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Conformationally Restricted Analogues of the Potent CCK-B Antagonist CI-988

M. Higginbottom, D. R. Hill, D. C. Horwell, E. Mostafai, N. Suman-Chauhan and Edward Roberts*
Parke-Davis Neuroscience Research Centre, Addenbrookes Hospital Site, Hills Road, Cambridge, CB2 2QB, U.K.

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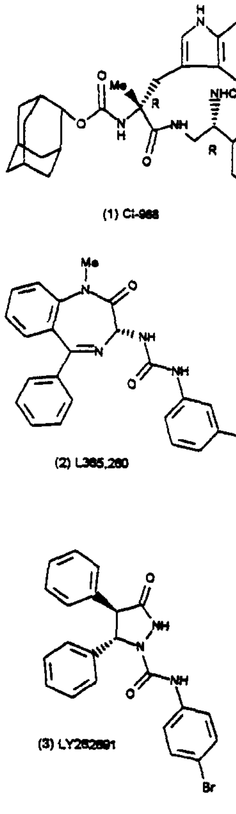
Abstract—The synthesis and structure–activity relationships (SAR) for a series of conformationally restricted analogues of the selective cholecystokinin (CCK) antagonist CI-988 and some closely related analogues are described. A series of appropriately substituted *cis*- and *trans*-amino decalins are prepared that mimic the through bond distances between the functional groups in the parent compound CI-988 whilst restricting bond rotation. This strategy has led to conformationally more rigid derivatives that have increased CCK-B receptor binding affinity.

Introduction

Peptidic and non-peptidic ligands for the two cholecystokinin (CCK) receptor subtypes, CCK-A and CCK-B, have been reported.[1,2] The CCK-B receptor is found in the central nervous system (CNS), whilst the CCK-A receptor is found predominantly in the periphery.[3,4] Figure 1 shows three chemically distinct ligands for the CCK-B receptor subtype The compound CI-988 (**1**) (Figure 1) has been reported to be a CCK-B receptor antagonist displaying potent anxiolytic properties in a number of models and is currently under clinical trials as an antipanic/antianxiety agent.[5,6] Similarly compounds L-365260 (**2**)[7,8] and LY-262691 (**3**)[9,10] have also been shown to be selective CCK-B receptor antagonists.



(1) CI-988

(2) L365,260

(3) LY262691

Figure 1.

Whilst **1** has excellent affinity (IC$_{50}$ CCK-B = 1.7 nM) and selectivity for the CCK-B receptor over the CCK-A receptor (CCK-A/CCK-B ratio = 2500),[5] it remains a very flexible molecule. Reducing the entropy of the system may be achieved by decreasing the number of rotatable bonds. As each rotatable bond is thought to lessen the energy of binding by an average of 0.7 Kcal per bond[11] an increase in receptor affinity may be envisaged. Less flexible analogues could also result in a rise in receptor selectivity.[12–14] Ligands that are of a rigid or semi-rigid construction have been used to study the three dimensional conformation of bioactive molecules and develop pharmacophore models from which novel molecules with enhanced acceptor affinity and selectivity may be designed.[15–17] Such conformational restrictions may be accomplished by the introduction of cyclic structures into the parent molecule (**1**). Initially, it was decided to link the aromatic ring with the carbon atom alpha to the amine group in order to restrict rotation of the phenyl ring as found in a tetrahydronaphthyl group (Figure 2). The alpha carbon atom was chosen over the nitrogen atom as the X-ray crystal structure of **1** shows that the N–H group of the phenethylamine may be involved in intramolecular hydrogen bonding to the urethane carbonyl.[18]

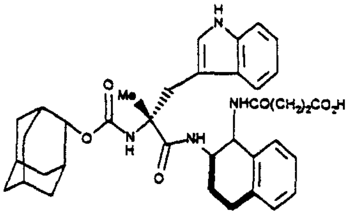
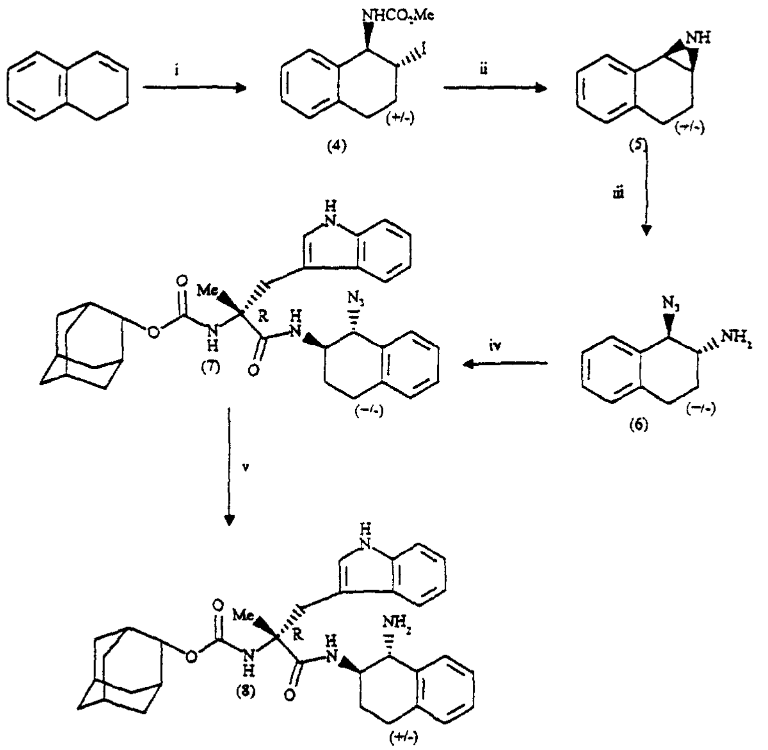


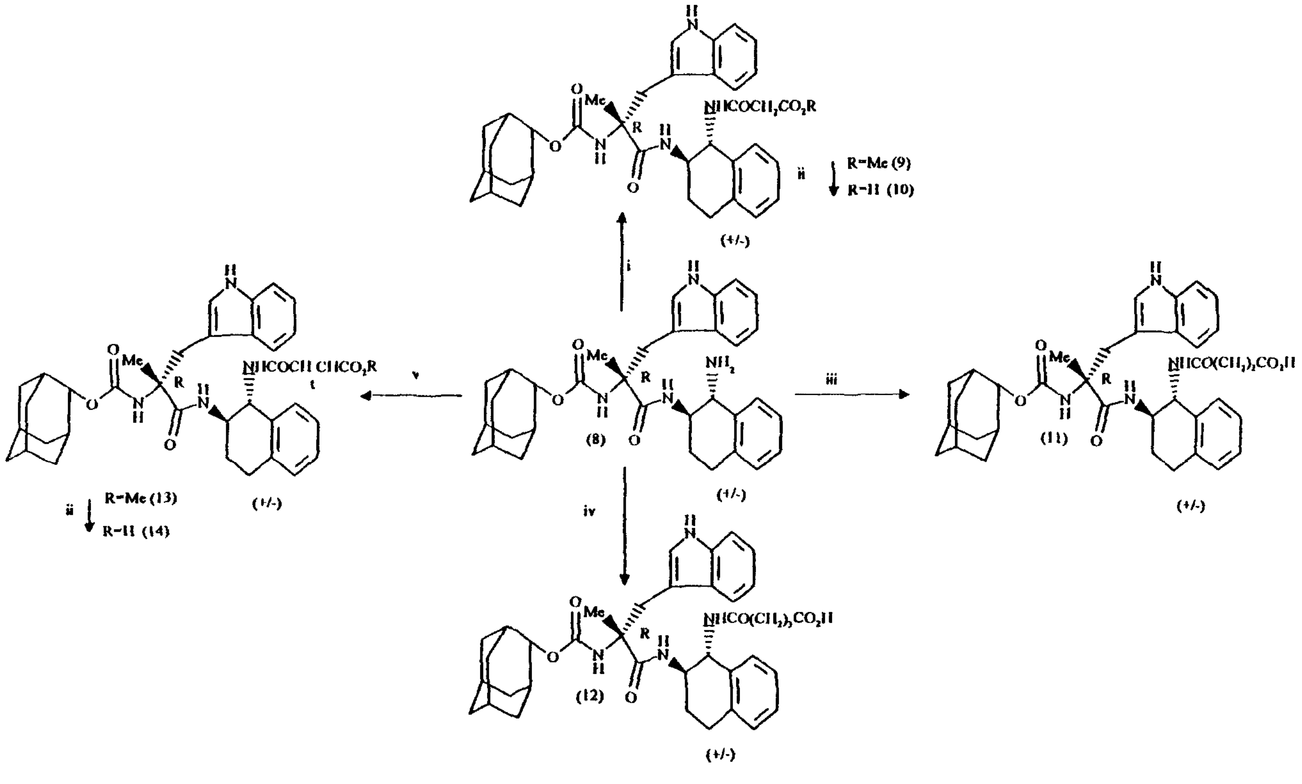
Figure 2.

Chemistry

Scheme I outlines the synthesis of the versatile intermediate amine **8**. Compounds **4**, **5** and **6** were prepared according to literature precedent.[19] Simple coupling of the azido amine **6** to 2-adamantyloxycarbonyl-α-methyl-*R*-tryptophan pentafluorophenyl ester in EtOAc afforded the amide **7**. Hydrogenation of the azide group using Lindlar's catalyst yielded the amine **8**. This amine



Scheme I. Reagents: i) I_2, AgOCN, MeOH; ii) KOH, EtOH; iii) NaN_3, NH_4Cl, EtOH, H_2O; iv) 2-adamantyloxycarbonyl-α-methyl-*R*-tryptophan pentafluorophenyl ester; v) Lindlar catalyst, H_2.



Scheme II. Reagents: i) methyl malonyl chloride; ii) aq. LiOH; iii) succinic anhydride, DMAP; iv) glutaric anhydride, DMAP; v) methyl pentafluorophenyl.

tended to decompose on storage and was therefore prepared fresh as required and was utilised according to Scheme II. Compound **9** was prepared by the action of methyl malonyl chloride on amine **8** and could be separated into its two diastereoisomers **9a** and **9b** by chromatography. A 1:1 diastereomeric mixture of **9** was saponified using a dropwise addition of aqueous lithium hydroxide being careful to avoid possible hydantoin formation,[20] to give the carboxylic acid **10**. Amine **8** opened both succinic and glutaric anhydrides in refluxing EtOAc and in the presence of *N,N*-dimethylaminopyridine (DMAP) to produce **11** and **12** respectively. The ester **13** was made by the action of **8** on the activated ester; methyl pentafluorophenyl fumarate. Hydrolysis of **13** to its acid **14** was done using aqueous lithium hydroxide.

Scheme III shows the synthetic route to the intermediate **19**. Compound **15** was prepared in an exactly analogous way to **4** except using benzyl alcohol instead of methanol. Substitution of the iodine with azide using sodium azide in DMF gave the *cis*-substituted product **16**. The azide group was reduced to the amine selectively using Lindlar's catalyst in EtOH under an atmosphere of hydrogen. The resulting amine **17** was coupled with 2-adamantyloxycarbonyl-α-methyl-*R*-tryptophan pentafluorophenyl ester in the same manner as **7** to give **18**. Reduction of the benzyl urethane group to the amine **19** was done by hydrogenation in EtOH using 10% palladium on carbon as catalyst. This amine was also unstable on storage and was therefore prepared fresh when required from its precursor. Reaction of **19** with active esters and anhydrides gave compounds **20**, **21** and **22** as performed in Scheme II. Saponification of **22** with aqueous lithium hydroxide yielded **23**.

Results/Discussion

Table 1 shows the CCK-A and CCK-B receptor binding affinities for the conformationally restricted analogues of CI-988 (**1**) that were prepared according to Schemes I–IV. It has previously been reported that the stereocentres in CI-988 are crucial to its CCK-B receptor binding affinity and selectivity.[5,6] This information must be considered in all evaluations of data shown in Table 1 as all but a few compounds are approximately 1:1 mixtures (as determined by NMR spectroscopy) of isomers about the naphthyl centres analogous to the β-carbon centre of the substituted phenethylamine centre in CI-988. However, some trends are apparent from the data. The *trans*-substituted naphthyl isomers **11**, **12** and **14** (CCK-B IC_{50}'s = 2.31, 1.51 and 0.89 nM respectively) generally have more binding affinity at the CCK-B receptor than the corresponding *cis*-substituted naphthyl isomers **20**, **21** and **23a** and **b** (CCK-B IC_{50}'s = 6.16, 10.3, 99.5 and 11.3 nM respectively). Interestingly, intermediate esters **13** and **22** from each series are equipotent.

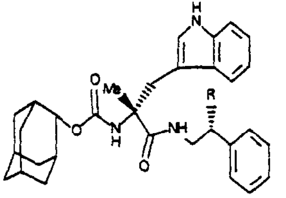
Trans-derivatives **10**, **11** and **14** show very similar binding affinity at the CCK-B receptor to the parent compounds listed in Table 2 for reference. Only compound **12** (CCK-B IC_{50} = 1.51nM) shows a significantly enhanced affinity (ca. 10-fold) when compared to the corresponding parent (CCK-B IC_{50} = 14 nM). These semi-rigid analogues do, however, show enhanced affinity for the CCK-A receptor subtype and accordingly are less selective than their parents.

Table 1. CCK Receptor binding affinities[a] of conformationally constrained analogues

	Receptor Binding Affinity	
Compound Number	IC_{50} CCK-B (nM)	IC_{50} CCK-A (nM)
9a	10.4 (7 97-17 5)	911 (819-1040)
9b	34.2 (23.1-42.3)	1140 (684-2710)
10	1.48 (1.15-2.26)	357 (287-452)
11	2.31 (1.69-2.85)	460 (369-565)
12	1.51 (1.23-1.89)	437 (373-518)
13	11.5 (8.72-14.1)	338 (240-452)
14	0.89 (0.77-1.03)	116 (104-133)
20	6.16 (4.12-9.24)	1690 (929-4930)
21	10.3 (7.81-14.8)	1170 (893-1760)
22	12.2 (8.11-2.15)	1610 (1160-2190)
23a	99.5 (68.3-151)	309 (284-336)
23b	11.3 (7.69-17.9)	717 (555-898)

[a] IC_{50} represents the concentration (nM) producing half maximal inhibition of specific binding of [^{125}I]-Bolton Hunter CCK-8 to CCK receptors in the mouse cerebral cortex (CCK-B) or the rat pancreas (CCK-A). The values given are the geometric mean and the range from at least three separate experiments.

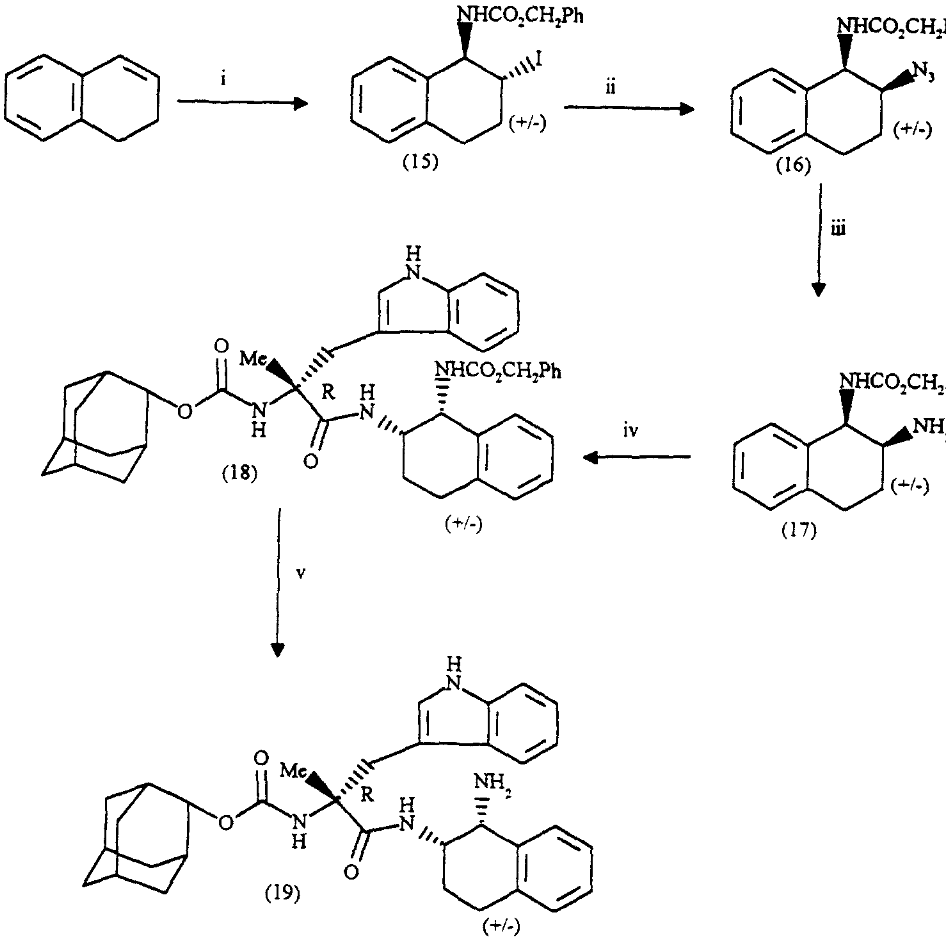
Table 2. CCK Receptor binding affinities[a] of reference compounds[5]



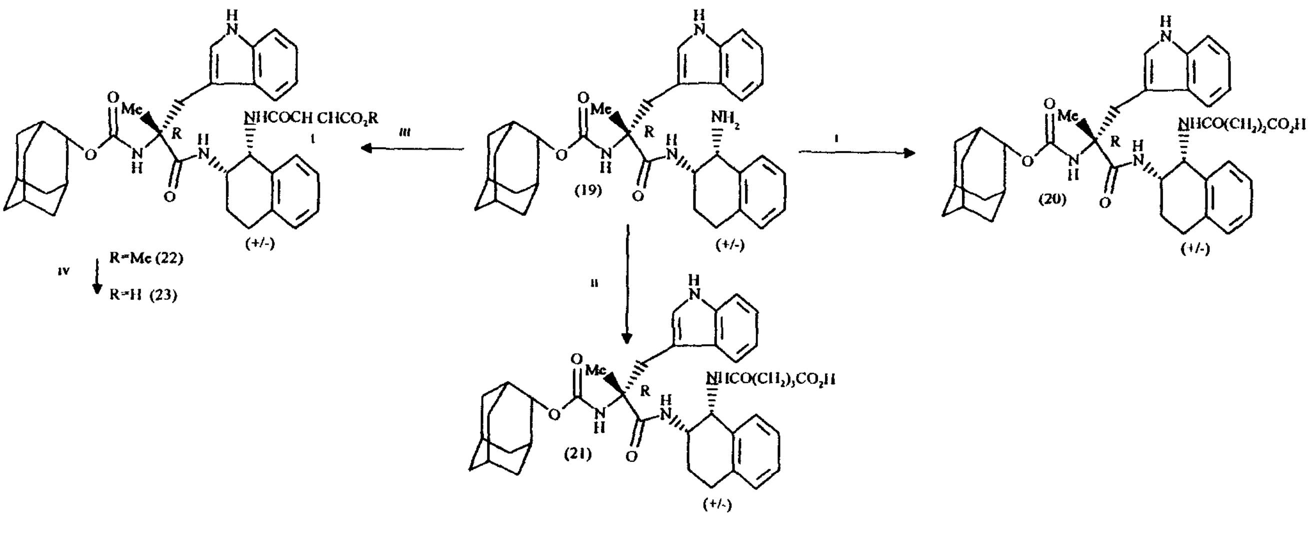
		CCK Receptor Binding Affinity	
	R	IC_{50} CCK-B (nM)	IC_{50} CCK-A (nM)
	NHCOCH:CHCO$_2$H	0.7 (0.5-1.0)	790 (680-1000)
	NHCO(CH$_2$)$_3$CO$_2$H	14 (12-17)	1300 (250-3000)
(1)	NHCO(CH$_2$)$_2$CO$_2$H	1.7 (1.3-2.7)	4300 (1200-8500)
	NHCOCH$_2$CO$_2$H	0.8 (0.5-1.0)	870 (620-1500)

[a] Binding affinities are as defined in the footnote to Table 1.

All but two of these compounds (**23a** and **23b**) are approximately 1:1 mixtures of isomers as determined by NMR spectroscopy. As stated earlier, the absolute stereochemistry of this class of compound plays a crucial role in receptor affinity and selectivity such that one isomer may have superior CCK-B binding and/or



Scheme III. Reagents: i) I_2, AgOCN, $PhCH_2OH$; ii) NaN_3, DMF; iii) Lindlar catalyst, H_2; iv) 2-adamantyloxycarbonyl-α-methyl-*R*-tryptophan pentafluorophenyl ester; v) 10%Pd/C, H_2.



Scheme IV. Reagents: i) succinic anhydride, DMAP; ii) glutaric anhydride; iii) methyl pentafluorophenyl fumarate, H_2; iv) aq. LiOH.

selectivity to the second. This "active" isomer from the *trans*-series would show an increase in affinity when compared to its acyclic counterpart. This disparity between individual isomers is exemplified by the difference seen in receptor affinity and selectivity shown by **23a** and **23b** albeit in the less active *cis*-series. We may therefore assume that in either series, one isomer will be more active than the other in binding to the CCK-B receptor. This would mean that the more active components of the *trans*-series of compounds would possess greater affinity for the CCK-B receptor than their corresponding parents. This result is a direct consequence of ring formation and conformational restriction. The *cis*-series of compounds, being less potent, presumably offers the aromatic ring and/or it's side chain a manner which is unfavourable for receptor binding. It is more difficult to draw any conclusions about receptor selectivity.

Conclusion

In conclusion, the potent central cholecystokinin receptor antagonist CI-988 has been modified at its C-terminal substituted phenethylamine moiety to produce less flexible cyclic molecules. Investigation of both the *trans*- and *cis*-isomers about the naphthyl centres and examination of the CCK-A and CCK-B binding affinities of these compounds suggests that restricting the conformational freedom of the acyclic parent may increase receptor binding affinity. The *trans*-substituted tetralin series binds to the CCK-B receptor in a manner more favourable than the *cis*-series as determined by their respective inhibition constants (IC$_{50}$).

Experimental Section

Biology

Receptor binding assays. CCK-A receptor binding assays were performed on male rat pancreas in triplicate. Tissue (250 mg) homogenized in ice-cold Tris-HCl (pH 7.4) (50 mL of a 50 mM soln) was centrifuged at 20,000 x *g*. The pellet was washed once by resuspension in Tris-HCl followed by recentrifugation and then resuspended in a standard assay buffer (SAB) comprising 10 mM Hepes (pH 7.2 at 21 °C), 130 mM NaCl, 5 mM $MgCl_2$, 4.7 mM KCl, 1 mM 1,2-bis(2-aminoethoxy)ethane and 0.25 mg/ mL bacitracin at a tissue concentration of 0.5 mg original wet weight per mL of buffer.

CCK-B receptor binding assays were performed on male mouse cerebral cortex. Tissue homogenized in 10 volumes of 50 mM ice-cold Tris-HCl buffer (pH 6.9 at 21 °C) was centrifuged for 15 min at 20,000 x *g*. The pellet was washed by resuspension in ice-cold 50 mM Tris-HCl and recentrifuged as above. The final pellet was then washed and resuspended in a standard assay buffer (SAB) comprising 10 mM Hepes (pH 7.2 at 21 °C), 130 mM NaCl, 5 mM $MgCl_2$, 4.7 mM KCl, 1mM 1,2-bis(2-aminoethoxy)ethane and 0.25 mg/ mL bacitracin at a tissue concentration of 2 mg original wet weight per mL of SAB.

For each of the binding assays, aliquots of tissue (400 µL) were incubated at 21 °C for 120 min with 35 pM [^{125}I]-Bolton Hunter conjugated CCK (26-33) (^{125}I-CCK 8S) in the absence and presence of a range of concentrations of the test compound in a final volume of 500 µL. Non-specific binding was estimated by 1 µM CCK-8S.

After each incubation, the assay was terminated by rapid filtration under vacuum through Whatman GF/B filterstrips followed by washing three times with 4 mL of ice-cold NaCl. Radioactivity was then measured using a Packard series 5000 gamma counter.

Chemistry

Melting points were determined with a Mettler FP800 or a Reichart Thermovar hot-stage apparatus and are uncorrected. Proton NMR spectra were recorded on a Bruker AM300 spectrometer; chemical shifts were recorded in parts per million (ppm) downfield from tetramethylsilane. IR spectra were recorded using the compound (neat) on a sodium chloride disk with a Perkin-Elmer 1750 Fourier transform spectrophotometer. Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Mass spectra were recorded with a Finnegan 4500 or a ZAB-E VG Analytical. Elemental analyses were determined by Medac Ltd., Uxbridge, U.K. Normal phase silica gel used for chromatography was Kieselgel-60 (230–400 mesh), reverse phase silica gel used was Lichroprep® RP-18 (230–400 mesh) both supplied by E. Merck, A.G., Darmstadt, Germany. Anhydrous solvents were dried over 4Å molecular sieves prior to use. The filter aid used throughout was Celite® purchased from the Aldrich Chemical Co. Ltd., Gillingham, U.K.

*Carbamic acid, [2-[(1-azido-1,2,3,4-tetrahydro-2-naphthalenyl)amino]1-(1*H*-indol-3-yl-methyl)-1-methyl-2-oxoethyl] 1-tricyclo[3.3.1.1^{3,7}]dec-2-yl ester. Ring is* trans-+/-, *Trp centre is* R *(7)*

A solution of 2-adamantyloxycarbonyl-α-methyl-*R*-tryptophan (3.00 g, 7.57 mmol) and pentafluorophenol (1.39 g, 7.57 mmol) in EtOAc (80 mL) was cooled to 0 °C and treated with *N,N'*-dicyclohexylcarbodiimide (1.56 g, 7.57 mmol). This reaction mixture was stirred for 30 min at 0 °C, filtered, and the filtrate treated with (+/-) *trans*-2-amino-1-azido-1,2,3,4-tetrahydronaphthalene **6** (1.56 g, 8.32 mmol) and allowed to warm to room temperature. After 48 h the reaction mixture was washed with 1M citric acid solution (2 x 20 mL), saturated $NaHCO_3$ solution (2 x 20 mL), and H_2O (2 x 20 mL). The organic phase was dried over $MgSO_4$ and the solvent evaporated *in vacuo*. The residue was separated by reverse phase silica gel chromatography using 4:1 MeOH:H_2O as eluant to give the product (**7**) as a non-crystalline white solid (3.71 g, 86%). m.p. 105–110 °C; IR (film) 3500–3200, 2909, 2855, 2097, 1702, 1657, 1493 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (1H, s), 1.45 (2.5H, s), 1.55 (1.5H, s), 1.65–1.90 (13H, m), 2.00–2.20 (1H, m), 2.60–2.75 (1H, m), 2.81 (0.5H, d, *J* = 5.4 Hz), 2.87 (0.5H, d, *J* = 5.3 Hz), 3,17–3.27 (1H, m), 3.49 (0.5H, d, *J* = 14.8 Hz), 3.56 (0.5H, d, *J* = 14.7 Hz), 4.18 (0.5H, d, *J* = 4.6 Hz), 4.25–4.35 (1.5H, m), 4.60–4.70 (1H, m), 5.04 (1H, s), 6.40–6.45 (0.5H, m), 6.46–6.55 (0.5H, m), 6.94 (1H, s), 7.05–7.30 (6H, m), 7.36 (1H, d, *J* = 7.8 Hz), 7.55–7.65 (1H, m), 8.11 (1H, s); MS *m/e* (FAB) 567 (5), 173 (24), 146 (28), 135 (100), 109 (39); Anal. $C_{33}H_{38}N_6O_3$ requires: C 69.94; H 6.75; N 14.82%, found: C 69.81; H 6.90; N 14.66%.

*Carbamic acid, [2-[(1-amino-1,2,3,4-tetrahydro-2-naphthalenyl)amino]1-(1*H*-indol-3-yl-methyl)-1-methyl-2-oxoethyl] 1-tricyclo[3.3.1.1^{3,7}]dec-2-yl ester. Ring is* trans-*+/-, other centre is* R *(8)*

A solution of **7** (1.20 g, 2.11 mmol) in absolute EtOH (150 mL) was treated with Lindlar catalyst (0.6 g, 50% w/w) and put under an atmosphere of hydrogen at a pressure of 50 psi for 12 h at room temperature. This was then filtered and evaporated *in vacuo* to give the crude amine as a syrup (1.14 g, 100%). This unstable amine was used immediately without further purification. NMR ($CDCl_3$) δ 1.40–2.00 (21H, m), 2.65–2.80 (1H, m), 2.81–2.95 (1H, m), 3.28 (0.5H, d, *J* = 14.6 Hz), 3.30 (0.5H, d, *J* = 14.7 Hz), 3.45–3.65 (2H, m), 3.90–4.00 (1H, m), 4.75–4.80 (1H, m), 5.09 (0.5H, s), 5.19 (0.5H, s), 6.20–6.30 (1H, m), 6.95–7.30 (6H, m), 7.37 (1H, d, *J* = 8.0 Hz), 7.45–7.55 (1H, m), 7.63 (1H, d, *J* = 7.9 Hz), 8.19 (1H, s).

*Propanoic acid, 3-oxo-3-[[1,2,3,4-tetrahydro-2-[[3-(1*H*-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl amino]propyl]amino]-1-naphthalenyl]-amino]-, methyl ester. Trp centre is* R*, ring is* trans- *(9)*

A solution of amine **8** (0.20 g, 0.4 mmol) in EtOAc (15 mL) was treated with methyl malonyl chloride (0.06 g, 0.44 mmol) followed by triethylamine (0.03 g, 0.37 mmol) and stirred for 30 min at room temperature. This was then evaporated *in vacuo* and the residue separated by silica gel chromatography using 1:1 *n*-hexane:EtOAc as eluant to give two diastereoisomers separated as **9a** (isomer I) (0.05 g) and **9b** (isomer II) (0.06 g) as white amorphous solids combined yield 46%.

Isomer I **9a**: m.p. 140–145 °C; $[\alpha]_D^{20}$= +38.4° (*c* = 0.25, MeOH); IR (film) 3500–3200, 2907, 2857, 1760–1700 (br), 1651, 1491 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.15 (19H, m), 2.75–2.87 (1H, m), 2.90–3.05 (1H, m), 3.35 (2H, s), 3.40 (2H, s), 3.74 (3H, s), 3.95–4.05 (1H, m), 4.82 (1H, s), 5.15 (1H, d, *J* = 10 Hz), 5.34 (1H, s), 6.86 (1H, d, *J* = 7.5 Hz), 7.00–7.35 (9H, m), 7.65 (1H, d, *J* = 8.0 Hz), 8.17 (1H, s); MS *m/e* (FAB) 641 (10), 263 (10), 173 (39), 135 (100); Anal. $C_{37}H_{44}N_4O_6$ requires: C 69.35; H 6.92; N 8.74%, found: C 69.22; H 6.86; N 8.72.

Isomer II **9b**: m.p. 142–183 °C; $[\alpha]_D^{20}$= +26.8° (c =0.25, MeOH); IR (film) 3500–3200, 2910, 2854, 1760–1700(br), 1651, 1536, 1493, 1342 cm^{-1}; NMR ($CDCl_3$) δ 1.45–2.05 (18H, m), 2.15–2.30 (1H, m), 2.80–2.90 (1H, m), 2.95–3.10 (1H, m), 3.24 (1H, d, *J* = 17.4 Hz), 3.31 (1H, d, *J* = 17.3 Hz), 3.39 (1H, d, *J* = 14.8 Hz), 3.45 (1H, d, *J* = 15.1 Hz), 3.73 (3H, s), 3.95–4.10 (1H, m), 4.81 (1H, s), 5.17 (1H, t, *J* = 6.7 Hz), 5.23 (1H, s), 6.93 (1H, d, *J* = 7.2 Hz), 6.97 (1H, d, *J* = 2.1 Hz), 7.05–7.30 (6H, m), 7.34 (1H, d, *J* = 8.1 Hz), 7.38 (1H, d, *J* = 8.9 Hz), 7.60 (1H, d, *J* = 7.8 Hz), 8.23 (1H, s); MS *m/e* (FAB) 641 (7.5), 263 (9.8), 173 (40), 135 (100), 113 (20); Anal. $C_{37}H_{44}N_4O_6{\cdot}0.25H_2O$ requires: C 68.87; H 6.95; N 8.68%, found: C 68.98; H 7.08; N 8.33%.

*Propanoic acid, 3-oxo-3-[[1,2,3,4-tetrahydro-2-[[3-(1*H*-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl amino]propyl]amino]-1-naphthalenyl]-amino]-. Trp centre is* R*, ring is* trans- *(10)*

A solution of **9** as a 1:1 diastereomeric mixture of isomers I **9a** and II **9b** (0.25 g, 0.39 mmol) in THF (50 mL) was treated with a solution of LiOH (0.016 g, 0.39 mmol) in H_2O (50 mL) dropwise at room temperature. This mixture was left stirring for 3 days, diluted with EtOAc (100 mL), washed with 1N HCl (2 x 30 mL) and H_2O (2 x 30 mL). The organic phase was dried over $MgSO_4$, evaporated and the residue purified by reverse phase silica gel chromatography using 3:2 MeOH:H_2O as eluant to give the product **10** as a white non-crystalline solid (0.12 g, 49%). m.p. 137–140 °C; IR (film) 3500–3200, 2909, 1711, 1657, 1530, 1453 cm^{-1}; NMR (DMSO-d_6) δ 1.28 (1.5H, s), 1.35 (1.5H, s), 1.42–1.60 (2H, m), 1.62–2.08 (14H, m), 2.80 (2H, br s), 2.98–3.85 (4H, m), 3.87–4.06 (1H, m), 4.62–4.82 (1H, m), 5.00–5.18 (1H, m), 6.68 (0.5H, s), 6.74 (0.5H, s), 6.83–7.70 (10H, m), 8.50 (1H, d, *J* = 9.0 Hz), 10.91 (1H, s); Anal. $C_{36}H_{42}N_4O_6$ requires: C 68.99; H 6.75; N 8.94%, found: C 68.80; H 6.78; N 8.87%.

*Butanoic acid, 4-[[1,2,3,4-tetrahydro-2-[[3-(1*H*-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-carbonyl]amino]propyl]amino]-1-naphthalenyl]amino]-4-oxo-, ring centre is* trans-*, Trp centre is* R *(11)*

A solution of the amine **8** (0.20 g, 0.37 mmol) in EtOAc (15 mL) was treated with succinic anhydride (0.044 g, 0.44 mmol) and stirred at reflux with *N,N*-dimethylaminopyridine (0.061 g, 0.50 mmol) for 18 h. This mixture was then evaporated to dryness and the residue chromatographed over reverse phase silica using 5:1 MeOH:H_2O as eluant to give the product **11** as a non-crystalline white solid (0.16 g, 66%). m.p. 137–150 °C; IR (film) 3500–3200, 2910, 2856, 1712, 1651, 1531 cm^{-1}; NMR (DMSO-d_6,D_2O) δ 1.23 (1.5H, s), 1.29 (1.5H, s), 1.35–1.55 (2H, m), 1,60–2.00 (14H, m), 2.20–2.55 (4H, m), 2.70–2.85 (2H, m), 3.10–3.60 (2H, m), 3.85–4.00 (1H, m), 4.60–4.70 (1H, m), 6.60–6.70 (1H, m), 6.85–7.25 (7H, m), 7.31 (1H, d, *J* = 7.9 Hz), 7.46 (1H, d, *J* = 8.1 Hz), 7.30–7.55 (1H, br), 8.23 (1H, d, *J* = 9.3 Hz); Anal. $C_{37}H_{44}N_4O_6$ requires: C 67.92; H 7.00; N 8.56%, found: C 67.96; H 6.87; N 8.65%.

*Pentanoic acid, 5-[[1,2,3,4-tetrahydro-2-[[3-(1*H*-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-carbonyl amino]propyl]amino]-1-naphthalenyl]amino]-5-oxo-, ring centres are* trans- *, Trp centre is* R *(12)*

Method exactly as for **11** except using glutaric anhydride (yield = 87%). m.p. 148–159 °C; IR (film) 3500–3200, 2911, 1709, 1647, 1532, 1453 cm^{-1}; NMR (DMSO-d_6,

D_2O) δ 1.23 (1.5H, s), 1.32 (1.5H, s), 1.37–1.56 (2H, m), 1.65–2.00 (16H, m), 2.10–2.30 (4H, m), 2.70–2.85 (2H, m), 3.10–3.50 (2H, m), 3.81–4.00 (1H, m), 4.65 (1H, br s), 5.10 (1H, m), 6.62 (0.5H, s), 6.72 (0.5H, s), 6.85–7.65 (10H, m), 8.15 (1H, m); Anal. $C_{38}H_{46}N_4O_6{\cdot}0.25\,H_2O$ requires: C 69.22; H 7.10; N 8.49%, found: C 69.11; H 7.14; N 8.51%.

*Butenoic acid, 4-[[1,2,3,4-tetrahydro-2-[[3-(1*H*-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-carbonyl]amino]propyl]amino]-1-naphthalenyl]amino]-4-oxo-, methyl ester. Ring centres are* trans-, *Trp centre is* R *(13)*

A solution of the amine **8** (0.60 g, 1.1 mmol) in EtOAc (25 mL) was treated with methyl pentafluorophenyl fumarate (0.50 g, 1.7 mmol) and the resultant solution stirred for 18 h at room temperature. The solvent was then removed *in vacuo* and the residue chromatographed over silica gel using 3:1 *n*-hexane:EtOAc as eluant to give the product **13** as a non-crystalline solid and a mixture of two diastereoisomers (0.42 g, 58%). m.p. 234–236 °C; IR (film) 3500–3200, 2912, 2854, 1715, 1646, 1538 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (1.5H, s), 1.45–2.20 (17.5H, m), 2.70–2.90 (2H, m), 3.16 (0.5H, d, J = 14.5 Hz), 3.27 (0.5H, d, J = 6.5 Hz), 3.32 (0.5H, d, J = 7.0 Hz), 3.42 (0.5H, d, J = 14.5 Hz), 3.72 (1.5H, s), 3.74 (1.5H, s), 3.90–4.10 (1H, m), 4.80 (1H, m), 5.10–5.30 (2H, m), 6.70–7.35 (12H, m), 7.53 (0.5H, d, J = 8.0 Hz), 7.60 (0.5H, d, J = 8.0 Hz), 8.31 (0.5H, s), 8.37 (0.5H, s); Anal. $C_{38}H_{44}N_4O_6{\cdot}0.25H_2O$ requires: C 69.44; H 6.82; N 8.52%, found: C 69.55; H 6.71; N 8.49%.

*Butenoic acid 4-[[1,2,3,4-tetrahydro-2-[[3-(1*H*-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-carbonyl]amino]propyl]amino]-1-naphthalenyl]amino]-4-oxo-. Ring centres are* trans-, *Trp centre is* R *(14)*

Method as for **10** except using ester **13** (yield = 65%). m.p. 170–173 °C; IR (film) 3500–3200, 2906, 1709, 1657, 1535, 1453 cm^{-1}; NMR (DMSO-d_6) δ 1.17 (1.5H, s), 1.25 (1.5H, s), 1.36–1.58 (2H, m), 1.61–2.00 (14H, m), 2.78–2.95 (2H, m), 3.09 (0.5H, d, J = 14.5 Hz), 3.22 (0.5H, d, J = 14.8 Hz), 3.33 (1H, m), 4.65 (1H, s), 5.20 (1H, m), 6.57 (0.5H, d, J = 15.4 Hz), 6.60 (0.5H, d, J = 15.4 Hz), 6.61 (0.5H, s), 6.75 (0.5H, s), 6.80–7.27 (8H, m), 7.31 (1H, d, J = 8. 1 Hz), 7.37–7.57 (1.5H, m), 7.60–7.76 (0.5H, m), 8.85 (1H, d, J = 9.2 Hz), 10.87 (1H, s); Anal. $C_{37}H_{42}N_4O_6$ requires: C 69.57; H 6.63; N 8.77%, found: C 69.40; H 6.58; N 8.67%.

cis-*Benzyl 1,2,3,4-tetrahydro-2-azido-1-naphthylcarbamate (16)*

A solution of *trans*-benzyl 1,2,3,4-tetrahydro-2-iodo-1-naphthylcarbamate **15** (7.625 g, 18.72 mmol), in anhydrous DMF (100 mL) was treated with sodium azide (1.46 g 22.5 mmol). This mixture was stirred for 18 h at room temperature. The solvent was removed *in vacuo* and the residue diluted with EtOAc (100 mL). This mixture was then washed with H_2O (2 x 100 mL), saturated $NaHCO_3$ solution (100 mL) and H_2O (100 mL). The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was crystallised and recrystallised from MeOH until analytically pure, giving the product as a white clystalline solid, 2.94 g, 49%, m.p. 103.7 °C; IR (film) 3315, 2937, 2101, 1697, 1505, 1455 cm^{-1}; NMR ($CDCl_3$) δ 2.05–2.28 (2H, m), 2.77 (1H, m), 3.03 (1H, m), 4.16 (1H, s), 5.05–5.28 (4H, m), 7.08–7.45 (9H, m); Anal. $C_{18}H_{18}N_4O_2$ requires: C 67.07; H 5.63; N 17.38%, found: C 66.72; H 5.54; N 17.37%.

cis-*Benzyl 1,2,3,4-tetrahydro-2-amino-1-naphthylcarbamate (17)*

Method as for **8** except using azide **16** (yield = 62%). m.p. 102–145 °C; IR (film) 3500–3200, 1710, 1530, 1454 cm^{-1}; NMR ($CDCl_3$) δ 1.70–1.95 (2H, m), 2.75–3.00 (2H, m), 3.20 (1H, m), 4.80 (3H, br s), 4.91 (1H, d, J = 4.0 Hz), 5.10 (1H, d, J = 12.6 Hz), 5.16 (1H, d, J = 12.4 Hz), 7.05–7.40 (9H, m); Anal. $C_{18}H_{20}N_2O_2$ requires: C 72.94; H 6.80; N 9.45%, found: C 72.84; H 6.81; N 9.44%.

*Carbamic acid, [1-(1*H*-indol-3-ylmethyl)-1-methyl-2-2-oxo-2-[[1,2,3,4-tetrahydro-1-[[(phenylmethoxy)carbonyl]-amino]-2-naphthalenyl]-amino]ethyl]-tricyclo[3.3.1.1^{3,7}]-dec-2-yl ester. Ring centres are* cis-, *Trp centre is* R *(18)*

Method as for **7** except using amine **17** to give the product (**18**) (yield = 70%). m.p. 115–173 °C; IR (film) 3500–3200, 2907, 1697, 1665, 1495 cm^{-1}; NMR ($CDCl_3$) δ 1.30–2.10 (19H, m), 2.38–2.57 (0.5H, m), 2.62–2.90 (1.5H, m), 3.22 (0.5H, d, J = 14.7 Hz), 3.36 (0.5H, d, J = 14.9 Hz), 3.38 (0.5H, d, J = 14.7 Hz), 3.49 (0.5, d, J = 14.9 Hz), 4.32–4.65 (2H, m), 4.85–5.00 (1H, m), 5.05 (0.5H, s), 5.18 (2H, d, J = 7.3 Hz), 5.23 (0.5H, s), 5.50–5.80 (1H, br s), 6.40–6.55 (0.5H, br s), 6.56–6.65 (0.5H, br s), 6.85–7.46 (13H, m), 7.54 (0.5H, d, J = 7.9 Hz), 7.59 (0.5H, d, J = 7.9 Hz), 8.05 (0.5H, br s), 8.25 (0.5H, br s); Anal. $C_{41}H_{46}N_4O_6{\cdot}0.25H_2O$ requires: C 72.49; H 6.90; N 8.25%, found: C 72.67; H 6.91; N 8.12%.

*Tricyclo[3.3.1.1^{3,7}]dec-2-yl[1*R*-[1α,2α(*R**)]]and [1*S*-[1α,2α(S*)]]-[2-[(1-amino-1,2,3,4-tetrahydro-2-naphthalenyl)amino]1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]carbamate (19)*

A solution of **18** (1.0 g, 1.5 mmol) in absolute EtOH (150 mL) was treated with 10% palladium on carbon (0.2 g, 20% w/w) and put under an atmosphere of hydrogen at a pressure of 50 psi at 25 °C for 4 h. The mixture was then filtered and the filtrate evaporated to dryness *in vacuo* to give the unstable product **19** (0.79 g, 100%), which was used immediately in the following steps.

*Butanoic acid, 4-[[1,2,3,4-tetrahydro-2-[[3-(1*H*-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-carbonyl]amino]propyl]amino]-1-naphthalenyl]amino]-4-oxo (ring centres are* cis-, *Trp centre is* R*) (20)*

A solution of freshly prepared amine **19** (0.40 g, 0.73 mmol) in EtOAc (30 mL) was treated with succinic anhydride (0.09 g, 0.90 mmol) and the resulting solution stirred for 18 h at room temperature. The mixture was then washed with 1M HCl solution (20 mL), saturated $NaHCO_3$ solution (2 x 20 mL) and H_2O (2 x 20 mL). The organic phase was dried over $MgSO_4$, filtered and the filtrate evaporated to dryness *in vacuo*. The residue was purified by reverse phase silica gel chromatography using 3:1 MeOH:H_2O as eluant then rechromatographed over normal phase silica using 1:1 MeOH:CH_2Cl_2 as eluant to give the product **20** as a white non-crystalline solid and a mixture of two diastereoisomers (0.27 g, 57%). m.p. 213–238 °C; IR (film) 3500–3200, 2911, 2853, 1696, 1661, 1515, 1452 cm^{-1}; NMR (DMSO-d_6, D_2O) δ 1,27 (1.5H, s), 1.33 (1.5H, s), 1.36–1.50 (2H, m), 1.67–2.06 (14H, m), 2.17–2.40 (4H, m), 2.60–2.95 (2H, m), 3.12 (0.5H, d, J = 14.3 Hz), 3.18–3.34 (1H, m), 3.40 (0.5H, m), 4.10 (1H, br s), 4.60 (1H, br s), 5.12 (0.5H, d, J = 4.4 Hz), 5.15 (0.5H, d, J = 4.3 Hz), 6.90 (1H, m), 6.97–7,24 (6H, m), 7.30 (0.5H, d, J = 8.1 Hz), 7.31 (0.5H, d, J = 8.0 Hz), 7.50 (1H, m); Anal. $C_{37}H_{44}N_4O_6\cdot 0.5CH_2Cl_2$ requires: C 65.96; H 6.64; N 8.20%, found: C 65.81; H 6.45; N 8.39%.

Pentanoic acid, 5-[[1,2,3,4-tetrahydro-2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-carbonyl]amino]propyl]amino]-1-naphthalenyl]amino]-5-oxo-, methyl ester. Ring centres are cis-, *Trp centre is* R *(21)*

Method as for **11** and **12** except using amine **19** and rechromatographing using 1:1 MeOH in CH_2Cl_2 as eluant. Yield = 60%. m.p. 196–206 °C; IR (film) 3500–3200, 2924, 2856, 1712, 1659, 1515 cm^{-1}; NMR (DMSO-d_6, D_2O) δ 1.27 (1.5H, s), 1.31 (1.5H, s), 1.37–1.53 (2H, m), 1.57–2.25 (20H, m), 2.60–2.95 (2H, m), 3.10 (0.5H, d, J = 14.7 Hz), 3.28 (0.5H, d, J = 16.3 Hz), 3.37 (0.5H, d, J = 16.3 Hz), 3.45 (0.5H, m), 4.05 (1H, br s), 4.60 (1H, br s), 5.13 (0.5H, d, J = 4.0 Hz), 5.20 (0.5H, br s), 5.71 (s, CH_2Cl_2), 6.83–7.24 (7H, m), 7.31 (1H, d, J = 7.3 Hz), 7.44 (0.5H, d, J = 8.5 Hz), 7.46 (0.5H, d, J = 8.2 Hz); Anal. $C_{38}H_{46}N_4O_6\cdot 0.75CH_2Cl_2$ requires: C 64.82; H 6.66; N 7.80%, found: C 64.68; H 6.46; N 8.11%.

*Butenoic acid, 4-[[1,2,3,4-tetrahydro-2-[[3-(1*H*-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-carbonyl]amino]propyl]amino]-1-naphthalenyl]amino]-4-oxo-, methyl ester. Ring centres are* cis-, *Trp centre is* R *(22)*

Method as for **13** except using amine **19** yield = 54%. m.p. 143–146 °C; IR (film) 3500–3200, 2901, 2851, 1751, 1645, 1538 cm^{-1}; NMR ($CDCl_3$) δ 1.10–2.00 (18.5H, m), 2.07–2.25 (1H, m), 2.60 (0.5H, m), 2.80 (1H, m), 3.06 (0.5H, d, J = 14.9 Hz), 3.28 (0.5H, d, J = 14.7 Hz), 3.35 (0.5H, d, J = 14.8 Hz), 3.59 (0.5H, d, J = 14.9 Hz), 3.79 (3H, s), 4.47 (0.5H, s), 4.51 (0.5H, s), 4.60 (0.5H, m), 4.80 (1H, br s), 5.19 (0.5H, s), 5.30 (0.5H, m), 5.41 (0.5H, dd, J = 4.0 and 8.7 Hz), 6.01 (0.5H, d, J = 10.1 Hz), 6.32 (0.5H, d, J = 10.2 Hz), 6.86–7.24 (9H, m), 7.35 (0.5H, d, J = 8.1 Hz), 7.39 (0.5H, d, J = 8.1 Hz), 7.40 (0.5H, m), 7.50–7.60 (1H, m), 8.30 (0.5H, s), 8.33 (0.5H, s); Anal. $C_{38}H_{44}N_4O_6$ requires: C 69.92; H 6.79; N 8.50%, found: C 69.84; H 6.75; N 8.75%.

*Butenoic acid, 4-[[1,2,3,4-tetrahydro-2-[[3-(1*H*-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-carbonyl]amino]propyl]amino]-1-naphthalenyl]amino]-4-oxo-. Ring centres are* cis-, *Trp centre is* R *(23)*

Method as for **10** and **14** except using ester **22**. Yield = 51%. The two diastereoisomers were partially separated by selective crystallisation from CH_2Cl_2. Isomer I (**23a**) was obtained as a white crystalline solid with a d.e. >90% and Isomer II (**23b**) was a non-crystalline solid with a d.e. of ca.50% by NMR spectroscopy.

Isomer I (**23a**): m.p. 179–187 °C; IR (film) 3500–3200, 2921, 1705–1666 br, 1514 cm^{-1}; NMR (DMSO-d_6, D_2O) δ 1.20 (3H, br s), 1.40 (2H, m), 1.60–2.00 (14H, m), 2.71 (2H, br s), 3.09 (1H, d, J = 14.4 Hz), 3.40 (1H, d, J = 14.5 Hz), 4.13(1H, br s), 4 62 (1H, br s), 5.24 (1H, m), 6.59 (1H, d, J = 15.4 Hz), 6.78–7.27 (10H, m), 7.34 (1H, d, J = 8.1 Hz), 7.44 (1H, d, J = 7.9 Hz), 8.57 (1H, d, J = 9.0 Hz); Anal. $C_{37}H_{42}N_4O_6\cdot$ 0.2H_2O requires: C 69.18, H 6.65, N 8.72%, found: C 69.16, H 6.44, N 8.72%.

Isomer II (**23b**): m.p. 173–178 °C; IR (film) 3500–3043, 2909, 1729, 1633, 1538 1493 cm^{-1}; NMR (DMSO-d_6, D_2O) *inter alia* δ 1.30 (3H, s), 1.37–1.52 (2H, m), 1.65–2.10 (14H, m), 2.60–3.50 (4H, m), 4.14 (1H, m), 4.62 (1H, br s), 5.27 (1H, m), 5.71 (s CH_2Cl_2), 6.62 (1H, d, J = 15.3 Hz) 6.70–7.85 (12H, m), 8.49 (1H, br s); Anal. $C_{37}H_{42}N_4O_6\cdot CH_2Cl_2$ requires: C 61.41 H 6.13, N 7.58%, found: C 61.22, H 5.91, N 7.58%.

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