Purification of reagents and solvents was effected according to standard methods. Anhydrous reactions were carried out in dry solvents, under N_2 or Ar atmosphere. Prior to concentration under reduced pressure, all extracts were dried over anhydrous Na_2SO_4. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Departament de Química Orgànica i Biològica, CID, Barcelona.

1-Benzylindol-3-carbaldehyde (8). To a dispersion of NaH (55%, 9.03 g, 206.89 mmol) in DMSO (75 ml), a solution of indol-3-carbaldehyde (30 g, 206.89 mmol) in DMSO (120 ml) was slowly added, and the resulting mixture was stirred at 50°C for 30 min. BnCl (28.5 ml, 248.27 mmol) was added and the mixture heated at 80°C for 30 min. The reaction was quenched with H_2O and extracted with C_6H_6. The organic layer was washed twice with 5% HCl and with brine. The organic phase, dried and evaporated, furnished compound **8** (24.79 g, 51%), which was washed with dry hexane: mp 114°C (Et_2O); IR (KBr) 1632 cm^{-1} (CO); ^1H NMR 5.35 (s, 2H, CH_2Ph), 7.1-7.4 (m, 8H, Ar-H), 7.72 (s, 1H, In-2H), 8.30 (m, 1H, Ar-H), 9.99 (s, 1H, CHO); ^{13}C NMR 51.0 (CH_2Ph), 110.5 (In-C7), 122.3 and 123.2 (In-C4 and In-C5), 124.3 (In-C6), 127.3 (Ph-*o*), 128.5(Ph-*p*), 129.2 (Ph-*m*), 138.7 (In-C2), 184.7 (CHO); EIMS *m/z* (%) 236 (M^++1, 57), 91 (100), 65 (10). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.70; H, 5.53; N, 5.96. Found: C, 81.68; H, 5.66; N, 5.91.

Ethyl 3-(1-benzyl-3-indolyl)-2-propenoate (9). To a dispersion of NaH (55%, 2.23 g, 51.06 mmol) in DME (75 ml) a solution of triethyl phosphonoacetate (10 g, 42.55 mmol) in dry DME (50 ml) was added dropwise. After stirring for 30 min at rt, a solution of carbaldehyde **8** (10 g, 42.55 mmol) in dry DME (50 ml) was added dropwise and the mixture was heated at reflux for 3 h. The reaction mixture was poured on ice-H_2O and extracted with CH_2Cl_2. The organic extracts were washed twice with 20% aqueous K_2CO_3, dried and evaporated to give an oil which was flash chromatographed (Et_2O-hexane, 7:3) yielding **9** (11.92 g, 92%): mp 94-96°C (Et_2O); IR (KBr) 1625 (C=C), 1702 cm^{-1} (CO); ^1H NMR 1.35 (t, J = 7 Hz, 3H, CH_3), 4.25 (q, J = 7 Hz, 2H, CH_2CH_3), 5.30 (s, 2H, CH_2Ph), 6.45 (d, J = 15 Hz, 1H, =CH), 7.1-7.3 (m, 8H, Ar-H), 7.35 (s, 1H, In-2H), 7.90 (d, J = 15 Hz, 1H, =CH), 7.95 (m, 1H, In-4H); ^{13}C NMR 14.6 (CH_2CH_3), 50.5 (CH_2Ph), 60.2 (CH_2CH_3), 110.6 (In-C7), 113.1 (C-2), 120.8 (In-C4), 121.5 (In-C5), 123.2 (In-C6), 127.0 (Ph-*o*), 128.1 (Ph-*p*), 129.0 (Ph-*m*), 132.6 (C-3), 138.0 (In-C2), 168.4

(CO); EIMS *m/z* (%): 305 (M^+, 100), 260 (16), 233 (42), 169 (3), 114 (7), 140 (4), 91 (97). Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.68; H, 6.23; N, 4.59. Found: C, 78.51; H, 6.49; N, 4.60.

Diethyl 3-(1-benzyl-3-indolyl)-2-ethoxycarbonyl glutarate (10). To a solution of NaOMe prepared from sodium (270 mg, 11.7 mmol) and EtOH (30 ml), diethyl malonate (8.16 ml, 53.8 mmol) was added dropwise. After stirring at rt for 20 min, a solution of acrylate **9** (2.61 g, 8.97 mmol) in EtOH (40 ml) was slowly added and the resulting mixture was heated at 80°C for 24 h. The reaction was neutralized with AcOH (4-5 drops) and the solvent was evaporated. The residue was extracted with CH_2Cl_2 and the organic extracts, dried and evaporated, yielded compound **10** (3.75 g, 90 %) after flash chromatography (Et_2O-hexane, 1:1): IR (NaCl) 1732 cm^{-1} (CO); ^1H NMR 0.90 and 1.00 (2t, J = 6 Hz, 3H each, CH_3), 1.25 (t, J = 6 Hz, 3H, CH_3), 2.90 (d, J =6 Hz, 2H, 4-H), 3.85- 4.00 (m, 5H, 2xCH_2 CH_3 and 2-H), 4.05-4.30 (m, 3H, CH_2 CH_3 and 3-H), 5.23 (s, 2H, CH_2Ph), 7.00-7.35(m, 9H, Ar-H), 7.65 (m, 1H, In-4H); ^{13}C NMR 13.5 (CH_3), 13.8 (2xCH_3), 32.8 (C-3), 38.3 (C-4), 49.8 (CH_2Ph), 56.6 (C-2), 60.2 (OCH_2), 61.2 and 61.3 (OCH_2), 109.6 (In-C7), 113.8 (In-C3), 119.2 (In-C4 and In-C5), 121.7 (In-C6), 126.5 (In-C2), 126.6 (Ph-*o*), 127.4 (Ph-*p*), 128.5 (Ph-*m*), 168.0, 168.5 and 172.0 (CO); EIMS *m/z* (%) 465 (M^+, 32), 378 (11), 306 (100), 260 (10), 233 (12), 173 (18), 127 (12), 91 (92). Anal. Calcd for $C_{27}H_{31}NO_6$: C, 69.65; H, 6.72; N, 3.01. Found: C, 69.55; H, 6.69; N, 2.90.

3-(1-Benzyl-3-indolyl)glutaric acid (11). To a solution of compound **10** (7.0 g, 15.1 mmol) in dioxane (150 ml), 5% aqueous KOH (254 ml) was added. After heating for 30 min at 100°C, 4N HCl was added dropwise until pH = 3, and the mixture was heated at reflux for 4 h. Once cooled to rt the reaction mixture was neutralizated by addition of aqueous NaOAc. The aqueous layer was exhaustively extracted with small portions of

Et_2O. The organic extracts were dried and evaporated to give diacid **11** (3.14 g, 79%): IR ($CHCl_3$) 3600-2700 (OH), 1698 (CO) cm^{-1}; ^1H NMR 2.85 (d, J = 7 Hz, 4H, 2-H and 4-H), 4.05 (q, J = 7 Hz, 1H, 3-H), 5.33 (s, 2H, CH_2Ph), 7.0-7.4 (m, 9H, Ar-H), 7.70 (dd, J = 7 and 1.5 Hz, 1H, In-4H); ^{13}C NMR 31.3 (C-3), 41.1 (C-2 and C-4), 50.5 (CH_2Ph), 110.9 (In-C7), 120.0 (In-C4), 120.2 (In-C5), 122.6 (In-C6), 126.7 (In-C2), 127.6 (Ph-*o*), 128.2 (Ph-*p*), 129.5 (Ph-*m*), 176.0 (CO); EIMS *m/z* (%) 337 (M^+,16), 278 (39), 233 (6), 91 (100). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.19; H, 5.68; N, 4.15. Found: C, 70.95; H, 5.69; N, 4.10.

3-(1-Benzyl-3-indolyl)glutaric anhydride (12). To a stirred solution of diacid **11** (1.9 g, 5.64 mmol) in THF (130 ml) Et_3N (0.79 ml, 5.64 mmol) was added. The reaction mixture was cooled to -20°C. After stirring for 15 min, MsCl (0.44 ml, 5.64 mmol) was added, followed by a solution of Et_3N (1.57 ml, 11.27 mmol) in THF (10 ml). The reaction mixture was stirred at -15°C for 2 h. The solvent was evaporated. The residue, dissolved in CH_2Cl_2 (50 ml), was washed successively with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated to give anhydride **12** (1.51 g, 84%): IR (KBr) 1809 and 1763 cm^{-1} (CO); ^1H NMR 3.00 (dd, J = 17 and 9 Hz, 2H, 2-H and 4-H), 3.19 (dd, J = 17 and 5 Hz, 2H, 2-H and 4-H), 3.65-3.85 (m, 1H, 3-H), 5.28 (s, 2H, CH_2Ph), 6.90 (s, 1H, In-2H), 7.0-7.4 (m, 8H, Ar-H), 7.5 (dd, J = 7 and 1.5 Hz, 1H, In-4H); ^{13}C NMR 25.8 (C-3), 36.1 (C-2 and C-4), 49.8 (CH_2Ph), 110.2 (In-C7), 118.4 (In-C4), 119.7 (In-C5), 122.5 (In-C6), 124.1 (In-C2), 126.6 (Ph-*o*), 127.6 (Ph-*p*), 128.6 (Ph-*m*), 166.5 (CO); EIMS *m/z* (%) 318 (M^+-1,11), 277 (10), 232 (9), 114 (6), 90 (100).

(α*R*)-*N*-(2-Acetoxy-1-phenylethyl)-4-(1-benzyl-3-indolyl)glutarimide (13). To a solution of anhydride **12** (1.29 g, 4.04 mmol) in $CHCl_3$ (100 ml), *(R)*-(-)-phenylglycinol (0.46 g, 3.37 mmol) was added, and the resulting mixture was refluxed for 6 h. The solvent was evaporated, the residue was dissolved in AcCl (1.67 ml, 23.59 mmol), and

the solution was refluxed for 4 h. AcCl was evaporated under reduced pressure, H_2O was added, and the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$, dried and evaporated to give imide **13** (1.21 g, 62%) after flash chromatography (EtOAc - Hexane, 7:3): $[\alpha]_D$ = -32.5 (c = 0.2, CH_2Cl_2); IR (NaCl) 1736 (CO), 1677 cm^{-1} (CO); ^1H NMR 2.00 (s, 3H, $COCH_3$), 2.93 (2 dd, *J* = 17 and 5 Hz, 2H, 2-H and 4-H), 3.16 (2 dd, *J* = 17 and 2 Hz, 2H, 2-H and 4-H), 3.55-3.75 (m, 1H, 3-H), 4.92 (d, *J* = 7 Hz, 2H, β-H), 5.20 (s, 2H, CH_2Ph), 6.20 (t, *J* = 7 Hz, 1H, α-H), 6.75 (s, 1H, In-2H), 7.0-7.45 (m, 13H, Ar-H), 7.60 (d, *J* = 7 Hz, 1H, In-4H); ^{13}C NMR 20.8 ($COCH_3$), 26.5 (C-3), 39.7 (C-2 and C-4), 49.9 (CH_2Ph), 53.1 (C-α), 63.1 (C-β), 110.1 (In-C7), 118.7 (In-C4), 119.6 (In-C5), 122.4 (In-C6), 124.2 (In-C2), 126.3, 126.6, 127.7, 128.0, 128.3, and 128.8 (Ph), 170.0 (CO), 172.2 (CO); EIMS *m/z* (%) 479 (M^+-1, 2), 418 (3), 376 (1), 317 (1), 258 (2), 212 (12), 206 (22), 90 (100). Anal. Calcd for $C_{30}H_{28}N_2O_4 \cdot 1/2\ H_2O$: C, 74.98; H, 5.87; N, 5.83; Found: C, 74.74; H, 6.07; N, 5.65.

Reduction of imide 13. Method A: To a solution of imide **13** (1.37 g, 2.85 mmol) in EtOH-THF (1:1, 150 ml), $NaBH_4$ (0.54 g, 14.27 mmol) was added. The resulting mixture was stirred for 3 h at -15°C, adding 3 drops of a (1:1) EtOH-35% HCl solution every 15 min. Then the mixture was cooled to -40°C, acidified with 2N EtOH-HCl_{gas} until pH = 3, and stirred for 1 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$, the EtOH was evaporated, and the aqueous residue was extracted with CH_2Cl_2. The combined organic extracts, dried and evaporated, were flash chromatographed (CH_2Cl_2). A 3:1 mixture of diastereomeric (**α*R*,4*RS*,6*R**-*N*-(2-Acetoxy-1-phenylethyl)-4-(1-benzyl-3-indolyl)-6-ethoxypiperidin-2-ones (14)** were obtained together with diastereomeric (**α*R*,3*RS*)-*N*-(2-acetoxy-1-phenylethyl)-3-(1-benzyl-2-indolyl)-5-hydroxypentanamides (16). 2-Piperidones 14** (Higher Rf, 370 mg, 26%): IR ($CHCl_3$) 1730 and 1650 cm^{-1}(CO); ^1H NMR 0.92 and 1.05* (2t, *J* = 6 Hz, 3H, CH_2CH_3), 2.05 and 2.10*(minor isomer) (2 s, 3H, $COCH_3$), 2.50 (t, *J* = 12 Hz, 1H, 3-H_a), 2.72-3.00 (m, 1H, 5-H_a), 3.05 (dd, *J* = 12 and 6 Hz, 1H, 3-H_e), 3.30-3.60 (m, 1H, 5-H_e),

3.70-3.90 (m, 1H, 4-H), 4.70 (br s, 1H, 6-H), 4.80 (d, J = 7 Hz, 2H, β-H), 5.30 (s, 2H, CH_2Ph), 5.50 (t, J = 7 Hz, 1H, α-H) 6.85 and 6.90* (2s, 1H each, In-2H), 7.10-7.70 (m, 14H, Ar-H); ^{13}C NMR 15.0 (CH_2CH_3), 21.0 (CH_3CO), 24.2 (C-4), 33.9 (C-5), 39.7 (C-3), 49.9 (CH_2Ph and CH_2CH_3), 55.0* and 58.0 (C-α), 63.3 (C-β), 83.0* and 85.0 (C-6), 110 (In-C7), 118.9 (In-C4), 119.2 (In-C5), 122.1 (In-C6), 123.9, 126.8, 127.3, 128.0, 128.3, 128.4, and 128.8 (Ph), 168.0 and 170.0* (COO), 170.4 and 170.9* (CON); EIMS *m/z* (%) 510 (M^+,8), 480 (60), 422 (6), 301 (29), 233 (23), 163 (6), 132 (9), 91 (100). Anal. Calcd for $C_{32}H_{34}N_2O_4$: C, 75.29; H, 6.66; N, 5.49. Found: C, 75.13; H, 6.46; N, 5.56. **5-Hydroxyamide 16a** (300 mg, 22%) : $[\alpha]_D$ = -18.5 (c = 0.3, CH_2Cl_2); IR ($CHCl_3$) 3450 (NH), 3450-3250 (OH), 1736 and 1664 (CO) cm^{-1}; ^1H NMR 1.80 (s, 3H, $COCH_3$), 2.01 (quint., J = 8 Hz, 1H, 3-H), 2.71 (d, J = 8 Hz, 2H, 2-H), 3.50-3.65 (m, 4H, 4-H and 5-H), 3.85 (dd, J = 10 and 5 Hz, 1H, β-H_A), 4.12 (dd, J = 10 and 7 Hz, 1H, β-H_B), 5.05-5.20 (m, 1H, α-H), 5.20 (s, 2H, CH_2Ph), 6.10 (d, J = 8 Hz, 1H, NH), 6.95 (s, 1H, In-2H), 6.95-7.20 (m, 13 H, Ar-H), 7.69 (d, J = 7 Hz, 1H, In-4H); ^{13}C NMR 20.6 ($COCH_3$), 30.9 (C-3), 38.1 (C-2), 42.9 (C-4), 49.8 (CH_2Ph), 52.1 (C-α), 60.7 (C-5), 65.8 (C-β), 110.1 (In-C7), 119.3 (In-C4 and In-C5), 122.0 (In-C6), 125.8 (In-C2), 126.5, 126.6, 127.6, 127.7, and 128.6 (Ph), 172.0 (CO), 176.0 (CO); EIMS *m/z* (%) 484 (M^+, 6), 424 (6), 393 (4),305 (15), 264 (27), 246 (14), 234 (11), 91 (100). Anal. Calcd for $C_{30}H_{32}N_2O_4$: C, 70.45; H, 6.84; N, 5.47. Found: C, 70.11; H, 6.34; N, 5.50. **5-Hydroxyamide 16b** (Lower Rf, 100 mg, 7%): $[\alpha]_D$ = -2.12 (c = 0.2, CH_2Cl_2); ^1H NMR 1.88 (s, 3H, $COCH_3$), 2.01 (quint., J = 8 Hz, 1 H, 3-H), 2.65 (s a, 1H, OH), 2.70 (d, J = 7 Hz, 2-H), 3.50-3.70 (m, 4 H, 4-H and 5-H), 4.09 (dd, J = 10 and 5 Hz, β-H_A), 4.19 (dd, J = 10 and 7 Hz, β-H_B), 5.15 (s, 2H, CH_2Ph), 5.10-5.20 (m, 1H, α-H), 6.28 (d, J = 7 Hz, 1H, NH), 6.89 (s, 1H, In-2H), 6.85-7.25 (m, 13 H, Ar-H), 7.65 (d, J = 7 Hz, In-4H); ^{13}C NMR 20.5 ($COCH_3$), 30.8 (C-3), 38.0 (C-2), 42.8 (C-4), 49.7 (CH_2Ph), 52.0 (C-α), 60.5 (C-5), 65.9 (C-β), 109.9 (In-C7), 119.1 (In-C4), 119.3 (In-C5), 121.8 (In-C6), 125.7 (In-C2), 126.3, 126.5, 126.7 , 127.4, 128.4, and 128.6 (Ph), 171.0 (CO), 172.0 (CO).

Method B: Operating as above, from imide **13** (2 g, 4.17 mmol), $NaBH_4$ (780 mg, 20.85 mmol) in EtOH-THF (1:1, 80 ml) and using 2N HCl instead of $EtOH\text{-}HCl_{gas}$, 5-hydroyamides **16** (lower Rf, 450 mg, 22%) and 6-hydroxylactams **15** (higher Rf, 1 g, 50%) were isolated after flash chromatography (EtOAc-hexane, 1:1). **2-Piperidones 15** (from a 3:1 diastereomeric mixture): IR (NaCl) 3600-3500 (OH), 1737 and 1648 (CO) cm^{-1}; ^1H NMR 2.05 and 2.06* (2s, 3H each, $COCH_3$), 2.05-2.20 (m, 1H, 5-H_a), 2.40 (dt, J = 13 and 6 Hz, 2H, 5-H_e), 2.75-2.95 (m, 2H, 3-H), 3.15 (d, J = 13 Hz, 1H, OH), 3.30-3.45 (m, 1H, 4-H), 4.65 (dd, J = 11 and 7.5 Hz, 1H, β-H_A), 4.70-4.88 (m, 1H, 6-H), 4.92 (dd, J = 11 and 7.5 Hz, 1H, β-H_B), 5.26 (s, CH_2Ph), 5.55* and 6.05 (2t, J = 7.5 Hz, 1H each, α-H), 6.91 (s, 1H, In-2H), 7.02-7.40 (m, 13 H, Ar-H), 7.60 and 7.61* (2d, J = 7 Hz, 1H each, In-4H); ^{13}C NMR 20.9 (CH_3CO), 27.1 and 27.4*(minor isomer) (C-4), 38.0* and 38.4 (C-3), 39.3 and 39.4* (C-5), 49.8 (CH_2Ph), 54.9 and 56.2* (C-α), 64.0* and 64.4 (C-β), 78.8 and 80.0* (C-6), 109.9 (In-C7), 119.0 and 119.3 (In-C4), 122.1* and 122.2 (In-C5), 124.2* and 124.3 (In-C6), 126.4* and 126.6 (In-C2), 127.6 and 127.9*, 128.4, 128.5, and 128.7 (Ph), 170.8 and 171.9* (CO), 172.0 and 172.1* (CO); MS m/z (%) 482 (M^+, 9), 439 (3), 422 (8), 393 (8), 301 (8), 262 (23), 234 (29), 233 (14), 207 (42), 91 (100). Anal. Calcd for $C_{30}H_{30}N_2O_4$: C, 74.65; H, 6.27; N, 5.81. Found : C, 74.58; H, 6.21; N, 5.79.

(α*R,4R)-*N*-(2-Acetoxy-1-phenylethyl)-4-(1-benzyl-3-indolyl)piperidin-2-one (17).**

From ethoxylactams 14: To a solution of ethoxylactams **14** (150 mg, 0.294 mmol) in CH_2Cl_2 (15 ml), TFA-Et_3SiH (1:1, 1 ml) was added. The resulting mixture was stirred for 30 min at rt and diluted with CH_2Cl_2 (20 ml). The organic solution was washed with 2x20 ml of H_2O. The organic extract was dried and evaporated to yield lactams **17** (70 mg, 51%) after flash chromatography (EtOAc-hexane, 7:3): $[\alpha]_D$ = -46.81 (c = 0.326, CH_2Cl_2); IR ($CHCl_3$) 1737 (CO), 1640 (CO) cm^{-1}; ^1H NMR 2.01 (s, 3H, $COCH_3$), 1.85-2.10 (m, 2H, 5-H), 2.70 (dd, J = 18 and 10 Hz, 1H, 3-H_a), 2.90-3.10 (m, 2H, 3-H_e and 6-H_a), 3.18 (dt, J = 12 and 6 Hz,1H, 6-H_e), 3.30-3.50 (m, 1H, 4-H), 4.60 (d, J = 7 Hz, 2H, β-

H), 5.28 (s, 2H, CH_2Ph), 6.22 (t, J = 7 Hz, 1H, α-H), 6.90 (s, 1H, In-2H), 7.10-7.40 (m, 13H, Ar-H), 7.60 (d, J = 7 Hz, 1H, In-4H); ^{13}C NMR 20.8 ($CO\underline{C}H_3$), 29.5 (C-4), 29.7 (C-5), 38.9 (C-3), 41.7 (C-6), 49.9 (CH_2Ph), 53.7 (C-α), 61.5 (C-β), 109.9 (In-C7), 119.0 (In-C4), 119.1 (In-C5), 122.0 (In-C6), 124.3 (In-C2), 126.7, 127.6, 127.9, and 128.7 (Ph), 171.0 (CO), 170.5 (CO); EIMS *m/z* (%) 466 (M^+, 17), 406 (10), 377 (1), 304 (4), 246 (6), 208 (15), 118 (8), 91 (100). Anal. Calcd for $C_{30}H_{30}N_2O_3$: C, 77.25; H, 6.43; N, 6.01. Found : C, 77.48; H, 6.47; N, 5.63.

From hydroxylactams **15**: Operating as above, from 6-hydroxylactams **15** (100 mg, 0.21 mmol), CH_2Cl_2 (5 ml), TFA-Et_3SiH (1:1, 1 ml) lactams **17** (65 mg, 66 %) were obtained after flash chromatography (EtOAc-hexane, 7:3).

(α*R*,4*R)-4-(1-Benzyl-3-indolyl)-*N*-(2-hydroxy-1-phenylethyl)-piperidin-2-one (18).**

From lactam **17a**: To a solution of lactam **17a** (160 mg, 0.34 mmol) in THF (15 ml) a 5% aqueous KOH (0.38 ml, 0.34 mmol) was added. The resulting mixture was stirred for 24 h at rt. The mixture was successively extracted with Et_2O and CH_2Cl_2 and the combined organic extracts, dried and evaporated, yielded piperidone **18** (70 mg, 48%), after flash chromatography (CH_2Cl_2-CH_3OH, 97:3): $[\alpha]_D$ = -18.2 (c = 0.4, CH_2Cl_2); IR ($CHCl_3$) 3450-3200 (OH), 1620 (CO) cm^{-1}; ^1H NMR (500 MHz) 1.89 (tm, J = 12 Hz, 1H, 5-H_a), 2.19 (dm, J = 12 Hz, 1H, 5-H_e), 2.68 (dd, J = 18 and 8 Hz, 3-H_a), 2.86-2.90 (m, 1H, 3-H_e), 2.92 (td, J = 12 and 2 Hz, 1H, 6-H_a), 3.10 (dt, J = 12 and 5 Hz, 1H, 6-H_e), 3.36-3.40 (m, 1H, 4-H), 3.67 (s, 1H, OH), 4.02 (dd, J = 17 and 10 Hz, 1H, β-H_A), 4.03 (dd, J = 17 and 5 Hz, 1H, β-H_B), 5.20 (s, 2H, CH_2Ph), 5.73 (dd, J = 10 and 5 Hz, 1H, α-H), 6.95 (s, 1H, In-2H), 7.10-7.40 (m, 14H, Ar-H), 7.55 (d, J = 7 Hz, 1H, In-4H); ^{13}C NMR 29.3 (C-4), 29.4 (C-5), 38.9 (C-3), 42.4 (C-6), 50.0 (CH_2Ph), 59.1 (C-α), 61.8 (C-β), 109.9 (In-C7), 118.9 (In-C4), 119.1 (In-C5), 122.0 (In-C6), 124.8 (In-C2), 126.8, 127.6, 127.9, 128.0, and 128.7 (Ph), 172.0 (CO); EIMS *m/z* (%) 424 (M^+,5), 393 (1), 305 (4), 264 (3), 233 (5),

106(4), 91(100), 65(14). Anal. Calcd for $C_{28}H_{28}N_2O_2.3/2\ H_2O$: C, 74.50; H, 6.78; N, 6.20. Found: C, 74.15; H, 6.56; N, 6.04.

From hydroxyamide **16** : To a solution of compound **16** (490 mg, 1.012 mmol) in CH_2Cl_2 (20 ml), cooled at -10°C, Et_3N (0.14 ml, 1.01 mmol) and MsCl (79.31 ml, 1.012 mmol) were added. The resulting mixture was stirred for 30 min at -10°C. Hexane (20 ml) was added to afford the $Et_3N.HCl$ precipitation. The precipitate was filtered off, the solvent was evaporated, and the residue dissolved in THF (20 ml). To the resulting solution, NaH (0.44 g, 18.22 mmol) was added and the mixture was stirred for 4 h at rt. The reaction was quenched with H_2O (10 ml) and the solvent was removed. The residue was extracted with CH_2Cl_2 and the organic extracts, dried and evaporated, yielded piperidone **18** (100 mg, 23%), after flash chromatography (CH_2Cl_2).

(α*R*)-4-(1-Benzyl-3-indolyl)-3-bromo-*N*-(2-hydroxy-1-phenylethyl)-piperidin-2-one (19, *cis-trans*). To a solution of piperidone **18** (350 mg, 0.83 mmol) in THF (2 ml) cooled at -78°C, *sec*-BuLi (1.59 ml, 2.06 mmol) was added, and the solution was stirred for 20 min. Cooled Br_2 (0.05 ml, 0.91 mmol) was added dropwise. The resulting mixture was stirred for 1 min 45 s at -78°C and the reaction was quenched with aqueous NH_4Cl. The solvent was evaporated and the residue, dissolved in CH_2Cl_2, was extracted with brine. The organic extracts were dried and evaporated, yielding a mixture of *cis* and *trans*-**19** which was flash chromatographed (EtOAc-hexane, 1:2). ***trans*-19**: (180 mg, 43%): $[\alpha]_D$ = -15.6 (c = 1.15, $CHCl_3$); IR ($CHCl_3$) 3390 (OH), 1623 (CO) cm^{-1}; ^1H NMR 1.93-2.00 (m, 1H, 5-H), 2.40-2.49 (m, 1H, 5-H), 3.20-3.29 (m. 1H, 6-H), 3.30-3.35 (m, 1H, 6-H), 4.21 (dd, J = 12 and 6 Hz, 1H, β-H_A 4.26 (dd, J = 12 and 3 Hz, 1H, β-H_B), 4.50 (d, J = 2 Hz, 1H, 3-H), 4.65 (m, 1H, 4-H), 5.24 (s, 2H, CH_2Ph), 7.10 (s, 1H, In-2H), 7.20-7.40 (m, 13H, Ar-H), 7.60 (d, J = 7 Hz, 1H, In-4H); ^{13}C NMR 27.1 (C-5), 39.1 (C-6), 48.9 (C-3), 49.0 (CH_2Ph), 49.2 (C-3), 56.9 (C-α), 60.2 (C-β), 109.2 (In-C7), 117.6 (In-C4), 118.7 (In-C5), 121.1 (In-C6), 124.8 (In-C2), 125.7, 126.6, 126.8, 127.0 and 127.7 (Ph), 168.8 (CO);

EIMS *m/z* (%) 504 (M^++1, 1), 502 (M^+-1, 1), 422 (7), 363 (10), 246 (10), 118 (9), 91(100). Anal. Calcd for $C_{28}H_{27}N_2O_2Br$: C, 66.92; H, 5.42; N, 5.58; Br, 15.72. Found: C, 68.88; H, 5.64; N, 4.85; Br, 15.65. ***cis*-19** (from a 4:1 mixture of *cis-trans* isomers) IR ($CHCl_3$) 3380 (OH), 1640 (CO) cm^{-1}; ^1H NMR 1.80-2.00 (m, 1H, 5-H), 2.50-2.70 (m, 1H, 5-H), 2.97 (dt, *J* = 12 and 5 Hz, 1H, 6-H), 3.21 (td, *J* = 12 and 5 Hz, 1H, 6-H), 3.87 (m, 1H, 4-H), 4.00-4.25 (m, 2H, β-H), 4.79 (d, *J* = 2 Hz, 1H, 3-H), 5.21 (s, 2H, CH_2Ph), 5.90 (dd, *J* = 10 and 5 Hz, 1H, α-H), 7.02-7.40 (m, 14H, Ar-H), 7.55 (d, *J* = 7 Hz, 1H, In-4H); ^{13}C NMR 24.3 (C-5), 38.6 (C-4), 40.2 (C-6), 48.8 (C-3), 50.6 (CH_2Ph), 58.6 (C-α), 61.5 (C-β), 110.6 (In-C7), 119.1 (In-C4), 119.9 (In-C5), 122.8 (In-C6), 126.3 (In-C2), 127.3, 128.1, 128.5, 129.2 and 129.3 (Ph), 168.9 (CO). Compound ***cis*-19** epimerises on SiO_2 to give the major *trans* isomer.

(α*R*)-4-(1-Benzyl-3-indolyl)-*N*-(2-hydroxy-1-phenylethyl)-Δ^3-piperidein-2-one (20) Procedure A: To a solution of bromide *trans*-**19** (60 mg, 0.12 mmol) in DMF (1 ml), potassium phthalimide (44 mg, 0.24 mmol) was added. After refluxing for 2 h, the mixture was washed 5 times with brine. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts, dried and evaporated, were flash chromatographed (EtOAc-hexane, 1:2) to yield **20** (40 mg, 79%): $[\alpha]_D$ = -9.2 (c = 0.9, $CHCl_3$); IR ($CHCl_3$) 3400 (OH), 1648 (CO), 1615 (C=C) cm^{-1}; ^1H NMR 2.40-2.48 (m, 2H, 5-H), 3.22 (dt, *J* = 12 and 6 Hz, 1H, 6-H), 3.44 (ddd, *J* = 12, 10 and 9 Hz, 1H, 6-H), 4.21 (t, *J* = 9 Hz, 1H, β-H_A), 4.25 (dd, *J* = 9 and 5 Hz, 1H, β-H_B), 5.34 (s, 2H, CH_2Ph), 5.89 (dd, *J* = 9 and 5 Hz, 1H, α-H), 6.93 (t, *J* = 4.5 Hz, 1H, 3-H), 7.00-7.40 (m, 14H, Ar-H), 7.75 (d, *J* = 7 Hz, 1H, In-4H); ^{13}C NMR 24.7 (C-5), 41.8 (C-6), 50.3 (CH_2Ph), 58.9 (C-α), 62.5 (C-β), 110.0 (In-C7), 119.9 (In-C4 and In-C5), 121.7 (In-C6), 126.9, 127.6, 127.8, 128.7, 128.8 and 129.7 (Ph), 132.9 (C-3), 167.9 (CO); EIMS *m/z* (%) 422 (M^+, 11), 404 (4), 363 (16), 300 (8), 245 (8), 209(6), 91(100). Anal. Calcd for $C_{28}H_{26}N_2O_2$: C, 79.58; H, 6.21; N, 6.63. Found: C, 78.98; H, 6.08; N, 6.53.

Procedure B: To a solution of bromide *trans*-**19** (40 mg, 0.08 mmol) in THF (1 ml), benzyl amine (0.02 ml, 0.16 mmol) was added. The resulting mixture was stirred for 24 h, then the solvent was evaporated. The residue was extracted with CH_2Cl_2 and the organic extracts, dried and evaporated, yielded **20** (40 mg, 79%), after flash chromatography (EtOAc-hexane, 2:1).

Procedure C: To a solution of bromide *trans*-**19** (50 mg, 0.1 mmol) and AcOH (0.1 ml) in DMF (1 ml) cooled at 0°C, a solution of NaN_3 (12.9 mg, 0.2 mmol) in H_20 (0.1 ml) was added. No evolution was observed at 0°C nor at rt. After 1 h at reflux, the transformation was complete, H_2O and EtOAc were added. The layers were separated and the organic solution was washed 3 times with brine. The organic extracts, dried and evaporated yielded piperidein-2-one **20** (35 mg, 84%).

(α*R*)-4-(1-Benzyl-3-indolyl)-3-diazo-*N*-(2-hydroxy-1-phenylethyl)-piperidin-2-one (21) and (α*R*)-*trans*-3-Azido-4-(1-benzyl-3-indolyl)-*N*-(2-hydroxy-1-phenylethyl)-piperidin-2-one (22). To a solution of piperidone **18** (60 mg, 0.14 mmol) in THF (2 ml) at -78°C, *sec*-BuLi (0.3 ml, 0.35 mmol) was added, and the solution was stirred for 15 min. A solution of trisylazide (66 mg, 0.21 mmol) in THF (1 ml) was added dropwise. After 15 min at -78°C, AcOH (1 ml) was added and the mixture was stirred until it reached rt. The solvent was evaporated, the residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. The organic extracts were dried and evaporated, yielding diazolactam **21** (60 mg, 63%) after flash chromatography (EtOAc-hexane, 2:1): $[\alpha]_D$ = -21.3 (c = 0.95, $CHCl_3$); IR ($CHCl_3$) 3384 (OH), 2082 (diazo), 1630 (CO) cm^{-1}; ^1H NMR 2.09 (m, 2H, 5-H), 2.93 (dd, *J* = 12 and 5 Hz, 1H, 6-H), 3.17 (dd, *J* = 12 and 6.6 Hz, 1H, 6-H), 4.05-4.20 (m, 2H, β-H), 4.47 (dd, *J* = 6 and 5.3 Hz, 1H,4-H), 5.23 (s, 2H, CH_2Ph), 5.80 (dd, *J* = 9 and 5 Hz, 1H, α-H), 7.00-7.40 (m, 14H, Ar-H), 7.59 (d, *J* = 8 Hz, 1H, In-4H); ^{13}C NMR 30.4 (C-5), 31.1 (C-4), 41.3 (C-6), 50.0 (CH_2Ph), 59.9 (C-α), 62.5 (C-β), 110.7 (In-C7), 119.2 (In-C4), 120.2 (In-C5), 122.8 (In-C6), 127.2, 127.3, 128.2, 128.3,

129.2 and 129.3 (Ph), 166.8 (CO); EIMS *m/z* (%) 450 (M^+, 1), 422 (9), 391 (33), 301 (9), 118 (10), 91 (100). Anal. Calcd for $C_{28}H_{26}N_4O_2$: C, 74.63; H, 5.82; N, 12.44. Found: C, 74.42; H, 5.96; N, 12.21.

Operating as above, only in one occasion *trans*-azidolactam **22** (20 mg, 31%) was isolated: $[\alpha]_D$ = -15.7 (c = 0.4, $CHCl_3$); IR ($CHCl_3$) 3380 (OH), 2100 (N_3), 1642 (CO) cm^{-1}; ^1H NMR 2.05-2.15 and 2.30-2.45 (2m, 1H each, 5-H), 2.95 (ddd, *J* = 12, 8 and 3 Hz, 1H, 6-H), 3.19 (ddd, *J* = 12, 7 and 1 Hz, 1H, 6-H), 3.32 (td, *J* = 7.4 and 4 Hz, 1H, 4-H), 4.05-4.15 (m, 2H, β-H), 4.38 (d, *J* = 7.4 Hz, 1H, 3-H), 5.28 (s, 2H, CH_2Ph), 5.85 (dd, *J* = 9 and 5.4 Hz, 1H, α-H), 7.00 (s, 1H, In-2H), 7.05-7.40 (m, 13H, Ar-H), 7.60 (d, *J* = 7 Hz, 1H, In-4H); ^{13}C NMR 26.5 (C-5), 35.7 (C-4), 41.6 (C-6), 50.1 (CH_2Ph), 58.9 (C-3), 61.4 (C-β), 64.8 (C-α), 110.1 (In-C7), 118.9 (In-C4), 119.4 (In-C5), 122.2 (In-C6), 125.4 (In-C2), 126.7, 127.7, 127.9, 128.2, and 128.9 (Ph), 169.2 (CO); EIMS *m/z* (%) 465 (M^+, 1), 437 (11), 423 (2), 406 (6), 391 (6), 316 (7), 273 (7), 220 (8), 91 (100). Anal. Calcd for $C_{28}H_{27}N_5O_2$: C, 72.22; H, 5.85; N, 15.05. Found: C, 72.10; H, 5.54; N, 14.59.

Ethyl 3-(1-benzyl-3-indolyl)-2-nitro-2-propenoate (23). A solution of carbaldehyde **8** (15 g, 63.8 mmol) in THF (319 ml, 0.2 M) was added dropwise at rt to a solution of $TiCl_4$ (7 ml, 63.8 mmol) in THF (127.6 ml) under mechanical stirring. Ethyl nitroacetate (10.6 ml, 95.7 mmol) and pyridine (20 ml) were subsequently added and the mixture was stirred at rt for 24 h. For the reaction to be complete, the addition of more $TiCl_4$ (14 ml, 127.6 mmol) was necessary. After 24 h, the reaction was quenched with H_2O (200 ml) and the solvent was evaporated. The aqueous residue was extracted with CH_2Cl_2 and the organic extracts, dried and evaporated, furnished an oil which was flash chromatographed (EtOAc-hexane 1:1) to yield of a mixture of nitroacrylates **21** (***E:Z*** = 2:1, 3.5 g, 78%) as a pale oil. **Isomer *(E)*-23** (higher Rf): IR ($CHCl_3$) 1720 (CO), 1630 (C=C), 1525 (NO_2) cm^{-1}; ^1H NMR 1.35 (t, *J* = 7 Hz, 3H, CH_3CH_2), 4.34 (q, *J* = 7 Hz, 2H, CH_3CH_2), 5.25 (s, 2H, CH_2Ph), 7.10-7.40 (m, 9H, Ar-H), 7.73 (m, 1H, In-4H), 7.94 (s,

1H, 3-H); ^{13}C NMR 14.1 (CH_3), 51.0 (CH_2Ph), 62.2 (CH_2CH_3), 110.9 (In-C7), 118.3 (In-C4), 122.3 (In-C5), 123.7 (In-C6), 126.4 (In-C2), 126.7 (Ph-*m*), 128.1 (Ph-*p*), 128.3, 128.7 (Ph-*o*), 132.9 (C-3), 136.2 (C-2), 160.2 (CO); EIMS *m/z* (%) 350 (M^+, 20), 303 (1), 261 (2), 231 (6), 170 (1), 128 (2), 91 (100).

5-*tert*-Butyl 1-ethyl 3-(1-benzyl-3-indolyl)-4-*tert*-butoxycarbonyl-2-nitroglutarates (24). To a solution of K^{t}BuO (176.2 mg, 1.57 mmol) in *tert*-BuOH (7.8 ml), di-*tert*-butyl malonate (0.35 ml, 1.57 mmol) was added and the resulting mixture was stirred for 30 min at rt. A solution of nitroacrylates **23** (500 mg, 1.43 mmol) in CH_2Cl_2 (7.2 ml) was added dropwise and stirring at rt was continued for 1h. The reaction was quenched with AcOH (2 ml) and the solvent was evaporated. The residue was extracted with CH_2Cl_2 and the organic extracts, dried and evaporated, yielded an oil which was flash chromatographed (EtOAc-hexane 1:2) to give a mixture of diastereoisomeric triesters **24** (700 mg, 87 %): IR (NaCl) 1750 and 1737 (CO), 1566 (NO_2) cm^{-1}; ^1H NMR 0.89 and 1.10 (2t, J = 7 Hz, 3H each, CH_3CH_2), 0.98 and 1.14 (2s, 6H and 3H, $C(CH_3)_3$), 1.28 and 1.39 (2s, 3H and 6H, $C(CH_3)_3$), 3.88 and 4.07 (2q, J = 7 Hz, 2H each, CH_3CH_2), 3.98 and 4.02 (2d, J = 7 Hz and J = 6 Hz, 1H each, 4-H),4.70 and 4.79 (2dd, J = 7 and 4.4 Hz and J = 6 and 5 Hz, 1H, 3-H), 5.25 (s, 2H, CH_2Ph), 5.83 and 5.99 (2d, J = 5 Hz and J = 4.4 Hz, 1H, 2-H), 7.00-7.40 (m, Ar-H), 7.73 (m, In-4H); ^{13}C NMR 13.3 and 13. 6 (CH_3), 27.1 and 27.5 ($C(CH_3)_3$), 27.7 and 27.8 ($C(CH_3)_3$), 36.0 and 36.2 (C-3), 51.2 (CH_2Ph), 55.9 and 56.3 (C-4), 62.5 and 62.8 (CH_2CH_3), 81.5 and 81.7 ($C(CH_3)_3$), 89.2 and 89.6 (C-2), 110.9 (In-C7), 119.3 and 119.4 (In-C4), 119.5 and 119.6 (In-C5), 121.9 and 122.0 (In-C6), 126.6 , 127.5, 127.9, 128.4 and 128.6 (Ph), 129.0 and 129.2 (In-C-2), 163.0 (2xCO), 166.1 (2xCO), 167.0 (2xCO); EIMS *m/z* (%) 566 (M^+, 7), 408 (21), 305 (20), 290 (11), 91 (100), 57 (29). Anal. Calcd for $C_{31}H_{38}N_2O_8$: C, 65.71; H, 6.76; N, 4.94. Found : C, 65.59; H, 6.76; N, 4.88.

5-*tert*-Butyl 1-ethyl 2-amino-1-ethyl-3-(1-benzyl-3-indolyl)-4-*tert*-butoxycarbonyl glutarates (25). A mixture of triesters **24** (4 g, 7.08 mmol), and W-2 Raney-Ni (50% in H_2O, 3 ml) in EtOH (300 ml) was hydrogenated in a Parr apparatus (1 atm) for 15 h. The catalyst was filtered off on Celite® washing thoroughly with EtOAc. The filtrate was evaporated to yield an oil which was flash chromatographed (EtOAc-hexane, 1:2) to give a diastereomeric mixture of **aminotriesters 25** (3.5 g, 6.53 mmol, 92 %) as a green oil: IR (NaCl) 3395 and 3345 (NH_2), 1722 (CO) cm^{-1}; ^1H NMR 0.92 and 0.98 (2 s, 6H and 3H, $C(CH_3)_3$), 1.04 and 1.15 (2t, J = 7 Hz, 3H each, CH_2CH_3), 1.44 and 1.50 (2s, 3H and 6H, $C(CH_3)_3$), 1.60-1.75 (br s, NH_2), 3.81 and 3.86 (2q, J = 7 Hz, 2H each, CH_3CH_2), 3.98 and 3.99 (2d, J = 3.5 Hz, 1H each, 4-H), 4.07 and 4.15 (2t, J = 3.5 Hz, 1H each, 3-H), 4.31 and 4.38 (2d, J = 3.5 Hz, 1H each, 2-H), 5.25 (s, CH_2Ph), 7.00-7.30 (m, Ar-H), 7.65 and 7.70 (2d, J = 7 Hz, 1H each, In-4H); ^{13}C NMR 14.0 (CH_3CH_2), 27.1 and 27.8 ($C(CH_3)_3$), 38.6 and 39.9 (C-3), 50.0 (CH_2Ph), 55.2 and 56.4 (C-4), 57.2 and 58.0 (C-2), 60.6 and 61.0 (CH_2CH_3), 109.4 (In-C-7), 119.0 and 119.4 (In-C4), 120.0 and 120.2 (In-C5), 121.8 and 122.0 (In-C6), 126.7 and 126.8 (Ph-*p*), 127.4 and 127.5 (Ph-*o*), 128.6 (Ph-*m*), 162.4, 167.0 and 168.0 (CO). EIMS *m/z* (%) 536 (M^+, 5), 463 (6), 434 (48), 278 (90), 260 (29), 91 (100), 57 (51). Anal. Calcd for $C_{31}H_{40}N_2O_6$: C, 69.38; H, 7.51; N, 5.22. Found : C, 67.66; H, 6.98; N, 5.00.

5-*tert*-Butyl 1-ethyl 2-(allyloxycarbonylamino)-3-(1-benzyl-3-indolyl)-4-*tert*-butoxycarbonyl glutarates (26 and 27). To a solution of **25** (3.5 g, 6.53 mmol) and pyridine (0.66 ml, 8.16 mmol) in THF (33 ml), cooled at 0°C, allyl chloroformate (0.87 ml, 8.16 mmol) was added dropwise. The reaction mixture was allowed to reach rt. After 1 h the precipitated pyridine.HCl was filtered off, washing with Et_2O. The solvent was evaporated to give an oil which was flash chromatographed (EtO_2-hexane, 1:3) to isolate diastereoisomeric triesters **26** and **27**. **Compound 26** (1.17 g, 29 %): IR (NaCl) 3430 (NH), 1740 and 1728 (CO) cm^{-1}; ^1H NMR 0.95 (s, 9H, $C(CH_3)_3$), 1.05 (t, J = 7 Hz, 3H,

CH_3CH_2), 1.50 (s, 9H, $C(CH_3)_3$), 3.49 (d, J = 5.3 Hz, 1H, 4-H), 3.98 (q, J = 7 Hz, 2H, CH_3CH_2), 4.23 (dd, J = 12 and 6 Hz, 1H, 3-H), 4.58 (d, J = 5.6 Hz, 2H, CH_2CH=), 4.99 (dd, J = 8.2 and 6.4 Hz, 1H, 2-H), 5.27 (s, 2H, CH_2Ph), 5.20-5.40 (m, 2H, CH=CH_2), 5.90 (m, 1H, CH=CH_2), 7.0-7.4 (m, 9H, Ar-H), 7.76 (m, 1H, In-4H); ^{13}C NMR 13.8 (CH_3), 27.1 ($C(CH_3)_3$), 27.8 ($C(CH_3)_3$), 37.9 (C-3), 50.1 (CH_2Ph), 56.9 (C-4), 57.2 (C-2), 61.2 (CH_2CH_3), 65.7 (CH_2CH=), 81.2 ($C(CH_3)_3$), 81.9 ($C(CH_3)_3$), 109.6 (In-C7), 117.7 (CH=CH_2), 119.4 (In-C4), 119.6 (In-C5), 121.9 (In-C6), 126.8, 127.3, 127.6, 128.4, and 128.6 (Ph), 132.6 (CH=CH_2), 155.4 (CON), 166.6, 167.5 and 171 (COO); EIMS *m/z* (%) 620 (M^+, 2), 562 (6), 491 (12), 434 (59), 278 (100), 91 (99), 57 (65). Anal. Calcd for $C_{35}H_{44}N_2O_8$: C, 67.72; H, 7.14; N, 4.51. Found : C, 66.82; H, 7.13; N, 4.26. **Compound 27** (2.3 g, 58%): IR (NaCl) 3440 (NH), 1744 (COO), 1730 (CON) cm^{-1}; ^1H NMR 0.90 (s, 9H, *tert*Bu), 1.17 (t, J = 7 Hz, 3H, CH_3CH_2), 1.50 (s, 9H, $C(CH_3)_3$), 3.37 (d, J = 11.8 Hz, 1H, 4-H), 3.95 (q, J = 7 Hz, 2H, CH_3CH_2), 4.45 (dd, J = 12 and 2.7 Hz, 1H, 3-H), 4.59 (d, J = 5.6 Hz, 2H, CH_2CH=), 5.08 (dd, J = 8.8 and 2.4 Hz, 1H, 2-H), 5.26 (s, 2H, CH_2Ph), 5.20-5.40 (m, 2H, CH=CH_2), 5.90 (m, 1H, CH=CH_2), 7.00-7.40 (m, 9H, Ar-H), 7.79 (m, 1H, In-4H); ^{13}C NMR 13.9 (CH_3), 27.0 ($C(CH_3)_3$), 27.8 ($C(CH_3)_3$), 38.3 (C-3), 50.0 (CH_2Ph), 55.4 (C-4), 56.1 (C-2), 61.6 (CH_2CH_3), 65.9 (CH_2CH=), 80.9 ($C(CH_3)_3$), 81.8 ($C(CH_3)_3$), 109.5 (In-C7), 117.9 (CH=CH_2), 119.2 (In-C4), 119.6 (In-C5), 121.9 (In-C6), 126.6, 127.1, 127.5, 127.9, and 128.6 (Ph), 132.5 (CH=CH_2), 156.3 (CON), 166.6, 167.1, and 170.9 (COO); EIMS *m/z*, (%) 620 (M^+, 2), 562 (6), 491 (12), 434 (59), 278 (100), 91 (99), 57 (65). Anal. Calcd for $C_{35}H_{44}N_2O_8$: C, 67.72; H, 7.14; N, 4.51. Found: C, 67.45; H, 7.50; N, 4.01.

***threo*-2-[2-(Allyloxycarbonylamino)-1-(1-benzyl-3-indolyl)-2-(ethoxycarbonyl)ethyl] malonic acid (28).** To a solution of triester *threo*-**27** (7.3 g, 11.8 mmol) in CH_2Cl_2 (60 ml), cooled to 0°C, TFA (4.5 ml, 58.85 mmol) was added dropwise. The reaction mixture was allowed to reach rt, and the reaction was monitored by TLC. After 48 h, the TFA was

evaporated and the residue, dissolved in CH_2Cl_2, was washed with brine. A white precipitate appeared at the interface, which was collected by filtration and dried yielding compound **28** (4.78 g, 9.42 mmol, 80 %): mp 152.8-153°C (MeOH); IR ($CHCl_3$) 3300-3100 OH), 1744, 1735, and 1700 (CO) cm^{-1}; ^1H NMR (CD_3OD) 1.17 (t, J = 7 Hz, 3H, CH_3CH_2), 3.90 (m, 1H, 4-H), 3.97 (q, J = 7 Hz, 2H, CH_3CH_2), 4.60 (br d, J = 3.5 Hz, 1H, 3-H), 4.66 (d, J = 4 Hz, 2H, CH_2CH=), 5.11 (d, J = 3.5 Hz, 1H, 2-H), 5.26-5.36 (dt, J = 10 and 1.6 Hz, 2H, CH=CH_2), 5.46 (s, 2H, CH_2Ph), 6.05 (m, 1H, CH=CH_2), 7.00-7.40 (m, 9H, Ar-H), 7.79 (m, 1H, In-4H); ^{13}C NMR (CD_3OD) 14.2 (CH_2CH_3), 39.4 (C-3), 50.9 (CH_2Ph), 55.9 (C-4), 57.1 (C-2), 62.7 (CH_2CH_3), 67.0 (CH_2CH=), 110.9 (In-C7), 117.9 (CH=CH_2), 120.3 (In-C4), 120.4 (In-C5), 122.9 (In-C6), 127.7, 128.1, 128.37, 128.5, 129.2, 129.5, and 129.7 (Ph), 139.5 (CH=CH_2), 158.6 (CON), 171.2, 171.5, and 172.4 (CO); EIMS *m/z* (%) 508 (M^+, 2), 446 (6), 334 (13), 278 (32), 233 (9), 91 (100), 57 (37). Anal. Calcd for $C_{27}H_{28}N_2O_8$: C, 63.77; H, 5.55; N, 5.51. Found: C, 63.97; H, 5.39; N, 5.44.

2-(Allyloxycarbonylamino)-3-(1-benzyl-3-indolyl) glutaric acids (29, *erythro-threo*). From diacid **28**: A solution of malonic diacid **28** (4.78 g, 9.42 mmol) in dioxane (50 ml) and 5% aqueous KOH (100 ml) was stirred for 30 min at rt. 4N HCl was added (pH = 3) and the mixture was refluxed for 4h. After cooling to rt, the reaction mixture was poured on saturated aqueous $NaHCO_3$ (pH > 7). The solution was then extracted with small portions of Et_2O. The aqueous layer was acidified (4N HCl) and extracted with CH_2Cl_2. The organic extracts, dried and evaporated, yielded diacid *threo*-**29** (4 g, 97 %), as an oil which was used without further purification: IR (NaCl) 3150 (OH), 1717 (br, CO), 1625 (C=C) cm^{-1}; ^1H NMR 2.81 (dd, J = 17 and 6 Hz, 1H, 4-H), 3.08 (dd, J = 17 and 9 Hz, 1 H, 4-H), 4.18 (dt, J = 9 and 6 Hz, 1H, 3-H), 4.53 (d, J = 6 Hz, 2H, CH_2CH=), 4.84 (dd, J = 9 and 5 Hz, 1H, 2-H), 5.15-5.30 (m, 2H, CH=CH_2), 5.21 (s, 2H, CH_2Ph), 5.85 (m, 1H, CH=CH_2), 6.90-7.30 (m, 9H, Ar-H), 7.66 (d, J = 8 Hz, 1H, In-4H), 8.90 (br s, 2H, OH);

^{13}C NMR 35.6 (C-3), 37.3 (C-4), 49.9 (CH_2Ph), 57.1 (C-2), 66.2 ($CH_2CH=$), 111.9 (In-C7), 118.0 ($CH=CH_2$), 119.4 (In-C4), 119.8 (In-C5), 122.3 (In-C6), 126.5 , 127.1, 127.6, and 128.8 (Ph), 132.3 ($CH=CH_2$), 156.3 (CON), 176.0 and177.1 (COO); EIMS *m/z* (%) 436 (M^+, 1), 418 (2), 334 (33), 261 (9), 233 (15), 91 (100), 65 (14). Anal. Calcd for $C_{24}H_{24}N_2O_6$: C, 66.03; H, 5.55; N, 6.42. Found: C, 66.09; H, 5.70; N, 6.53.

From triester **27 (or 27+28)**: A mixture of triester **27** (7.4 g, 11.9 mmol) in dioxane (40 ml) and 5% aqueous KOH (100 ml) was refluxed for 3 h. The reaction mixture was acidified with 4N HCl, and refluxed for 4 h. After work-up as above, a mixture of glutaric acids *erythro*- and *threo*-**29** was obtained (3.7 g, 71%).

2-(Allyloxycarbonylamino)-3-(1-benzyl-3-indolyl)glutaric anhydrides (30, *cis-trans*). From ***threo*-29**: To a stirred solution of diacid **29** (2.5 g, 5.74 mmol) in THF (120 ml) Et_3N (0.8 ml, 5.74 mmol) was added. The reaction mixture was cooled to -20°C. After stirring for 15 min, MsCl (446 µl, 5.74 mmol) was added, followed by a solution of Et_3N (1.6 ml, 11.48 mmol) in THF (20 ml). The reaction mixture was stirred at -30°C for 2 h. The solvent was evaporated. The residue, dissolved in CH_2Cl_2 (50 ml), was washed successively with saturated aqueous $NaHCO_3$ and brine, dried and evaporated to give anhydride **30** (3.1 g, 88 %): IR (NaCl) 1720 (CO), 1650 (C=C) cm^{-1}; ^1H NMR 3.00-3.40 (m, 2H, 4-H), 3.95 (m, 1H, 3-H), 4.23 (d, *J*= 7 Hz, 2H, $CH_2CH=$), 4.68 (dt, *J*=6 and 2 Hz, 1H, 2-H), 5.00-5.50 (m, 4H, $CH_2=CH$ and CH_2Ph), 5.80 (m, 1H, $CH_2=CH$), 6.90-7.30 (m, 9H, Ar-H), 7.60 (d, *J* = 8 Hz, 1H, In-4H); ^{13}C NMR 31.8 (C-3), 37.2 (C-4), 49.9 (CH_2Ph), 55.8 (C-2), 65.8 ($CH_2CH=$), 111.2 (In-C7), 117.4 ($CH=CH_2$), 118.5 (In-C4), 119.6 (In-C5), 122.14 (In-C6), 126.6, 127.3, 127.5, 128.5, and 128.6 (Ph), 132.1 ($CH=CH_2$), 156.1 (CON), 173.1 (CO), 174.2 (CO); EIMS *m/z* (%) 418 (M^+, 7), 334 (14), 278 (58), 91 (100). CIMS 447 (M^++ 29, 65), 432 (M^++ 14, 2), 419 (M^++ 1, 40), 375 (100).

From the mixture ***erythro*- and *threo*-29**: Operating as above, from diacids **29** (3.7 g,

8.48 mmol), THF (150 ml), Et_3N (3.54 ml, 25.44 mmol), and MsCl (0.66 ml, 8.48 mmol), a mixture of anhydrides *cis*- and *trans*-**30** was obtained (3.1 g, 88 %)

(αR)-*N*-(2-Acetoxy-1-phenylethyl)-3-(allyloxycarbonylamino)-4-(1-benzyl-3-indolyl)-glutarimides (31, *cis-trans*). From the mixture of *cis*- and *trans*-30. To a solution of a mixture of anhydrides **30** (3.1 g, 7.42 mmol) in $CHCl_3$ (37 ml), *(R)*-(-)-phenylglycinol (1.1 g, 7.42 mmol) was added, and the resulting solution was refluxed for 48 h. The solvent was evaporated and the residue, dissolved in AcCl (30 ml), was refluxed for 4 h. The excess of AcCl was evaporated under reduced pressure, and the resulting residue was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$, dried, and evaporated to give a 1:3.7 mixture of imides *cis*- and *trans*-**31** which were separated by flash chromatography (EtOAc - Hexane, 7:3). **Imide *trans*-31** (lower Rf, 2.07 g, 48%): $[\alpha]_D$ = -22.4 (c =0.8, $CHCl_3$); IR (NaCl) 1744 and 1696 (CO), 1539 (C=C) cm^{-1}; ^1H NMR 2.01 (s, 3H, $COCH_3$), 2.75 (dd, *J* = 17.5 and 4 Hz, 1H, 5-H), 3.21 (dd, *J* = 17.5 and 8.5 Hz, 1H, 5-H), 3.88 (m, 1H, 4-H), 4.24 (dd, *J* = 11.5 and 4.5 Hz, 1H, β-H_A), 4.38 (dd, *J* = 11.5 and 7.5 Hz, 1H, β-H_B), 4.59 (d, *J* = 3 Hz, 1H, 3-H); 4.68 (dd, *J* = 5.5 and 1 Hz, 2H, CH_2CH=), 5.22 (m, 1H, CH_2=CH), 5.24 (s, 2H, CH_2Ph), 5.34 (m, 2H, α-H and CH_2=CH), 5.83 (m, 1H, CH=CH_2), 6.95 (s, 1H, In-2H), 7.00-7.30 (m, 13H, Ar-H) and 7.55 (d, *J* = 8 Hz, 1H, In-4H); ^{13}C NMR : 20.8 ($COCH_3$), 32.5 (C-4), 38.3 (C-5), 50.1 (CH_2Ph), 52.9 (C-3), 65.9 (C-β), 67.0 (C-α), 67.6 (CH_2CH=), 110.3 (In-C7), 118.6 (CH=CH_2), 119.2 (In-C4), 119.9 (In-C5), 122.7 (In-C6), 125.0 (In-C2), 126.7, 126.8, 127.8, 128.1, 128.8, 130.9 (CH=CH_2), 151.5 (NCOO), 169.6 (CO), 171.3 (CO), 173.1 (CO); EIMS *m/z* (%) 579 (M^+, 4), 418 (4), 233 (7), 331 (8), 521 (11), 289 (13), 260 (35), 91 (100); Anal. Calcd for $C_{34}H_{33}N_3O_6$: C, 70.45; H, 5.74; N, 7.25. Found : C, 70.38; H, 5.65; N, 7.15. **Imide *cis*-31** (higher Rf, 559 mg, 13%): $[\alpha]_D$ = -10.1 (c =1.34, $CHCl_3$); IR (NaCl) : 1742 and 1731 (CO), 1710 (CO imide) cm^{-1}; ^1H NMR: 2.07 (s, 3H, $COCH_3$), 2.79 (dd, *J* = 17 and 7.5 Hz, 1H, 5-H), 3.18 (dd, *J* = 17 and 13.5 Hz, 1H, 5-H), 4.16 (m,

1H, 4-H), 4.73 (m, 2H, C*H*$_2$CH=), 4.78 (dd, *J* = 11 and 7.5 Hz, 1H, β-H$_A$), 4.85 (dd, *J* = 11 and 5.5 Hz, 1H, β-H$_B$), 5.04 (d, *J* = 8.5 Hz, 1H, 3-H), 5.24 (s, 2H, CH$_2$Ph), 5.26 (m, 2H, α-H and C*H*$_2$=CH), 5.38 (ddd, *J* = 12.5, 3, and 1.5 Hz, 1H, C*H*$_2$=CH), 5.91 (m, 1H, C*H*=CH$_2$), 6.92 (s, 1H, In-2H), 7.05-7.40 (m, 13H, Ar-H) , 7.61 (d, *J* = 7.5 Hz, 1H, In-4H); ^{13}C NMR : 20.1 (CO*C*H$_3$), 31.7 (C-4), 36.1 (C-5), 49.8 (CH$_2$Ph), 51.5 (C-α), 60.7 (C-β), 63.5 (C-3), 67.1 (*C*H$_2$CH=), 109.8 (In-C7), 118.8 (CH=*C*H$_2$), 119.1 (In-C4), 119.6 (In-C5), 122.4 (In-C6), 125.5 (In-C2), 126.5, 126.6, 127.6, and 128.6 (Ph), 130.9 (*C*H=CH$_2$), 150.6 (NCOO), 172.3 (CO),173.9 (CO). Anal. Calcd for $C_{34}H_{33}N_3O_6$: C, 70.45; H, 5.74; N, 7.25. Found : C, 70.51; H, 5.45; N, 7.21.

From ***trans*-30**: Operating as above from anhydride *trans*-**12** (1.5 g, 3.59 mmol), *(R)*-(-)-phenylglycinol (492 mg, 3.59 mmol) in CHCl$_3$ (20 ml) imide *trans*-**31** (0.95 g, 45%) was obtained.

(α*R*, 3*R, 4*R**)-*N*-(2-Acetoxy-1-phenylethyl)-2-(allyloxycarbonylamino)-3-(1-benzyl-3-indolyl)-5-hydroxypentanamide (*threo*-32).** To a solution of imide ***trans*-31** (100 mg, 0.17 mmol) in EtOH-THF (1:1, 30 ml), NaBH$_4$ (23 mg, 0.6 mmol) was added. The resulting mixture was stirred at -40°C, adding 3 drops of a 2N HCl every 15 min. After 2 h the mixture was acidified with 2N HCl (pH=3), and stirred at -40°C for 1 h. The reaction mixture was neutralized with saturated aqueous NaHCO$_3$. The EtOH was evaporated, the aqueous layer was extracted with CH$_2$Cl$_2$ and the combined organic extracts, dried and evaporated, were flash chromatographed (CH$_2$Cl$_2$) to give **32** (70 mg, 70%): $[\alpha]_D$ = -27.9 (c = 0.5, CHCl$_3$); IR (CHCl$_3$) 3450 (NH), 3420 (OH), 1685 (br, CO) cm^{-1}; ^{1}H NMR 2.01 (s, 3H, COCH$_3$), 2.11 (quint., *J* = 6 Hz, 2H, 4-H), 3.68 (dt, *J* = 11 and 6 Hz, 2H, 5-H), 3.76 (dd, *J* = 13 and 7 Hz, 1H, 3-H), 4.19 (dd, *J* = 11 and 4 Hz, 1H, β-H$_A$), 4.21 (dd, *J* = 11 and 7 Hz, 1H, β-H$_B$), 4.56 (dd, *J* = 8 and 2 Hz, 2H, C*H*$_2$CH=), 4.63 (t, *J* = 4 Hz, 1H, 2-H), 5.18 (br s, 2H, C*H*$_2$=CH), 5.21(d, *J* = 4 Hz, 1H, CH$_2$Ph), 5.24 (m, 1H, α-H), 5.26 (d, *J* = 4 Hz, 1H, CH$_2$Ph), 5.87 (m, 1H, C*H*=CH$_2$), 6.53 (br s, 1H, NH), 6.99 (s, 1H, In-2H),

7.00-7.30 (m, 13 H, Ar-H), 7.76 (d, J = 7 Hz, 1H, In-4H); ^{13}C NMR 20.5 ($COCH_3$), 33.9 (C-4), 36.2 (C-3), 49.9 (CH_2Ph), 52.5 (C-3), 58.1 (C-α), 60.7 (C-5), 65.7 (C-β), 65.8 (CH_2CH=), 109.9 (In-C7), 117.7 (CH=CH_2), 119.3 (In-C4), 119.5 (In-C5), 122.3 (In-C6), 125.8 (In-C2), 126.5, 126.6, 126.8, 126.9, 127.6, 128.6, and 128.9 (Ph), 132.4 (CH=CH_2), 150.2 (NCOO), 170.6 (CO), 171.1 (CO); EIMS *m/z* (%) 583 (M^+, 1), 482 (2), 357 (2), 264 (73), 246 (8), 220 (4), 91 (100). Anal. Calcd for $C_{34}H_{37}N_3O_6$: C, 69.95; H, 6.39; N, 7.20. Found: C, 69.99; H, 6.38; N, 7.23.

(*αR, 3R*, 4R)-*N*-(2-Acetoxy-1-phenylethyl)-3-(allyloxycarbonylamino)-4-(1-benzyl-3-indolyl)-piperidin-2-one (33).** To a solution of hydroxyamide **32** (140 mg, 0.24 mmol) in THF (5 ml), cooled at -40°C, Et_3N (0.033 ml, 0.24 mmol) and MsCl (0.02 ml, 0.24 mmol) were added sequentially . The resulting mixture was stirred for 2 h at -40°C. Hexane (20 ml) was added to afford the Et_3N.HCl precipitation. The precipitate was filtered off, the solvent was evaporated, and the residue was dissolved in CH_3CN (1 ml). To the resulting solution, DBU (0.05 ml, 0.3 mmol) was added and the mixture was stirred for 1 h at rt. The reaction was quenched with H_2O (1 ml) and the solvent was removed. The residue was extracted with CH_2Cl_2 and the organic extracts, dried and evaporated, yielded piperidone **33** (35 mg, 26%) after flash chromatography (EtOAc-hexane, 1:2): $[\alpha]_D$ = -19.6 (c = 0.5, $CHCl_3$); IR ($CHCl_3$) 3450-3200 (OH), 1750, 1700 and 1620 (CO) cm^{-1}; ^{1}H NMR (500 MHz) 1.62 (s, 3H, $COCH_3$), 2.19-2.28 (m, 1H, 5-H), 2.70 (br t, J = 10.5 Hz, 1H, 5-H), 2.77 (dd, J = 10.5 and 7 Hz, 1H, β-H_A), 3.57 (td, J = 10.5 and 6.5 Hz, 1H, 6-H), 3.66 (dd, J = 10.5 and 2.5 Hz, 1H, β-H_B), 3.84-3.98 (m,2H, 4-H and 6-H), 4.50-4.60 (m, 3H, α-H and CH_2CH=), 4.38 (d, J = 8 Hz, 1H, 3-H), 5.26 and 5.35 (2d, J = 14 Hz, 1H each, CH_2Ph), 5.00-5.50 (m, 2H, CH=CH_2), 5.88-5.98 (m, 1H, CH=CH_2), 6.78 (br s, 2H, Ph-H), 7.01 (s, 1H, In-2H), 7.11-7.31 (m, 10H, Ar-H), 7.34 (d, J = 7 Hz, 1H, In-7H), 7.62 (d, J = 7 Hz, 1H, In-4H); ^{13}C NMR 20.5 ($COCH_3$), 27.3 (C-5), 39.0 (C-4), 45.8 (C-6), 50.1 (CH_2Ph), 51.6 (C-3), 63.9 (C-α), 64.9 (C-β), 65.9 (CH_2CH=), 110.6 (In-C7), 117.3

(CH=CH_2), 118.2 (In-C4), 119.9 (In-C5), 122.4 (In-C6), 126.1 (In-C2), 126.5, 126.9, 127.6, 127.7, 128.5, and 128.5 (Ph) 128.7 (CH=CH_2), 169.5, 169.6 and 170.2 (CO); EIMS *m/z* (%) 565(M^+,8), 374 (8), 359 (30), 318 (41), 246 (15), 163(9), 91(100). Anal. Calcd for $C_{34}H_{35}N_3O_5$: C, 72.18; H, 6.24; N, 7.43. Found: C, 72.21; H, 5.98; N, 7.21.

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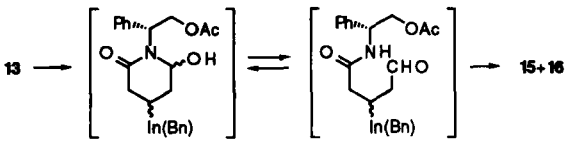

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22. When the reduction was carried out on the triethyl triester analogue of **24**, spontaneous intramolecular lactamization was observed.

23. Only one diastereomer of imide *trans*-**31** was isolated by column chromatography, even if the second diastereomer was detected in the crude reaction mixture. Similarly, only one diastereomer of imide *cis*-**31** was isolated.

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