Cholecystokinin Dipeptoid Antagonists: Design, Synthesis, and Anxiolytic Profile of Some Novel CCK-A and CCK-B Selective and "Mixed" CCK-A/CCK-B Antagonists

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Received September 10, 1992

The design, synthesis, and structure–activity relationships (SAR) for the development of selective dipeptoid ligands for both of the cholecystokinin (CCK) receptor subtypes CCK-A and CCK-B are described. The SAR developed is used to design a ligand with equal nanomolar binding affinity for both the CCK-A and CCK-B receptors. Example compounds such as [1*R*-[1α[*R**(*R**)],2β]]-4-[[2-[[3-(1*H*-indol-3-yl)-2-methyl-2-[[[(2-methylcyclohexyl)oxy]carbonyl]amino]-1-oxopropyl]-amino]-1-phenylethyl]amino]-4-oxo-butanoic acid (**24c**), (1*R*-*trans*)-*N*-[α-methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-D-tryptophyl]-L-3-(phenylmethyl)-β-alanine (**28i**), and *N*-[α-methyl-*N*-[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophanyl]-L-3-(phenylmethyl)-β-alanine (**30m**) are CCK-B selective compounds having CCK-B binding affinities of IC_{50} = 3.9, 0.34, and 0.15 nM with a CCK-A/CCK-B ratio of 464, 53, and 170, respectively. Other compounds such as (1*R*-*trans*)-*N*-[α-methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-L-tryptophyl]-D-3-(phenylmethyl)-β-alanine (**28l**) and *N*-(α-methyl-*N*-[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-L-tryptophyl]-D-3-(phenylmethyl)-β-alanine (**30p**) are CCK-A-selective compounds having CCK-A binding affinities of IC_{50} = 7.9 and 2.82 nM with a CCK-A/CCK-B ratio of 0.007 and 0.01, respectively. Further to these, (1*S*-*trans*)-*N*-[α-methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-D-tryptophyl]-L-3-(phenylmethyl)-β-alanine (**28h**) is a mixed CCK-A/CCK-B ligand with a CCK-A binding affinity of IC_{50} = 3.9 nM and a CCK-B binding affinity of IC_{50} = 4.2, producing a CCK-A/CCK-B ratio of unity. The CCK-B selective compounds are shown to be antagonists in electrophysiological tests on the rat ventromedial nucleus of the hypothalamus with an equilibrium constant (K_e) value of 2.8 nM for **30m** and are also shown to be anxiolytic in the mouse light/dark box test with a minimum effective dose of 0.01 mg/kg, sc, for **30m**. The CCK-A selective compounds are also shown to be competitive antagonists by the inhibition of CCK-8S-evoked amylase secretion from pancreatic acinar cells with a K_e value of 16 nM for **30p**. In electrophysiological tests on the rat dorsal raphé (an area rich in CCK-A receptors) **30p** had a K_e value of 12.8 nM. The mixed CCK-A/CCK-B compound **28h** showed antagonistic properties in both CCK-A and CCK-B models; thus it inhibited CCK-8S-evoked amylase secretion from pancreatic acinar cells *and* is anxiolytic in the light/dark box paradigm. It may be concluded, therefore, that it is the CCK-B receptor and not the CCK-A receptor that is responsible for the anxiolytic properties of these compounds in these test models.

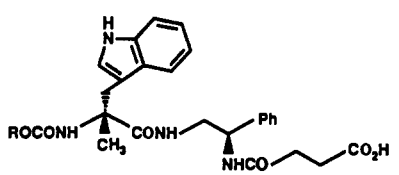
Introduction

We have previously described the rational and systematic design of novel "dipeptoids" that exhibit potent binding affinity and selectivity as central cholecystokinin (CCK-B) antagonists. These dipeptoids have also been shown to possess marked anxiolytic and antigastrin properties, (e.g. CI-988; **2**: R = 2-Adoc).[1-4] The design of these compounds was achieved by independently exploring the structure–activity relationships (SAR) of the N- and C-termini and combining the optimal groups.[5,6] We now report the further development of the nature of R (**2**), which was highly influential in determining CCK A and B receptor selectivities of these dipeptoid ligands.

Asp-Tyr (OSO_3H)-Met-Gly-Trp-Met-Asp-Phe-NH_2

1

CCK 8S



2

CI-988
R = 2-Adamantyl

Synthesis

All compounds and intermediates in Tables I–V were prepared according to Schemes I–VI.

Scheme I shows the synthesis of *N*-phenethyl-α-methyltryptophanamide and (α-methyltryptophanyl)-3-phenylalaninol derivatives **5–14**. The two amines **3** and **4** were prepared according to the literature and were treated with the appropriate chloroformate.[1,5]

The versatile intermediates **15a–f** were prepared according to the methods in Scheme II. α-Methyltryptophan methyl ester was treated with *trans*-[(2-methylcyclohexyl)-oxy]carbonyl chloride to give the esters **17a–f**. Lithium hydroxide saponification of the ester yielded the acids **15a–f**. These acids were used to prepare compounds **16a–c**. Treatment of **15b** and **15c** with pentafluorophenol (PfP) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) gave the active

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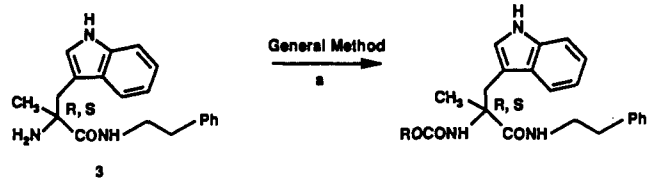
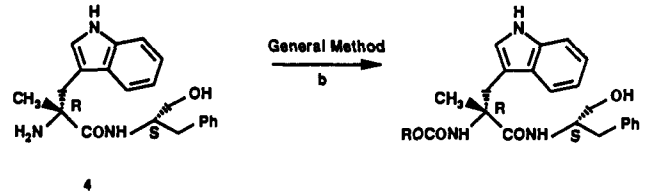
Scheme I[a]



3

5 R = 2-Adamantyl
6 R = 1-Adamantyl
10 R = Cyclohexyl
11 R = (+/-) *trans*-2-Chlorocyclohexyl (R-α-MeTrp)

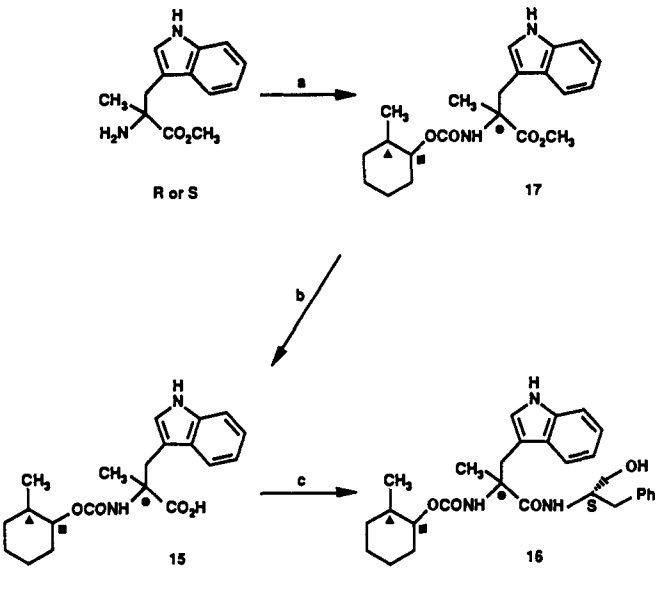


4

7 R = 2-Adamantyl
8 R = 1-Adamantyl
9 R = 2-Chloro-1-adamantyl
12a R = (+/-) *trans*-2-Chlorocyclohexyl
12b R = (+) *trans*-2-Chlorocyclohexyl isomer I
12c R = (-) *trans*-2-Chlorocyclohexyl isomer II
14a R = (+/-) *trans*-2-Fluorocyclohexyl
14b R = (+) *trans*-2-Fluorocyclohexyl isomer I
14c R = (-) *trans*-2-Fluorocyclohexyl isomer II

[a] (a) ROCOCl, Et_3N, THF; (b) ROCOCl, Et_3N, THF.

Scheme II[a]



R or S

17

15

16

	▲	■	●
a	RS	RS	R
b	S	S	R
c	R	R	R
d	RS	RS	S
e	S	S	S
f	R	R	S

[a] (a) *trans*-[(2-Methylcyclohexyl)oxy]carbonyl chloride, Et_3N, THF; (b) LiOH, aqueous THF; (c) phenylalaninol, DCC, PFP, EtOAc.

ester, which reacted readily with phenylalaninol to give **16a–c**. Compound **15c** under similar conditions reacted with (*S*)-α-(azidomethyl)-2-phenylethanamine to give the azide **18c** (Scheme III). The azide was reduced to the corresponding amine with 10% Pd/C under a hydrogen atmosphere and was treated without purification with succinic anhydride to give the succinamide **19c**. This same amine was treated with methyl pentafluorophenyl fumarate to give the ester **20c**, which was hydrolyzed with lithium hydroxide to the acid **21c**. Compound **21b** was similarly prepared from **15b**. Compound **22c** was prepared by reaction of the PfP ester of **15c** (DCC, PfP) with (*R*)-N^{β}-[(benzyloxy)carbonyl]-β-aminobenzeneethanamine (Scheme IV). Subsequent hydrogenation of **22c** with 10% Pd/C gave the amine **23c**, which was reacted further with succinic anhydride, giving **24c**. Similarly, **23c** was treated with pentafluorophenyl 2-(trimethylsilyl)ethyl fumarate to give **25c** and subsequent reaction with tetrabutylammonium fluoride in THF gave the required acid **26c**.

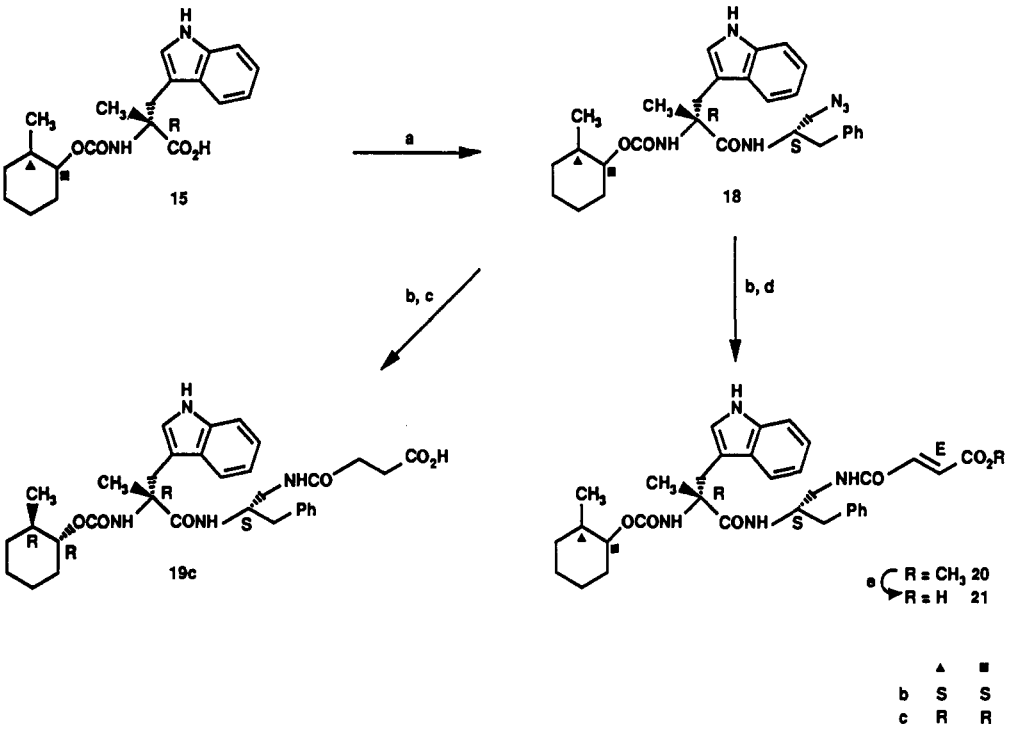
Scheme V shows how compounds **28g–l** can be prepared by reacting benzyl (*R* or *S*)-β-aminobenzenebutanoate with the active pentafluorophenyl ester of acids **15a–f**, then hydrogenating the benzyl esters to the corresponding acids **28g–l**. Compounds **29m–p** and **30m–p** were prepared according to Scheme VI. [(2-Adamantyloxy)carbonyl]-α-methyltryptophan (*R* or *S* isomer) was prepared according to the literature[1] procedure and reacted via its pentafluorophenyl ester (PfP, DCC) with benzyl (*R* or *S*)-β-aminobenzenebutanoate to give the benzyl esters **29m–p**. Subsequent hydrogenation using 10% Pd/C as catalyst gave the acids **30m–p**.

Results and Discussion

The SAR of the N-terminus reported earlier was described in terms of increasing the *C* log *P* and the steric requirements of the R (**2**) group appended to the N-terminus, resulting in an increase in the CCK-B receptor binding affinity.[5] Starting with the (cyclobutyloxy)-carbonyl group, carbon units were added which increased both ring size and branching, until the tricyclic structure, (adamantanyloxy)carbonyl, was optimally obtained. It was shown, however, that the (2-adamantyloxy)carbonyl moiety on **5** and **7** was more potent in CCK-B binding (IC_{50} = 48 and 6.4 nM, respectively) than the (1-adamantyloxy)carbonyl derivatives **6** and **8** (IC_{50} = 210 and 21.6 nM, respectively).[5] This observation and molecular modeling of these and related compounds suggested that there was a conformational requirement at this part of the molecule for optimal binding. On the basis of this rationale, the [(2-chloro-1-adamantyl)oxy]carbonyl derivative **9** was prepared. Compound **9** showed increased CCK-B binding affinity (IC_{50} = 8.8 nM) over the (1-adamantyloxy)carbonyl derivative **8** (IC_{50} = 21.6 nM) and was comparable with the (2-adamantyloxy)carbonyl derivative **7** (IC_{50} = 6.4 nM). The corresponding *trans*-[(2-chlorocyclohexyl)oxy]carbonyl analogue **11** showed substantially increased CCK-B binding affinity (IC_{50} = 49 nM) over the unsubstituted (cyclohexyloxy)carbonyl derivative **10** (IC_{50} = 517 nM). Another *trans*-[(2-chlorocyclohexyl)oxy]carbonyl derivative, **12a** (IC_{50} = 15 nM), was separated by chromatography into its two diastereoisomers, **12b** (IC_{50} = 140 nM) and **12c** (IC_{50} = 6.9 nM), confirming a requirement for chiral recognition in this region of the dipeptoid molecules by the CCK-B receptor.

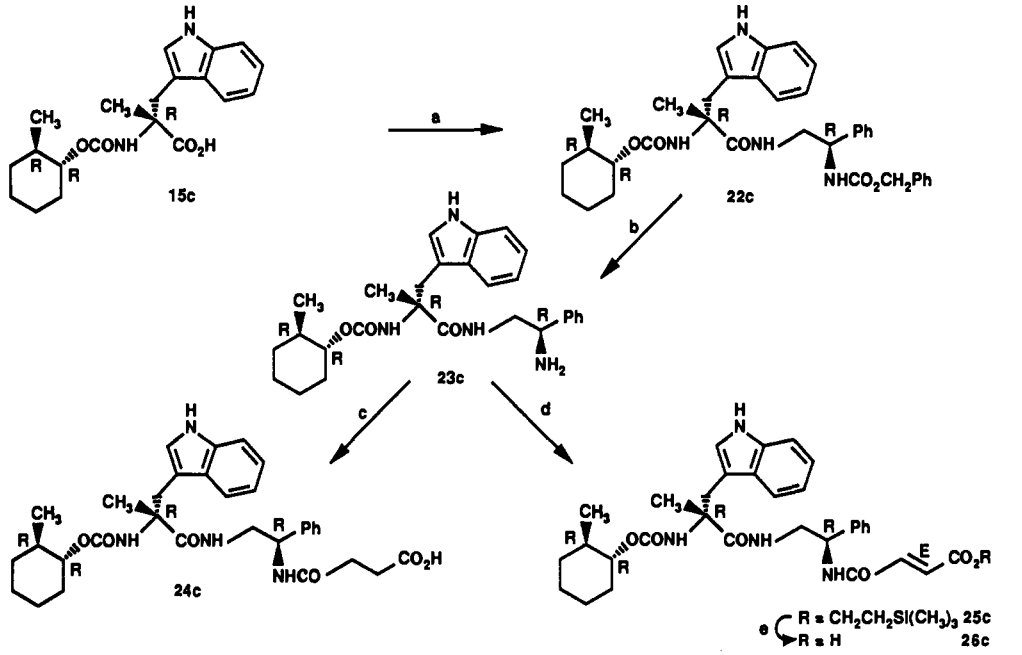
The electron-withdrawing effect of the chlorine group in these derivatives may stabilize the urethane linking group toward acidic hydrolysis. However, it was found that the chlorine atoms enhance the lability of the compound toward alkaline conditions, readily forming the

Scheme III[a]



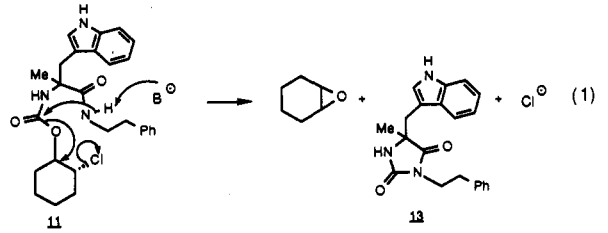
[a] (a) PFP, DCC, (*S*)-α-(azidomethyl)-2-phenylethanamine, EtOAc; (b) 10% Pd/C/H_2, 1% AcOH in EtOH; (c) succinic anhydride, EtOAc; (d) methyl pentafluorophenyl fumarate, EtOAc; (e) LiOH, aqueous THF.

Scheme IV[a]



[a] (a) PFP, DCC (R) N^{β}-[(benzyloxy)carbonyl]-β-amino-2-benzene ethanamine; (b) 10% Pd/C, H_2, EtOH; (c) succinic anhydride, EtOAc; (d) mono[2-(trimethylsilyl)ethyl] fumarate, DCC, PFP, EtOAc; (e) tetrabutylammonium fluoride, THF.

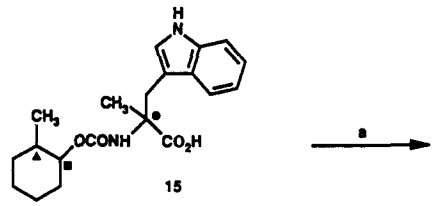
hydantoin **13** by intramolecular cyclization and liberating cyclohexene oxide[7] (eq 1).

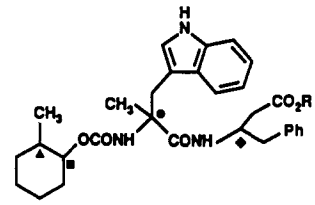


(1)

In order to avoid this undesirable reaction, surrogates for the chlorine atom were investigated. The fluorine-substituted analogue **14a** was prepared to investigate whether the electronic properties of chlorine were necessary for binding affinity. The binding affinity of the fluorine analogue was similar (IC_{50} = 36 nM) to that of **12a**, and when the two diastereoisomers **14b** and **14c** were separated, one isomer was more potent than the other (IC_{50} = 149 nM for isomer I and 23 nM for isomer II). Their affinity was, however, less than that for **7**. The

Scheme V[a]



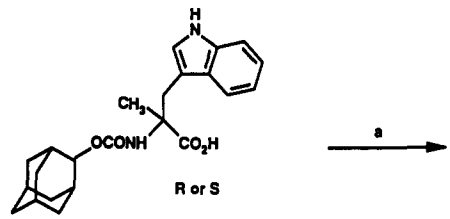


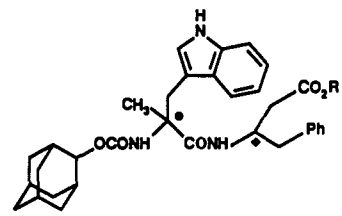
b R = CH_2Ph 27; R = H 28

	▲	■	●	◆
a	RS	RS	R	-
b	S	S	R	-
c	R	R	R	-
d	RS	RS	S	-
e	S	S	S	-
f	R	R	S	-
g	RS	RS	R	S
h	S	S	R	S
i	R	R	R	S
j	RS	RS	S	R
k	S	S	S	R
l	R	R	S	R

[a] (a) PFP, DCC, benzyl β-aminobenzenebutanoate, EtOAc; (b) 10% Pd/C, H_2, EtOH.

Scheme VI[a]





b R = CH_2Ph 29; R = H 30

	●	◆
m	R	S
n	R	R
o	S	S
p	S	R

[a] (a) PFP, DCC, benzyl β-aminobenzenebutanoate, EtOAc; (b) 10% Pd/C, H_2, EtOH.

spatial effect of the chlorine in **12a** was mimicked by the corresponding *trans*-[(2-methylcyclohexyl)oxy]carbonyl derivative **16a** [molecular refractivity (MR) of Cl = 4.8, Me = 4.7)].[10] The CCK-B binding affinity of **16a** (IC_{50} = 16 nM) was greater than that of the fluorine analogue **14a** (IC_{50} = 36 nM) but the same as that of the chlorine analogue **12a** (IC_{50} = 15 nM) and almost the same as that of the (2-adamantyloxy)carbonyl analogue **7** (IC_{50} = 6.4 nM).

Table I. Physical and Chemical Data of Compounds and Intermediates

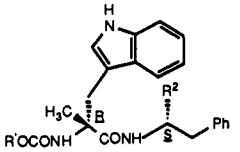
no.	molecular formula	mp (°C)	analysis	method of purification[a]
5	$C_{37}H_{37}N_3O_3 \cdot 0.25H_2O$	89–95	C, H, N	F
6	$C_{31}H_{37}N_3O_3$	82–88	C, H, N	J
7	$C_{32}H_{39}N_3O_4$	96–100	C, H, N	F
8	$C_{32}H_{39}N_3O_4$	147–155	C, H, N	F
9	$C_{32}H_{28}N_3O_4Cl$	98–104	C, H, N, Cl	F
10	$C_{27}H_{33}N_3O_3 \cdot 0.25H_2O$	62–66	C, H, N	E
11	$C_{27}H_{32}N_3O_3Cl$	69–73	C, H, N, Cl	I
12a	$C_{28}H_{34}N_3O_4Cl \cdot 0.25H_2O$	117–127	C, H, N, Cl	F
12b	$C_{28}H_{34}N_3O_4Cl$	128–136	C, H, N, Cl	H
12c	$C_{28}H_{34}N_3O_4Cl$	146–152	C, H, N, Cl	H
14a	$C_{28}H_{34}N_3O_4F \cdot 0.25H_2O$	61–65	C, H, N	F
14b	$C_{28}H_{34}N_3O_4F$	75–80	C, H, N	H
14c	$C_{28}H_{34}N_3O_4F$	75–81	C, H, N	H
15a	$C_{20}H_{26}N_2O_4$	81–86	C, H, N	A
15b	$C_{20}H_{26}N_2O_4$	85–89	C, H, N	A
15c	$C_{20}H_{26}N_2O_4$	84–89	C, H, N	A
15d	$C_{20}H_{26}N_2O_4$	80–88	C, H, N	A
15e	$C_{20}H_{26}N_2O_4$	83–88	C, H, N	A
15f	$C_{20}H_{26}N_2O_4$	82–87	C, H, N	A
16a	$C_{29}H_{37}N_3O_4 \cdot 0.25H_2O$	124–131	C, H, N	B
16b	$C_{29}H_{37}N_3O_4 \cdot 0.25H_2O$	107–112	C, H, N	B
16c	$C_{29}H_{37}N_3O_4$	76–80	C, H, N	B
17a	$C_{21}H_{28}N_2O_4$	45–48	C, H, N	D
17b	$C_{21}H_{28}N_2O_4$	50–55	C, H, N	A
17c	$C_{21}H_{28}N_2O_4$	50–55	C, H, N	A
17d	$C_{21}H_{28}N_2O_4 \cdot 0.75H_2O$	95–103	C, H, N	B
17e	$C_{21}H_{28}N_2O_4$	50–55	C, H, N	A
17f	$C_{21}H_{28}N_2O_4$	50–55	C, H, N	A
18b	$C_{29}H_{26}N_6O_3$	155–158	C, H, N	B
19c	$C_{33}H_{42}N_4O_6$	97–102	C, H, N	A
20c	$C_{34}H_{42}N_4O_6 \cdot 0.75H_2O$	95–103	C, H, N	B
21b	$C_{33}H_{40}N_4O_6 \cdot H_2O$	117–126	C, H, N	A
21c	$C_{33}H_{40}N_4O_6 \cdot H_2O$	118–128	C, H, N	A
24c	$C_{32}H_{40}N_4O_6 \cdot 0.5H_2O$	106–111	C, H, N	A
26c	$C_{32}H_{28}N_4O_6 \cdot 0.25H_2O$	131–135	C, H, N	A
27g	$C_{37}H_{43}N_3O_5$	169.1	C, H, N	C
27h	$C_{37}H_{43}N_3O_5$	179.1	C, H, N	C
27i	$C_{37}H_{43}N_3O_5$	59–62	C, H, N	C
27j	$C_{37}H_{43}N_3O_5$	172	C, H, N	C
27k	$C_{37}H_{43}N_3O_5$	55–57	C, H, N	C
27l	$C_{37}H_{43}N_3O_5$	179.2	C, H, N	C
28g	$C_{30}H_{37}N_3O_5$	179.3–183.5	C, H, N	B
28h	$C_{30}H_{37}N_3O_5$	194.3–194.8	C, H, N	A
28i	$C_{30}H_{37}N_3O_5 \cdot 0.5H_2O$	112–120	C, H, N	A
28j	$C_{30}H_{37}N_3O_5$	176.3–177.3	C, H, N	B
28k	$C_{30}H_{37}N_3O_5$	111–122	C, H, N	A
28l	$C_{30}H_{37}N_3O_5$	195.6	C, H, N	A
29m	$C_{40}H_{45}N_3O_5$	168.5–169.6	C, H, N	G
29n	$C_{40}H_{45}N_3O_5$	68–71	C, H, N	C
29o	$C_{40}H_{45}N_3O_5$	69–73	C, H, N	C
29p	$C_{40}H_{46}N_3O_5$	171.4	C, H, N	C
30m	$C_{33}H_{39}N_3O_5 \cdot 0.1H_2O$	123–127	C, H, N	F
30n	$C_{33}H_{39}N_3O_5$	108–112	C, H, N	F
30o	$C_{33}H_{39}N_3O_5$	102–106	C, H, N	B
30p	$C_{33}H_{39}N_3O_5$	102–107	C, H, N	C

[a] Methods of Purification: A = 30% H_2O in MeOH, reverse phase silica; B = 25% H_2O in MeOH, reverse phase silica; C = 20% H_2O in MeOH, reverse phase silica; D = CH_2Cl_2, normal phase silica; E = 1% MeOH in CH_2Cl_2, normal phase silica; F = 2% MeOH in CH_2Cl_2, normal phase silica; G = 25% EtOAc in *n*-hexane; H = 20% iPrOH in *n*-hexane, Pirkle, normal phase silica HPLC; I = Recrystallized from EtOAc/*n*-hexane; J >98% by HPLC.

This result supports the idea that not all the carbon atoms of the adamantane cage are employed in CCK-B receptor binding. The two individual diastereoisomers of **16a** were prepared by the enantioselective synthesis of the *trans*-2-methylcyclohexanols.[11-14] The (1*R*,2*R*)-*trans*-[(2-methylcyclohexyl)oxy]carbonyl group was deemed to be optimal for the CCK-B receptor having a binding affinity (IC_{50}) for **16c** of 9.3 nM compared to the (1*S*,2*S*)-isomer **16b**, which had an IC_{50} value of 73 nM at the CCK-B receptor.

The *trans*-[(2-methylcyclohexyl)oxy]carbonyl group was then appended to selected compounds, replacing the

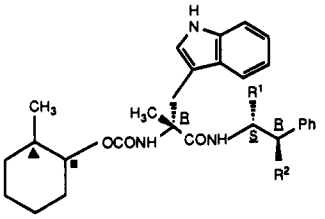
Table II. CCK Binding Affinities of N-Terminal Substituted Derivatives



no.	R^1	R^2	IC_{50}[a] (nM) CCK-A	IC_{50}[a] (nM) CCK-B	A/B ratio
5	2-adamantyl[b]	H	377 (250–559)	48 (38–59)	7.9
6	1-adamantyl[b]	H	785 (758–818)	210 (170–260)	3.9
7	2-adamantyl	CH_2OH	775 (691–885)	6.4 (4.2–8.9)	121
8	1-adamantyl	CH_2OH	1040 (840–1560)	21.6 (12–30)	48
9	2-chloro-1-adamantyl	CH_2OH	711 (575–961)	8.8 (4.4–14)	80
10	cyclohexyl[b]	H	625 (377–1040)	517 (444–565)	1.2
11	(±)-*trans*[2]-chlorocyclohexyl	H	196 (118–272)	49 (17–87)	4.0
12a	(±)-*trans*-2-chlorocyclohexyl	CH_2OH	66 (40–107)	15 (12–22)	4.4
12b	*trans*-2-chlorocyclohexyl isomer I	CH_2OH	118 (105–146)	140 (116–169)	0.8
12c	*trans*-2-chlorocyclohexyl isomer II	CH_2OH	265 (226–329)	6.95 (6.4–7.8)	38
14a	(±)-*trans*-2-fluorocyclohexyl	CH_2OH	288 (123–550)	36 (34–39)	8.0
14b	*trans*-2-fluorocyclohexyl isomer I	CH_2OH	251 (121–530)	149 (132–173)	1.7
14c	*trans*-2-fluorocyclohexyl isomer II	CH_2OH	266 (196–362)	23 (21–28)	12
16a	(±)-*trans*-2-methylcyclohexyl	CH_2OH	66 (31–120)	16 (14–19)	0.4
16b	(1*S*,2*S*)-*trans*-2-methylcyclohexyl	CH_2OH	75 (62–91)	73 (58–120)	1.0
16c	(1*R*,2*R*)-*trans*-2-methylcyclohexyl	CH_2OH	288 (227–424)	9.3 (6.6–14)	31

[a] IC_{50} represents the concentration (nM) producing half-maximal inhibition of specific binding of [^{125}I]Bolton–Hunter-labeled 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. [b] (*RS*)-α-methyltryptophan.

Table III. CCK Binding Affinities of Some [(2-Methylcyclohexyl)oxy]carbonyl-Substituted Dipeptoids



no.	▲	■	R^1	R^2	IC_{50}[a] (nM) CCK-A	IC_{50}[a] (nM) CCK-B	A/B ratio
21b	*S*	*S*	$CH_2NHCOCH{=}CHCO_2H$ (trans)	H	47 (39–53)	6.5 (4.6–9.1)	7
21c	*R*	*R*	$CH_2NHCOCH{=}CHCO_2H$ (trans)	H	154 (90–292)	1.2 (1.1–1.3)	128
19c	*R*	*R*	$CH_2NHCOCH_2CH_2CO_2H$	H	391 (233–1050)	13 (9–25)	30
26c	*R*	*R*	H	$NHCOCH{=}CHCO_2H$	511 (492–531)	4.0 (2.3–10)	128
24c	*R*	*R*	H	$NHCOCH_2CH_2CO_2H$	1810 (1310–2500)	3.9 (1.8–7.4)	464

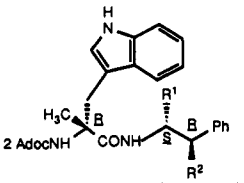
[a] Binding affinities as defined in footnote a, Table II.

2-adamantyl group. These are shown in Table III. Previously reported compounds[1,5,6] are shown in Table IV for comparison. Examination of these tables reveals that the (1*R*,2*R*)-[(2-methylcyclohexyl)oxy]carbonyl group is optimal for binding to the CCK-B receptor. This group, however, is better tolerated than the (2-adamantyloxy)-carbonyl group at the CCK-A receptor, thus the former show less CCK-B selectivity. The (1*S*,2*S*)-isomers have approximately 6–10-fold less affinity than the (1*R*,2*R*)-isomers for the CCK-B receptor.

A previous observation for some of the (2-adamantyloxy)carbonyl-containing series of compounds concluded that the inversion of stereochemical centers of the tryptophan and/or substituted phenethylamine groups independently decreased CCK-B binding affinity, but had little effect on CCK-A receptor binding affinity.[1,2] Therefore, taking a selective CCK-B receptor ligand with modest CCK-A binding affinity [for example **30m** (IC_{50} CCK-B = 0.15 nM; IC_{50} CCK-A = 25.5 nM)] and inverting the α-methyltryptophan center cause a decrease of approximately 100-fold in CCK-B binding affinity (**30o** IC_{50} CCK-B = 13.2 nM). Inverting the substituted phenethylamide center gives a similar decrease in CCK-B affinity (**30n** IC_{50} CCK-B = 9.3 nM). The combined effect of inverting *both* centers gave compound **30p** (IC_{50} CCK-B = 260 nM; IC_{50} CCK-A = 2.8 nM), which is now 100-fold selective for the CCK-A receptor over CCK-B. Hence, both CCK-B-selective (e.g. CI-988, **2**: R = 2-Adoc) and CCK-A-selective ligands (**30p**) have been produced from the dipeptoid chemical class of CCK ligands.

Ligands have also been discovered by this strategy that have equal high nanomolar binding affinity at both CCK-A and CCK-B receptor subtypes. This was achieved by the combined strategies of stereochemical inversion together with the *trans*-[(2-methylcyclohexyl)oxy]carbonyl selective groups. The results are summarized in Table V. For example, compound **28i**, which has the (*R*,*R*,*R*,*S*)-configurations at the optical centers has a 53-fold selectivity for the CCK-B receptor, but the (*S*,*S*,*R*,*S*)-diastereoisomer **28h** has decreased CCK-B affinity (10-fold) and modestly increased CCK-A binding affinity. The result is the ligand **28h** [Table V, IC_{50} = 3.9 nM (CCK-A), 4.2 nm (CCK-B)], which has mixed, nanomolar affinity for *both* CCK-A and CCK-B receptor subtypes.

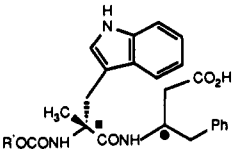
Table IV. CCK-B Receptor Binding Affinities of CCK-B-Selective Ligands



R^1	R^2	IC_{50}[a] (nM) CCK-A	IC_{50}[a] (nM) CCK-B	A/B ratio
CH_2OH	H	780 (690–850)	6.3 (4.2–8.9)	120
$CH_2OCO(CH_2)_2CO_2H$	H	740 (690–790)	3.4 (2.5–5.8)	220
$CH_2NHCOCH{=}CHCO_2H$	H	440 (430–440)	0.8 (0.4–1.2)	550
$CH_2NHCO(CH_2)_2CO_2H$	H	950 (740–1100)	4.2 (2.9–6.3)	230
CH_2CO_2H	H	69.7 (69.7–69.7)	0.21 (0.18–0.85)	332
H	$NHCOCH{=}CHCO_2H$	790 (680–1000)	0.7 (0.5–1.0)	1100
H	$NHCO(CH_2)_2CO_2H$	4300 (1200–8500)	1.7 (1.3–2.7)	2500
devazepide (MK329)		0.1 (0.3–0.2)	31 (18–43)	0.0032
L-365,260		230 (170–380)	5.1 (4.6–5.4)	45
sulfated CCK(26–33)		0.1 (0.08–0.2)	0.3 (0.2–0.3)	0.33
pentagastrin		600 (500–660)	0.8 (0.5–0.9)	750

[a] Binding affinity as defined in footnote a, Table II.

Table V. CCK Binding Affinities for the Stereoisomers of CCK Dipeptoids



no.	R	■	●	IC_{50}[a] (nM) CCK-A	IC_{50}[a] (nM) CCK-B	A/B ratio
30m	2-adamantyl	R	S	25.5 (18.1–35.8)	0.15 (0.09–0.21)	170
30o	2-adamantyl	S	S	539 (463–629)	13.2 (10.4–16.9)	41
30n	2-adamantyl	R	R	186 (133–268)	9.3 (8.4–10.5)	20
30p	2-adamantyl	S	R	2.82 (1.4–5.1)	260 (208–292)	0.01
28g	(±)-*trans*-2-methylcyclohexyl	R	S	8.9 (6.8–12)	0.6 (0.5–1)	15
28h	(1*S*,2*S*)-*trans*-2-methylcyclohexyl	R	S	3.9 (2.2–5.4)	4.2 (3.9–4.7)	1
28i	(1*R*,2*R*)-*trans*-2-methylcyclohexyl	R	S	18 (15–20)	0.34 (0.18–0.25)	53
28j	(±)-*trans*-2-methylcyclohexyl	S	R	12 (8–18)	815 (619–1200)	0.01
28k	(1*S*,2*S*)-*trans*-2-methylcyclohexyl	S	R	20 (20–21)	1260 (860–2180)	0.016
28l	(1*R*,2*R*)-*trans*-2-methylcyclohexyl	S	R	7.9 (6.5–9.4)	1160 (823–1680)	0.007

[a] Binding affinities as defined in footnote a, Table II.

Biological Results

We have, by evaluation of the structure–activity relationships described above, designed peptoid ligands with nanomolar affinity that possess selectivity for either the CCK-A or the CCK-B receptor and ligands that have high, but mixed, affinity for both receptor subtypes. The pharmacological properties of representative examples of compounds that are selective for the CCK-B receptor have been described elsewhere.[1,4] Here we report on some of the pharmacological properties of compounds that are selective for the CCK-A receptor, and for mixed A/B affinity ligands. Compound **30p** is a potent and selective antagonist for the CCK-A receptor. This has been demonstrated by its ability to block CCK-A-mediated responses in the rat dorsal raphé (K_e = 12.8 nM). It failed to block CCK-B-mediated responses in the rat ventromedial nucleus of the hypothalamus, except at elevated concentrations (K_e = 1150 nM), where the CCK-B component of **30p** may play a part. **30p** Also blocked CCK-8S-induced amylase secretion from pancreatic acinar cells. Figure 1 shows a parallel rightward shift in the concentration–response to CCK-8S (K_e = 16 nM). The Schild analysis of this curve gives a K_B = 13 nM, with a slope value of 0.9. These data support competitive antagonism of compound **30p** at the CCK-A receptor (Figure 2).

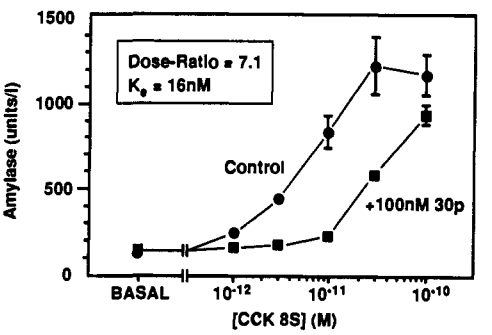


Figure 1. Inhibition by compound **30p** of CCK-8S-evoked amylase secretion from pancreatic acinar cells.

The CCK-A-selective compound **28l** has been shown not to block CCK-B-mediated responses in the rat ventromedial nucleus of the hypothalamus at concentrations up to 300 nM but does block CCK-8S-evoked amylase secretion in the pancreas (Figure 3). Compound **28h**, which has high affinity for both CCK-A and CCK-B receptors, blocks CCK-B-mediated effects in the rat ventromedial nucleus of the hypothalamus (K_e = 8.8 nM) *and* inhibits the CCK-A-mediated amylase release from the pancreas when stimulated with CCK-8S (Figure 3). We can therefore conclude that compounds **30p** and **28l** are

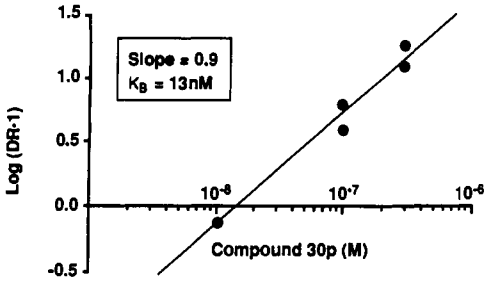


Figure 2. Schild analysis of compound **30p** inhibition of CCK-evoked amylase release.

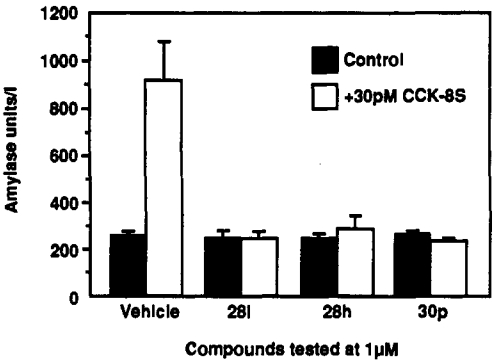


Figure 3. Antagonism of CCK-8S-evoked amylase secretion from rat dispersed pancreatic acini.

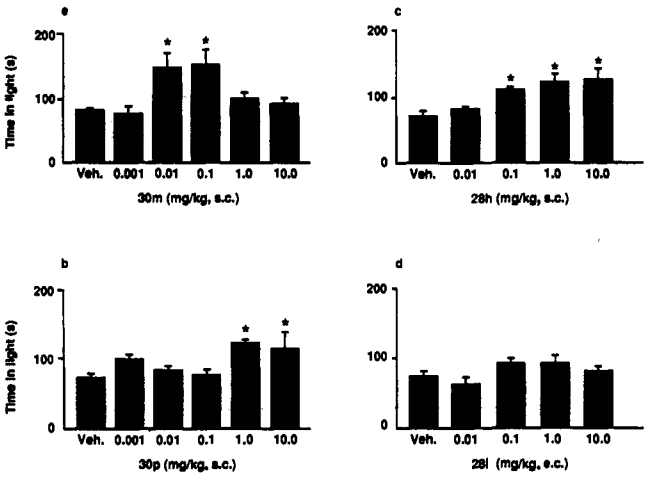


Figure 4. The effect of CCK-receptor antagonists in the mouse light/dark box.

selective, competitive antagonists for the CCK-A receptor, while **28h** is an antagonist at both the CCK-A and CCK-B receptors.

The role of CCK receptors in anxiety has been described previously.[1-4] However, the new ligands described above can be used to distinguish whether the anxiolytic effect is a CCK-A- or CCK-B-mediated effect. Thus it has been previously shown that selective CCK-B antagonists are potent anxiolytic agents, whereas agonists at this receptor increase anxiety levels in a wide range of animal models.[8] Similarly, in the mouse light/dark box test, the selective CCK-B antagonist **30m** was shown to have a minimum effective dose (MED) of 0.01 mg/kg sc (Figure 4). The enantiomer of **30m** (**30p**), which has a 100-fold selectivity for the CCK-A receptor, has an MED of 1 mg/kg sc. This is 100-fold less active in this test than the B-selective compound, a similar ratio to its CCK-A and CCK-B binding affinities (Table V) and to the K_e ratios from the dorsal raphé and the ventromedial hypothalamus (Table VI). Compound **28l**, which is a CCK-A-selective compound is inactive in the black/white box test up to a dose of 10 mg/kg sc. Its enantiomer, **28h**, which is a mixed CCK-A/-B compound, has equal affinity at both CCK-A and CCK-B receptor subtypes and has an MED in the light/dark box test of 0.1 mg/kg (sc). These data lend support to the hypothesis that the anxiolytic actions of these CCK-receptor dipeptoid ligands are mediated via the CCK-B receptor and not the CCK-A receptor.

Table VI. Electrophysiology Data: Equilibrium Constant (K_e) Values for Compounds Used in the Present Study

no.	rat VMH K_e[a] (nM)	range
30m	2.8	(0.1–8.4)
28h	8.8	(5.4–10.8)
30p	1150.0	(520–2500)
	12.8[b]	(5.2–26.7)
28l	inactive to 300 nM	

[a] All K_e determinations are the mean of at least three separate experiments. [b] Data from rat dorsal raphé (CCK-A receptors).

Conclusions

The current structure–activity relationships of the N-terminal groups of these dipeptoid ligands, together with the stereochemical requirements at the N-terminal group, the α-methyltryptophan, and the C-terminal groups, have identified selective CCK-A and CCK-B as well as mixed A/B ligands of high affinity. These compounds have been used to delineate the role of CCK-A and CCK-B receptors in models of anxiety and have added support to the hypothesis that the CCK-B receptor rather than the CCK-A receptor is primarily involved in anxiety, as assessed by the mouse light/dark box test.[3,8]

Experimental Section

(1) Biology. (a) Receptor Binding Assays. CCK-A receptor binding assays were performed on male rat pancreas. Tissue (250 mg) homogenized in ice-cold Tris-HCl (pH 7.4) (50 mL of a 50 mM solution) was centrifuged at 20000*g*. The pellet was washed once by resuspension in Tris-HCl followed by recentrifugation 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, 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 20000*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 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 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. Nonspecific binding was estimated by 1 μM CCK 8S.

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

(b) Amylase Release Experiments. Amylase release was measured from rat dispersed pancreatic acinar cells. Male Sprague–Dawley rats were sacrificed by decapitation and the

abdominal cavities opened. The bile duct was cannulated and 5 mL of Hanks Balanced Salt solution buffered to pH 7.4 using 10 nM HEPES containing 1500 units of collagenase (Sigma Type VII) and 500 000 KIU/mL Aprotinin (Trasylol, Bayer) infused into the pancreas. The pancreas was removed, placed in a conical flask and incubated for 15 min with 10 mL of digestion fluid that had been saturated with oxygen and then incubated at 37 °C with agitation for 30 min. The tissue was then dispersed using a pipet and the mixture filtered through nylon mesh (200 μM). The dispersed acini cells were then sedimented under mild centrifugation and washed by centrifuging through 41% BSA. The tissue was suspended in Hanks solution (pH 7.4) containing 0.1% BSA. Aliquots were then incubated in a final volume of 2 mL for 20 min at 37 °C with sulfated cholecystokinin octapeptide in the presence and absence of test compound. After the incubation, aliquots of the supernatant were taken for determination of amylase activity using a Phadebas kit (Phamacia Ltd., Milton Keynes, U.K.).

(c) Electrophysiology. CCK-B-mediated responses measured in the rat ventromedial nucleus of the hypothalamus (VMH) were as described earlier,[2] with the exception that all measurements were made using the CCK-B-selective agonist pentagastrin in order to eliminate possible CCK-A receptor activation.

CCK-A-mediated responses, which were measured in the rat dorsal raphé, were measured as described earlier.[9]

(d) Light/Dark Box Test. The mouse light/dark box test was carried out using male TO mice (20–25 g), obtained from Bantin and Kingman (Hull, U.K.). The time spent by the mice in the illuminated section of the box was determined as previously described.[3] All test compounds were dissolved in 0.9% (w/v) saline and administered subcutaneously (sc) 40 min before the test at a total volume of 10 mL/kg.

(2) 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 spectrometer. Elemental analyses were determined by Medac Ltd., Uxbridge, U.K. Normal-phase silica gel used for chromatography was Kieselgel-60 (230–400 mesh) and 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 4-Å molecular sieves prior to use. The filter aid used throughout was Celite, purchased from the Aldrich Chemical Co. Ltd., Gillingham, England.

General Method A. A solution of an appropriate chloroformate (1 mmol) and *N*-phenethyl-α-methyl-(*RS*)-tryptophanamide **3** (1 mmol) in anhydrous THF (20 mL) was treated by the dropwise addition of a solution of triethylamine (1.2 mmol) in THF (10 mL) at room temperature. The resulting mixture was left stirring for 4 h and filtered, and the filtrate was evaporated to dryness in vacuo. The residue was then subjected to chromatographic separation.

General Method B. A solution of α-methyl-(*R*)-tryptophanyl-(*S*)-phenylalaninol **4** (1.4 mmol) and triethylamine (1.6 mmol) in anhydrous THF (20 mL) was treated dropwise with a solution of an appropriate chloroformate (1.4 mmol) in anhydrous THF (20 mL) at room temperature. The resultant mixture was left for 4 h and filtered, and the filtrate was evaporated in vacuo. The residue was then subjected to chromatographic separation.

Tricyclo[3.3.1.1^{3,7}]dec-2-yl (±)-[1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(2-phenylethyl)amino]ethyl]carbamate (5) was prepared according to general method A: yield 77%; IR (film) 1701 and 1656 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.00 (17 H, m), 2.67 (2 H, t, J = 7 Hz), 3.26 (1 H, d, J = 15 Hz), 3.40–3.50 (3 H, m), 4.80 (1 H, br s), 5.25 (1 H, br s), 6.18 (1 H, br s), 6.95 (1 H, d, J = 2 Hz), 7.10–7.30 (7 H, m), 7.35 (1 H, d, J = 8 Hz), 7.58 (1 H, d, J = 8 Hz), 8.08 (1 H, br s); MS (FAB) *m/e* 500 (100).

Tricyclo[3.3.1.1^{3,7}]dec-1-yl (±)-[1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(2-phenylethyl)amino]ethyl]carbamate (6) was prepared according to general method A: yield 49%; IR (film) 1700 and 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (3 H, s), 1.63 (6 H, br s), 2.00–2.05 (6 H, m), 2.14 (3 H, br s), 2.66 (1 H, t, J = 7 Hz), 2.67 (1 H, t, J = 7 Hz), 3.19 (1 H, d, J = 14.5 Hz), 3.40–3.50 (3 H, m), 4.93 (1 H, br s), 6.30 (1 H, br s), 6.98–7.60 (10 H, m), 8.24 (1 H, br s).

Tricyclo[3.3.1.1^{3,7}]dec-2-yl [*R*-(*R,*S**)]-[2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]carbamate (7)** was prepared according to general method B: yield 80%; $[\alpha]^{20}_D$ = +11.6° (c = 1.02, MeOH); IR (film) 3500–3200, 2907, 2854, 1695, and 1659 cm^{-1}; NMR ($CDCl_3$) δ 1.39 (3 H, s), 1.50–2.00 (14 H, m), 2.75–2.85 (3 H, m), 3.32 (1 H, d, J = 15 Hz), 3.40–3.50 (2 H, m), 3.70–3.80 (1 H, m), 4.15–4.25 (1 H, m), 4.82 (1 H, br s), 5.01 (1 H, s), 6.19 (1 H, d, J = 8 Hz), 6.91 (1 H, d, J = 2.3 Hz), 7.05–7.25 (7 H, m), 7.35 (1 H, d, J = 8 Hz), 7.58 (1 H, d, J = 7.8 Hz), 8.10 (1 H, s).

Tricyclo[3.3.1.1^{3,7}]dec-1-yl [*R*-(*R,*S**)]-[2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]carbamate (8)** was prepared according to general method B: yield 66%; $[\alpha]^{20}_D$ = +23.4° (c = 1, MeOH); IR (film) 3500–3200, 2912, 2884, 1675, 1650, and 1520 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (3 H, s), 1.68 (6 H, s), 2.11 (6 H, s), 2.20 (3 H, s), 2.81 (1 H, d, J = 4.5 Hz), 2.84 (1 H, d, J = 4 Hz), 2.85–2.95 (1 H, m), 3.32 (1 H, d, J = 14.7 Hz), 3.46 (1 H, d, J = 15.2 Hz), 3.44–3.51 (1 H, m), 3.75–3.85 (1 H, m), 4.20–4.30 (1 H, m), 4.82 (1 H, s), 6.18 (1 H, d, J = 8.2 Hz), 6.95–7.31 (8 H, m), 7.38 (1 H, d, J = 8 Hz), 7.61 (1 H, d, J = 7.7 Hz), 8.15 (1 H, s); MS (EI) *m/e* 529.0 (0.2), 152.1 (11.4), 135.1 (46.4), 130.0 (100).

Carbamic acid, [1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(2-phenylethyl)amino]ethyl]-, cyclohexyl ester, (±)- (10), was prepared according to general method A: yield 74%; IR (film) 1702 and 1656 cm^{-1}; NMR ($CDCl_3$) δ 1.15–1.90 (13 H, m), 2.67 (2 H, t, J = 7 Hz), 3.22 (1 H, d, J = 14.5 Hz), 3.40–3.50 (3 H, m), 4.55–4.65 (1 H, m), 5.08 (1 H, s), 6.15–6.25 (1 H, br s), 6.96 (1 H, s), 7.05–7.30 (7 H, m), 7.35 (1 H, d, J = 8 Hz), 7.58 (1 H, d, J = 8 Hz), 8.15 (1 H, s); MS (CI) *m/e* 449 (9.1) and 83 (100).

Carbamic acid, [1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(2-phenylethyl)amino]ethyl]-, 2-chlorocyclohexyl ester, *trans*-(±)- (11), was prepared according to general method A: yield 79%; IR (film) 3500–3200, 2941, 2862, 1709, 1656, and 1495 cm^{-1}; NMR ($CDCl_3$) δ 1.20–1.40 (3 H, m), 1.53 (1.5 H, s), 1.56 (1.5 H, s), 1.60–1.80 (3 H, m), 1.95–2.20 (2 H, m), 2.55–2.70 (2 H, m), 3.15–3.50 (4 H, m), 3.70–3.80 (1 H, m), 4.60–4.75 (1 H, m), 5.28 (1 H, s), 6.10–6.25 (1 H, m), 6.96 (1 H, s), 7.00–7.25 (7 H, m), 7.35 (1 H, d, J = 8 Hz), 7.53–7.60 (1 H, m), 8.37 (1 H, s); MS *m/e* (FAB) 482.2 (100), 352.1 (71.8), 333.1 (84.3), 304.1 (95.6).

Carbamic acid, [2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-chlorocyclohexyl ester (Trp center is *R*, phenyl ethyl center is *S*, and ring centers are trans) (12a), was prepared according to general method B: yield 73%; IR (film) 3500–3200, 2940, 2864, 1699, and 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.20–1.45 (3 H, m), 1.32 (3 H, s), 1.40 (3 H, s), 1.70–1.80 (3 H, m), 2.09–2.25 (2 H, m), 2.67–2.83 (2 H, m), 3.28–3.52 (3 H, m), 3.63–3.83 (2 H, m), 4.10–4.30 (1 H, m), 4.68–4.80 (1 H, m), 5.97 (1 H, s), 6.08 (1 H, s), 6.09 (1 H, d, J = 8 Hz), 6.19 (1 H, d, J = 7.5 Hz), 6.91–7.60 (10 H, m), 8.08 (1 H, m).

Compound **12a** was separated into two isomers (I and II) on a Pirkle Prep-D-phenylglycine (Prep 1010) column using 20% iPrOH in *n*-hexane.

Carbamic acid, [2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-chlorocyclohexyl ester (isomer I) (ring centers are trans, Trp center is *R*, other center is *S*) [(+)-form of 12b]: $[\alpha]^{20}_D$ = +50.5° (c = 0.2, MeOH); IR (film) 3500–3200, 2931, 2862, 1699, 1661, and 1495 cm^{-1}; NMR ($CDCl_3$) δ 1.20–1.40 (3 H, m), 1.40 (3 H, s), 1.65–1.80 (3 H, m), 2.05–2.15 (1 H, m), 2.20–2.30 (1 H, m), 2.60–2.70 (1 H, br s), 2.78 (2 H, d, J = 7.5 Hz), 3.30 (1 H, d, J = 14.5 Hz), 3.42 (1 H, d, J = 14.5 Hz), 3.40–3.50 (1 H, m), 3.65–3.85 (2 H, m), 4.10–4.20 (1 H, m), 4.65–4.75 (1 H, m), 5.13 (1 H, s), 6.23 (1 H, d, J = 7.5 Hz), 7.02 (1 H, s), 7.10–7.28 (7 H, m), 7.35 (1 H, d, J = 8 Hz), 7.59 (1 H, d, J = 8 Hz), 8.20 (1 H, s).

Carbamic acid, [2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-chlorocyclohexyl ester (isomer II) (ring centers are trans, Trp center is *R*, other center is *S*) [(−)-form of 12b]: $[\alpha]^{20}_D$ = −1.0° (c = 0.2, MeOH); IR (film) 3500–3200, 2942, 2864, 1696,

1658, and 1515 cm^{-1}; NMR ($CDCl_3$) δ 1.20–1.45 (3 H, m), 1.32 (3 H, s), 1.65–1.85 (3 H, m), 2.00–2.30 (2 H, m), 2.70 (1 H, dd, J = 7.5 and 14 Hz), 2.79 (1 H, dd, J = 7 and 14 Hz), 3.33 (1 H, d, J = 14.5 Hz), 3.40–3.50 (1 H, m), 3.49 (1 H, d, J = 14.5 Hz), 3.70–3.80 (2 H, m), 4.20–4.30 (1 H, m), 4.70–4.80 (1 H, m), 5.02 (1 H, s), 6.11 (1 H, d, J = 8 Hz), 6.92 (1 H, s), 7.05–7.25 (7 H, m), 7.35 (1 H, d, J = 8 Hz), 7.55 (1 H, d, J = 8 Hz), 7.55 (1 H, d, J = 8 Hz), 8.18 (1 H, s).

Carbamic acid, [2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-fluorocyclohexyl ester (ring is trans-(±)-, Trp is *R*, other center is *S*) (14a), was prepared according to general method B: yield 77%; IR (film) 3500–3200, 2940, 2870, 1696, 1658, and 1515 cm^{-1}; NMR ($CDCl_3$) δ 1.26–1.39 (7 H, m), 1.53–1.78 (2 H, m), 2.04–2.12 (2 H, m), 2.67–2.81 (3 H, m), 3.31 (1 H, d, J = 14.5 Hz), 3.42–3.49 (2 H, m), 3.71 (1 H, m), 4.18–4.48 (2 H, m), 4.80 (1 H, m), 5.02 (0.5 H, s), 5.04 (0.5 H, s), 6.14 (0.5 H, d, J = 8 Hz), 6.25 (0.5 H, d, J = 8 Hz), 6.94 (1 H, m), 7.09–7.37 (8 H, m), 7.57 (1 H, m), 8.16 (1 H, s).

Compound **14a** was separated into two isomers (I and II) on a Pirkle Prep-D-phenylglycine (Prep 1010) column using 20% iPrOH in *n*-hexane as eluant.

Carbamic acid, [2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-fluorocyclohexyl ester (indole center is *R*, hydroxymethyl center is *S*) [(+)-isomer 14b]: $[\alpha]^{20}_D$ = +58° (c = 0.2, $CHCl_3$); IR (film) 3500–3200, 2945, 2870, 1700, 1664, and 1520 cm^{-1}; NMR ($CDCl_3$) δ 1.20–1.80 (6 H, m), 1.37 (3 H, s), 2.00–2.20 (2 H, m), 2.64 (1 H, t, J = 6.5 Hz), 2.79 (2 H, d, J = 7.5 Hz), 3.29 (1 H, d, J = 14.5 Hz), 3.40–3.50 (2 H, m), 3.68–3.77 (1 H, m), 4.10–4.30 (1.5 H, m), 4.4–4.8 (0.5 H, m), 4.70–4.85 (1 H, m), 5.01 (1 H, s), 6.23 (1 H, d, J = 8 Hz), 6.95 (1 H, d, J = 2 Hz), 7.09–7.30 (7 H, m), 7.35 (1 H, d, J = 8 Hz), 7.57 (1 H, d, J = 8 Hz), 8.12 (1 H, s); MS m/e (FAB) 496.3 (100), 366.2 (34), 317.2 (86).

Carbamic acid, [2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-fluorocyclohexyl ester (indole center is *R*, hydroxymethyl center is *S*) [(−)-isomer 14c]: $[\alpha]^{20}_D$ = −3° (c = 0.2, $CHCl_3$); IR (film) 3500–3200, 2920, 2880, 1697, 1660, and 1515 cm^{-1}; NMR ($CDCl_3$) δ 1.20–1.80 (6 H, m), 1.34 (3 H, s), 2.00–2.20 (2 H, m), 2.70–2.85 (3 H, m), 3.31 (1 H, d, J = 14.5 Hz), 3.40–3.50 (2 H, m), 3.70–3.80 (1 H, m), 4.15–4.50 (2 H, m), 4.75–4.90 (1 H, m), 4.98 (1 H, s), 6.11 (1 H, d, J = 8 Hz), 6.93 (1 H, s), 7.05–7.30 (7 H, m), 7.35 (1 H, d, J = 8 Hz), 7.55 (1 H, d, J = 8 Hz), 8.07 (1 H, s); MS m/e (FAB) 496.3 (100), 366.3 (30), 317.2 (68).

***trans*-(±)-α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-D-tryptophan Methyl Ester (17a)**. A stirred solution of (±)-*trans*-2-methylcyclohexanol (1.37 g, 12.0 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0 °C was treated with solid bis(trichloromethyl) carbonate (1.48 g, 4.99 mmol) followed by the dropwise addition of pyridine (0.95 g, 12 mmol) in anhydrous CH_2Cl_2 (15 mL). After 1 h at 0 °C the solvent was removed in vacuo at a temperature not exceeding 20 °C. The residue was redissolved in EtOAc (50 mL) and filtered. The solvent was then evaporated in vacuo and redissolved in anhydrous THF (20 mL). This solution was then added to a solution of D-α-methyltryptophan methyl ester (2.32 g, 10.0 mmol) in anhydrous THF (60 mL) at 0 °C. After the addition was complete, a solution of Et_3N (1.1 g, 11 mmol) in THF (20 mL) was added dropwise. This reaction mixture was then stirred for 3 h at ambient temperature and then the solvent removed in vacuo. The residue was dissolved in EtOAc (50 mL) and washed with 1 M citric acid solution (2 × 20 mL), H_2O (20 mL), saturated $NaHCO_3$ solution (2 × 20 mL), and H_2O (2 × 20 mL). The dried ($MgSO_4$) organic phase was evaporated to dryness and chromatographed to give the product as a foam (2.8 g, 75%): $[\alpha]^{20}_D$ = +34° (c = 1, MeOH); IR (film) 3280–3480, 2932, 2858, 1740, 1698, 1504, and 1457 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (1.5 H, d, J = 6.4 Hz), 0.93 (1.5 H, d, J = 6.4 Hz), 1.00–1.62 (6 H, m), 1.65 (1.5 H, s), 1.67 (1.5 H, s), 1.70–1.80 (2 H, m), 1.98–2.08 (1 H, m), 3.35 (0.5 H, d, J = 14.5 Hz), 3.38 (0.5 H, d, J = 14.5 Hz), 3.45–3.60 (1 H, m), 3.67 (3 H, s), 4.25–4.40 (1 H, m), 5.25–5.40 (1 H, br s), 6.94–6.97 (1 H, m), 7.05–7.20 (2 H, m), 7.33 (1 H, d, J = 8.0 Hz), 7.54 (1 H, d, J = 7.8 Hz), 8.11 (1 H, s); MS (FAB) m/e 373.2 (18), 313.2 (3.7), 275.2 (4.2), 233.1 (96.1), 216.1 (100).

***trans*-(±)-α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-D-tryptophan (15a)**. A solution of ester **17a** (3.7 g, 10 mmol) in aqueous 1,4-dioxane (100 mL of a 1:2, water/dioxane mixture) was treated with $LiOH \cdot H_2O$ (1.3 g, 30 mmol) and the mixture stirred at room temperature for 36 h. The reaction mixture was then concentrated in vacuo to one-third its original volume and diluted with H_2O (100 mL). This was then washed with EtOAc (50 mL). The aqueous phase was then acidified to pH 2 with 2 M HCl solution and extracted with EtOAc (2 × 50 mL). The organic phases were combined, washed with H_2O (3 × 20 mL), and dried over $MgSO_4$. This was filtered and the filtrate evaporated to dryness in vacuo to give the crude product which was chromatographed to give **15a** as a foam (2.7 g, 77%): $[\alpha]^{20}_D$ = +17.5° (c = 1, MeOH); IR (film) 3500–3200, 2936, 3200–2400, 1708, 1505, and 1456 cm^{-1}; NMR (DMSO-d_6) δ 0.87 (1.5 H, d, J = 6.5 Hz), 0.9 (1.5 H, d, J = 6.5 Hz), 0.95–1.75 (8 H, m), 1.27 (3 H, s), 1.85–2.00 (1 H, m), 3.09 (0.5 H, d, J = 14.3 Hz), 3.13 (0.5 H, d, J = 14.2 Hz), 3.30–3.45 (1 H, m), 4.13–4.28 (1 H, m), 6.85–7.05 (4 H, m), 7.31 (1 H, d, J = 8.0 Hz), 7.45 (1 H, d, J = 7.9 Hz), 10.90 (1 H, s), 12.30–12.45 (1 H, br); MS (FAB) m/e 359.2 (18.1), 313.2 (10.6), 263.1 (19.7), 219.1 (88.4), 202.1 (100).

Carbamic Acid, [2-[[1-(Hydroxymethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-Methylcyclohexyl Ester (ring centers are trans, Trp center is *R*, other center is *S*) (16a). A solution of the acid **15a** (1.79 g, 5.00 mmol) in EtOAc (20 mL) was treated with pentafluorophenol (0.92 g, 5.00 mmol) and then *N*,*N*′-dicyclohexylcarbodiimide (1.08 g, 5.30 mmol) at 0 °C for 1 h. The reaction mixture was filtered and the filtrate treated dropwise with a solution of (*S*)-(−)-2-amino-3-phenylpropanol (0.83 g, 5.50 mmol) in EtOAc (5 mL). This mixture was stirred for 4 h at room temperature and filtered, the filtrate evaporated to dryness in vacuo, and the residue chromatographed over reverse-phase silica to give the product **16a** as white needles (1.47 g, 60%): IR (film) 3500–3200, 2932, 2858, 1690, 1660, 1497, and 1255 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (1.5 H, d, J = 6.5 Hz), 0.91 (1.5 H, d, J = 6.3 Hz), 1.00–1.75 (8 H, m), 1.36 (1.5 H, s), 1.39 (1.5 H, s), 1.92–2.00 (1 H, m), 2.70–2.80 (3 H, m), 3.28–3.48 (3 H, m), 3.65–3.80 (1 H, m), 4.10–4.38 (2 H, m), 4.94 (0.5 H, s), 4.99 (0.5 H, s), 6.11 (0.5 H, d, J = 7.7 Hz), 6.14 (0.5 H, d, J = 7.8 Hz), 6.91 (1 H, s), 7.05–7.30 (7 H, m), 7.35 (1 H, d, J = 8.0 Hz), 7.57 (1 H, d, J = 7.8 Hz), 8.08 (1 H, s); MS (FAB) m/e 492.2 (100), 352.1 (43.4), 334.1 (25.2), 245.1 (14.6).

(1*S*-*trans*)-α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-D-tryptophan Methyl Ester (17b). The method was as for **17a** except using (1*S*,2*S*)-2-methylcyclohexanol: yield 89%; $[\alpha]^{20}_D$ = +54.3° (c = 1, MeOH); IR (film) 3500–3300, 2932, 1739, 1697, 1502, and 1456 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (3 H, d, J = 6.5 Hz), 1.00–1.80 (8 H, m), 1.67 (3 H, s), 2.00–2.10 (1 H, m), 3.36 (1 H, d, J = 14.4 Hz), 3.45–3.60 (1 H, br m), 3.67 (3 H, s), 4.25–4.40 (1 H, m), 5.35–5.50 (1 H, br s), 6.96 (1 H, s), 7.05–7.20 (2 H, m), 7.34 (1 H, d, J = 8.0 Hz), 7.55 (1 H, d, J = 7.7 Hz), 8.09 (1 H, s); MS (FAB) m/e 373.2 (34.5), 233.1 (86.2), 216.1 (100).

(1*S*-*trans*)-α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-D-tryptophan (15b). The method was as for **15a** except using **17b**: yield 96%; $[\alpha]^{20}_D$ = +42.3° (c = 1, MeOH); IR (film) 4000–2800, 1703, 1504, and 1456 cm^{-1}; NMR (DMSO-d_6) δ 0.91 (3 H, d, J = 0.4 Hz), 0.97–1.75 (8 H, m), 1.28 (3 H, s), 1.85–1.95 (1 H, m), 3.13 (1 H, d, J = 14 Hz), (1 H, d, J = 14.7 Hz), 4.15–4.25 (1 H, m), 6.80–7.06 (4 H, m), 7.31 (1 H, d, J = 8.0 Hz), 7.46 (1 H, d, J = 7.8 Hz), 10.90 (1 H, s), 12.20–12.50 (1 H, br s); MS (FAB) m/e 359.1 (100), 313.2 (13.8), 263.0 (25.1), 219.0 (75.1), 202.1 (85.0).

Carbamic Acid, [2-[[1-(Hydroxymethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-Methylcyclohexyl Ester, [1*S*-[1α[*S(*R**)],2β]]- (16b)**. The method was as for **16a** except using **15b**: yield = 44%; $[\alpha]^{20}_D$ = +32.3° (c = 1.04, MeOH); IR (film) 3500–3200, 2931, 2859, 1690, 1659, 1497, and 1254 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (3 H, d, J = 6.4 Hz), 1.00–1.80 (8 H, m), 1.39 (3 H, s), 1.90–2.00 (1 H, m), 2.76 (2 H, d, J = 7 Hz), 2.86 (1 H, t, J = 6 Hz), 3.31 (1 H, d, J = 14.7 Hz), 3.35–3.50 (2 H, m), 3.65–3.75 (1 H, m), 4.10–4.20 (1 H, m), 4.28 (1 H, dt, J = 4 and 10 Hz), 5.03 (1 H, s), 6.16 (1 H, d, J = 8.0 Hz), 6.91 (1 H, d, J = 2.2 Hz), 7.10–7.30 (7 H, m), 7.34 (1 H, d, J = 8.0 Hz), 7.57 (1 H, d, J = 7.8 Hz), 8.21 (1 H, s); MS (FAB) m/e 492.3 (100), 352.2 (90.8), 362.2 (55.0), 334.2 (44.6), 266.1 (35.5), 221.1 (280).

(1*R-trans*)-α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-D-tryptophan Methyl Ester (17c). The method was as for 17a except using (1*R*,2*R*)-*trans*-2-methylcyclohexanol: yield 86%; $[\alpha]^{20}_D$ = +11.5° (*c* = 1, MeOH); IR (film) 3500–3200, 2931, 2857, 1733, 1696, 1502, and 1457 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (3 H, d, *J* = 6.5 Hz), 0.99–1.75 (8 H, m), 1.64 (3 H, s), 1.98–2.08 (1 H, m), 3.38 (1 H, d, *J* = 14.5 Hz), 3.48 (1 H, br d, *J* = 14.5 Hz), 3.66 (3 H, s), 4.25–4.40 (1 H, m), 5.25–5.40 (1 H, br s), 6.94 (1 H, d, *J* = 2.3 Hz), 7.05–7.17 (2 H, m), 7.31 (1 H, d, *J* = 8.0 Hz), 7.53 (1 H, d, *J* = 7.9 Hz), 8.23 (1 H, s); MS (FAB) *m/e* 373.2 (30.6), 313.2 (6.5), 259.0 (9.7), 233.1 (79.2), 216.1 (100).

(1*R-trans*)-α-methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-(*R*)-tryptophan (15c). The method was as for 15a except using 17c: yield = 97%; $[\alpha]^{20}_D$ = −6.5° (*c* = 1, MeOH); IR (film) 3500–3200, 1703, 1503, and 1457 cm^{-1}; NMR (DMSO-d_6) δ 0.87 (3 H, d, *J* = 6.2 Hz), 0.95–1.77 (8 H, m), 1.25 (3 H, s), 1.88–2.00 (1 H, m), 3.08 (1 H, d, *J* = 14.3 Hz), 3.38 (1 H, d, *J* = 14.1 Hz), 4.15–4.25 (1 H, m), 6.88–7.05 (4 H, m), 7.31 (1 H, d, *J* = 8.0 Hz), 7.45 (1 H, d, *J* = 7.9 Hz), 10.90 (1 H, s), 12.20–12.50 (1 H, br s); MS (FAB) *m/e* 358.9 (100), 313.1 (7.2), 263.0 (21.9), 219.0 (57.4), 202.1 (62.0).

Carbamic Acid, [2-[[1-(Hydroxymethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-Methylcyclohexyl Ester, [1*R*-[1α[*R(*S**)],2β]]- (16c).** The method was as for 16a except using 15c: yield 81%; $[\alpha]^{20}_D$ = −3.25° (*c* = 0.52, MeOH); IR (film) 3500–3200, 2932, 2859, 1690, and 1663 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (3 H, d, *J* = 6.5 Hz), 1.00–1.80 (8 H, m), 1.35 (3 H, s), 1.90–2.00 (1 H, m), 2.70–2.85 (2 H, m), 2.90–3.00 (1 H, br s), 3.29 (1 H, d, *J* = 14.7 Hz), 3.43 (1 H, d, *J* = 14.7 Hz), 3.50–3.60 (1 H, m), 3.65–3.75 (1 H, m), 4.15–4.25 (1 H, m), 4.32 (1 H, dt, *J* = 4 and 10 Hz), 5.00 (1 H, s), 6.14 (1 H, d, *J* = 8.0 Hz), 6.90 (1 H, d, *J* = 3.2 Hz), 7.05–7.25 (7 H, m), 7.34 (1 H, d, *J* = 8.0 Hz), 7.55 (1 H, d, *J* = 7.8 Hz), 8.32 (1 H, s); MS (FAB) *m/e* 492.2 (100), 352.1 (39.2), 362.2 (27.2), 334.1 (25.1).

Carbamic Acid, [2-[[1-(Azidomethyl)-2-phenylethyl]amino]-1-(1*H*-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-, 2-Methylcyclohexyl Ester, [1*S*-[1α[*S(*R**)],2β]]- (18b).** A stirred solution of **15b** (1.79 g, 5.00 mmol) and pentafluorophenol (0.92 g, 5.00 mmol) in EtOAc (50 mL) at 0 °C was treated with *N,N'*-dicyclohexylcarbodiimide (1.08 g, 5.20 mmol). After 4 h at 0 °C the mixture was filtered and (*S*)-α-(azidomethyl)-2-phenylethanamine (0.968 g, 5.50 mmol) was added to the filtrate. This was stirred at room temperature for 18 h, washed with 1 M HCl (2 × 30 mL), H_2O (30 mL), saturated $NaHCO_3$ solution (2 × 30 mL), and H_2O (2 × 20 mL), dried ($MgSO_4$), and filtered and the filtrate evaporated to dryness. The residue was then separated by silica gel chromatography to give the product **18b** as a white solid (1.1 g, 43%): $[\alpha]^{19}_D$ = +41° (*c* = 1, MeOH); IR (film) 3440–3200, 2932, 2859, 2103, 1700, and 1658 cm^{-1}; NMR ($CDCl_3/D_2O$) δ 0.92 (3 H, d, *J* = 6.5 Hz), 1.00–1.80 (8 H, m), 1.50 (3 H, s), 1.95–2.05 (1 H, m), 2.65 (1 H, dd, *J* = 14 and 8 Hz), 2.75 (1 H, dd, *J* = 14 and 8 Hz), 3.10 (1 H, dd, *J* = 4 and 12 Hz), 3.21 (1 H, dd, *J* = 4 and 12 Hz), 3.23 (1 H, d, *J* = 15 Hz), 3.48 (1 H, d, *J* = 15 Hz), 4.05–4.15 (1 H, m), 4.32 (1 H, dt, *J* = 10 and 4 Hz), 5.08 (1 H, s), 6.39 (1 H, d, *J* = 8.3 Hz), 6.96 (1 H, d, *J* = 29 Hz), 7.10–7.30 (7 H, m), 7.34 (1 H, d, *J* = 8 Hz), 7.59 (1 H, d, *J* = 8 Hz), 8.21 (1 H, s); MS (FAB) *m/e* 517.3 (35.9), 491.3 (65.6), 377.2 (100), 359.1 (33.0), 291.1 (25.8), 245.0 (49.0).

2-Butenoic Acid, 4-[[2-[[3-(1*H*-Indol-3-yl)-2-methyl-2-[[[(2-methylcyclohexyl)oxy]carbonyl]amino]-1-oxopropyl]amino]-3-phenylpropyl]amino]-4-oxo-, [1*S*-[1α[*S[*R**(E)]],2β]]- (21b). Step 1.** The azide **18b** (1.08 g, 2.10 mmol) was suspended in 1% AcOH in EtOH (100 mL) with 10% Pd/C (0.1 g, 10% w/w) and put under an atmosphere of hydrogen at 50 psi at 30 °C for 2 h. The mixture was filtered and the solvent removed from the filtrate in vacuo. The residue was suspended between saturated $NaHCO_3$ solution (70 mL) and EtOAc (100 mL). The aqueous phase was reextracted with two further portions of EtOAc, and the combined organic phases were dried over $MgSO_4$, filtered, and evaporated in vacuo to dryness, to give the amine intermediate in quantitative yield, which was used immediately.

Step 2. A solution of the amine prepared in step 1 (0.5 g, 1.0 mmol) and methyl pentafluorophenyl fumarate (0.326 g, 1.10 mmol) in EtOAc (10 mL) was stirred for 16 h at room temperature. The solvent was evaporated in vacuo and the residue separated by silica gel chromatography to give the product as a white solid (0.34 g, 56%): IR (film) 3500–3200, 2930, 2858, 1750–1660, and 1666 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (3 H, d, *J* = 6.5 Hz), 1.00–1.90 (9 H, m), 1.34 (3 H, s), 2.73 (2 H, d, *J* = 6.8 Hz), 3.10–3.20 (1 H, m), 3.30 (2 H, s), 3.78 (3 H, s), 3.75–3.85 (1 H, m), 4.20–4.35 (2 H, m), 4.99 (1 H, s), 6.04 (1 H, d, *J* = 8.1 Hz), 6.82 (1 H, d, *J* = 15.5 Hz), 6.90–7.30 (10 H, m), 7.36 (1 H, d, *J* = 8.0 Hz), 7.58 (1 H, d, *J* = 8.0 Hz), 8.21 (1 H, s).

Step 3. The ester prepared in step 2 (0.34 g, 1.0 mmol) as a solution in THF (200 mL) was treated with LiOH solution (5.6 mL of a 0.1 M solution, 1 mmol). This mixture was left stirring for 16 h, and the reaction mixture was made slightly acidic with 1 N HCl. The solvents were removed in vacuo, and the residue was purified using silica gel chromatography to give the product **21b** as a crystalline white solid (0.25 g, 76%): $[\alpha]^{20}_D$ = +111.6° (*c* = 1.07, MeOH; IR (film) 3500–3200, 2932, 1700, and 1660 cm^{-1}; NMR (CD_3OD) δ 0.97 (3 H, d, *J* = 6.4 Hz), 1.00–1.80 (8 H, m), 1.21 (3 H, s), 1.90–2.00 (1 H, m), 2.60–2.75 (2 H, m), 2.95–3.05 (1 H, m), 3.18 (1 H, d, *J* = 14.5 Hz), 3.30–3.40 (1 H, d), 3.65–3.75 (1 H, m), 4.25–4.40 (2 H, m), 6.70 (1 H, d, *J* = 16 Hz), 6.94–7.25 (9 H, m), 7.30 (1 H, d, *J* = 7.8 Hz), 7.50 (1 H, d, *J* = 7.7 Hz); MS (FAB) *m/e* 589.3 (28.9), 516.4 (52.6), 428.3 (17.4), 307.1 (100), 289.1 (50.6).

2-Butenoic Acid, 4-[[2-[[3-(1*H*-Indol-3-yl)-2-methyl-2-[[[(2-methylcyclohexyl)oxy]carbonyl]amino]-1-oxopropyl]amino]-3-phenylpropyl]amino]-4-oxo-, [1*R*-[1α[*R[*S**(*E*)]],2β]]- (21c). Step 1.** The method was as for **18b** except using 15c: yield 92%; IR (film) 3450–3200, 2937, 2860, 2103, 1700, and 1660 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (3 H, d, *J* = 6.3 Hz), 1.00–1.80 (8 H, m), 1.47 (3 H, s), 1.95–2.05 (1 H, m), 2.67 (1 H, dd, *J* = 8.3 and 13.6 Hz), 2.75 (1 H, dd, *J* = 6.3 and 13.6 Hz), 3.10–3.30 (3 H, m), 3.5 (1 H, d, *J* = 14.8 Hz), 4.20–4.40 (2 H, m), 5.04 (1 H, s), 6.41 (1 H, d, *J* = 8.3 Hz), 6.97 (1 H, d, *J* = 2.3 Hz), 7.05–7.30 (7 H, m), 7.35 (1 H, d, *J* = 8.0 Hz), 7.59 (1 H, d, *J* = 7.8 Hz), 8.17 (1 H, s).

Step 2. The method was as for **21b**, step 1, (above), except using 18c: yield 100%; mp = 150–159 °C (EtOAc); $[\alpha]^{20}_D$ = +20.8° (*c* = 0.25, MeOH); IR (film) 3500–3200, 2930, 2857, 1690, 1657, 1515, and 1455 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (3 H, s), 1.00–1.80 (8 H, m), 1.37 (3 H, s), 1.95–2.05 (1 H, m), 2.51 (1 H, dd, *J* = 7.1 and 13.5 Hz), 2.65–2.80 (3 H, m), 3.31 (1 H, d, *J* = 14.6 Hz), 3.52 (1 H, d, *J* = 14.9 Hz), 4.10–4.25 (1 H, m), 4.30–4.40 (1 H, m), 4.95 (1 H, s), 6.25 (1 H, d, *J* = 8.1 Hz), 6.94 (1 H, d, *J* = 2.3 Hz), 7.05–7.30 (7 H, m), 7.35 (1 H, d, *J* = 8.0 Hz), 7.60 (1 H, d, *J* = 8.2 Hz), 8.07 (1 H, s).

Step 3. The method was as for **21b**, step 2, except using amine from step 2 above: yield 82%; $[\alpha]^{20}_D$ = +77.8° (*c* = 0.063, MeOH); IR (film) 3450–3200, 2931, 2858, 1728, 1691, and 1666 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (3 H, d, *J* = 6.4 Hz), 1.00–1.80 (8 H, m), 1.32 (3 H, s), 1.93–2.03 (1 H, m), 2.65–2.80 (2 H, m), 3.10–3.20 (1 H, m), 3.27 (1 H, d, *J* = 14.5 Hz), 3.37 (1 H, d, *J* = 14.6 Hz), 3.78 (3 H, s), 3.80–3.90 (1 H, m), 4.27–4.37 (2 H, m), 4.93 (1 H, s), 6.01 (1 H, d, *J* = 8.2 Hz), 6.83 (1 H, d, *J* = 15.7 Hz), 6.93 (1 H, d, *J* = 2.3 Hz), 6.98 (1 H, d, *J* = 15.5 Hz), 7.03–7.28 (8 H, m), 7.36 (1 H, d, *J* = 8 Hz), 7.57 (1 H, d, *J* = 7.7 Hz), 8.21 (1 H, s); MS (FAB) *m/e* 603.3 (7.7), 307.0 (25.4), 288.9 (20.1), 153.9 (100).

Step 4. The method was as for **21b**, step 3, except using ester **20c** from step 3 above: yield 73%; $[\alpha]^{20}_D$ = +74° (*c* = 0.42, MeOH); IR (film) 3500–3200, 2933, 2858, 1695, and 1662 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (3 H, d, *J* = 6.5 Hz), 1.00–1.80 (11 H, m), 2.00–2.10 (1 H, m), 2.60–2.75 (2 H, m), 2.95–3.05 (1 H, m), 3.16 (1 H, d, *J* = 14.5 Hz), 3.36 (1 H, d, *J* = 14.5 Hz), 3.60–3.70 (1 H, m), 4.25–4.40 (2 H, m), 6.72 (1 H, d, *J* = 15.4 Hz), 6.90–7.30 (9 H, m), 7.30 (1 H, d, *J* = 7.8 Hz), 7.50 (1 H, d, *J* = 7.8 Hz); MS (FAB) *m/e* 589.2 (13.1), 307.1 (66.7), 289.0 (42.5), 220.2 (100).

Butanoic Acid, 4-[[2-[[3-(1*H*-Indol-3-yl)-2-methyl-2-[[[(2-methylcyclohexyl)oxy]carbonyl]amino]-1-oxopropyl]amino]-3-phenylpropyl]amino]-4-oxo-, [1*R*-[1α[*R(*S**)],2β]]- (19c).** A solution of the amine prepared in the synthesis of **21c**, Step 2 (0.30 g, 0.6 mmol), and succinic anhydride (0.09 g, 0.90 mmol) in EtOAc (30 mL) was stirred for 16 h at room temperature. The solvent was removed in vacuo and the residue purified by chromatography to give the product (**19c**) (0.216 g, 61%): $[\alpha]^{20}_D$ = +37.0° (*c* = 0.224, MeOH); IR (film) 3500–3200, 2930, 2859, 1700, and 1660 cm^{-1}; NMR ($CDCl_3$) δ 0.82 (3 H, d, *J* = 6.4 Hz), 1.00–1.75 (8 H, m), 1.33 (3 H, s), 1.90–2.00 (1 H, m), 2.35–2.70

(6 H, m), 2.85–3.00 (1 H, m), 3.23 (1 H, d, J = 14.6 Hz), 3.30 (1 H, d, J = 14.6 Hz), 3.45–3.65 (1 H, m), 4.20–4.30 (2 H, m), 5,26 (1 H, s), 5.10–5.80 (1 H, br), 6.15–6.25 (1 H, br s), 6.90–7.20 (9 H, m), 7.33 (1 H, d, J = 7.8 Hz), 7.53 (1 H, d, J = 7.8 Hz), 8.72 (1 H, s); MS (FAB) 592.1 (100), 461.2 (36.5), 433.6 (41.8), 251.1 (98.5), 234.1 (43.6), 203.1 (90.5).

Butanoic Acid, 4-[[2-[[3-(1*H*-Indol-3-yl)-2-methyl-2-[[[(2-methylcyclohexyl)oxy]carbonyl]amino]-1-oxopropyl]amino]-1-phenylethyl]amino]-4-oxo-, [1*R*-[1α[*R(*R**)],2β]]- (24c).** **Step 1.** A solution of acid **15c** (0.34 g, 0.95 mmol) in EtOAc (20 mL) at 0 °C was treated with pentafluorophenol (0.175 g, 0.95 mmol) followed by *N,N'*-dicyclohexylcarbodiimide (0.206 g, 1.00 mmol). After 4 h, the reaction mixture was filtered and a solution of (*R*)-N^{β}-[(benzyloxy)carbonyl]-β-aminobenzeneethanamine (0.324 g, 1.20 mmol) in EtOAc (5 mL) was added. This mixture was left for 16 h at room temperature and evaporated to dryness *in vacuo*, and the residue was purified by reverse-phase silica gel chromatography using 3:1 MeOH/H_2O as eluant to give the product (0.55 g, 95%), which was used immediately in step 2: NMR ($CDCl_3$) δ 0.88 (3 H, d, J = 6.5 Hz), 0.90–1.80 (8 H, m), 1.50 (3 H, m), 1.90–2.00 (1 H, m), 3.23 (1 H, d, J = 14.6 Hz), 3.39 (1 H, d, J = 14.6 Hz), 3.30–3.45 (1 H, m), 3.60–3.73 (1 H, m), 4.20–4.30 (1 H, m), 4.70–4.80 (1 H, br s), 5.06 (2 H, s), 5.18 (1 H, s), 6.30–6.40 (1 H, m), 6.35–6.45 (1 H, br s), 6.94 (1 H, s), 7.08–7.38 (13 H, m), 7.55 (1 H, d, J = 7.8 Hz), 8.01 (1 H, s).

Step 2. A mixture of the benzylurethane from step 1 (0.55 g, 0.9 mmol) and 10% Pd/C (0.1 g), in absolute EtOH (100 mL), was put under an atmosphere of hydrogen at 50 psi and 30 °C for 2 h. The mixture was then filtered and the filtrate evaporated to dryness to give 0.372 g (80%) of product, which was used immediately without purification in step 3: IR (film) 3500–3200, 2930, 2860, 1699, and 1652 cm^{-1}.

Step 3. A solution of the amine prepared in step 2 (0.1 g, 0.21 mmol) and succinic anhydride (0.03 g, 0.30 mmol) in EtOAc (30 mL) was stirred at room temperature for 16 h. The solvent was removed under diminished pressure and the residue purified to give product **24c** (0.093 g, 77%) as a white, noncrystalline solid: $[\alpha]^{20}_D$ = −33.5° (c = 0.81, MeOH); IR (film) 3500–3100, 2933, 2860, 1714, and 16661 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (3 H, d, J = 6.4 Hz), 1.00–1.35 (4 H, m), 1.47 (3 H, s), 1.40–1.80 (4 H, m), 1.95–2.05 (1 H, m), 2.40–2.65 (4 H, m), 3.20–3.35 (3 H, m), 3.75–3.85 (1 H, m), 4.20–4.30 (1 H, m), 4.90–5.00 (1 H, m), 5.30–5.40 (1 H, br s), 6.40–6.55 (1 H, br s), 6.97 (1 H, s), 7.05–7.30 (8 H, m), 7.33 (1 H, d, J = 8.0 Hz), 7.54 (1 H, d, J = 7.7 Hz), 8.60 (1 H, s); MS (FAB) m/e 577.2 (12.7), 447.2 (2.9), 323.0 (6.0), 217.0 (100).

2-Butenoic Acid, 4-[[2-[[3-(1*H*-Indol-3-yl)-2-methyl-2-[[[(2-methylcyclohexyl)oxy]carbonyl]amino]-1-oxopropyl]amino]-1-phenylethyl]amino]-4-oxo-, [1*R*-[1α[*R[*R**(*E*)]],2β]]- (26c).** A solution of mono[2-(trimethylsilyl)ethyl] fumarate (0.216 g, 1.00 mmol) in EtOAc (20 mL) at 0 °C was treated with pentafluorophenol (0.184 g, 1.00 mmol) and *N,N'*-dicyclohexylcarbodiimide (0.218 g, 1.06 mmol). After 2 h, the amine prepared in example **24c**, step 2 (0.35 g, 0.74 mmol), was added and the resulting mixture left for 24 h at room temperature. The mixture was filtered, washed with H_2O (2 × 20 mL), dried over $MgSO_4$, and evaporated to dryness in vacuo. The residue was partially purified using reverse-phase silica gel chromatography, using 3:1 MeOH/H_2O as eluant to give 0.4 g of material which was taken up in THF (20 mL) and treated with tetrabutylammonium fluoride in THF (3 mL of a 1 *M* solution) and left for 12 h at room temperature. The solvent was then removed under diminished pressure and the residue purified by chromatography to give product **26c** (0.2 g, 47%) as a white, noncrystalline solid: $[\alpha]^{20}_D$ = +36.1° (c = 1, MeOH); IR (film) 3500–3000, 2933, 2858, 1707, and 1666 cm^{-1}; NMR ($CDCl_3$) δ 0.85 (3 H, d, J = 6.4 Hz), 1.00–1.75 (8 H, m), 1.41 (3 H, s), 1.95–2.05 (1 H, m), 3.22 (1 H, d, J = 14.5 Hz), 3.33 (1 H, d, J = 14.5 Hz), 3.50–3.80 (2 H, m), 3.50–4.20 (1 H, br), 4.20–4.30 (1 H, m), 5.10–5.20 (1 H, m), 5.30 (1 H, s), 6.60–6.80 (1 H, br s), 6.79 (1 H, d, J = 15.4 Hz), 6.90–7.35 (10 H, m), 7.50 (1 H, d, J = 7.8 Hz), 7.75–7.85 (1 H, m), 8.59 (1 H, s); MS (FAB) m/e 575.1 (54.2), 435.1 (28.7), 417.2 (46.0), 308.2 (34.5), 288.9 (100), 219.1 (48.7).

***trans*-(±)-α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-L-tryptophan, Methyl Ester (17d).** The method was as for **17a** except using L-α-methyltryptophan: yield = 90%; $[\alpha]^{20}_D$ = −34° (c = 1, MeOH); IR (film) 3240–3480, 2932, 2858, 1740, 1698, 1504, and 1457 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (1.5 H, d, J = 6.5 Hz), 0.93 (1.5 H, d, J = 6.5 Hz), 1.00–1.62 (6 H, m), 1.65 (1.5 H, s), 1.67 (1.5 H, s), 1.70–1.80 (2 H, m), 1.98–2.08 (1 H, m), 3.35 (0.5 H, d, J = 14.5 Hz), 3.38 (0.5 H, d, J = 14.5 Hz), 3.45–3.60 (1 H, m), 3.67 (3 H, s), 4.25–4.40 (1 H, m), 5.25–5.40 (1 H, br s), 6.94–6.98 (1 H, m), 7.05–7.20 (2 H, m), 7.33 (1 H, d, J = 8.0 Hz), 7.54 (1 H, d, J = 7.8 Hz), 8.09 (1 H, s); MS (FAB) m/e 373.2 (8.7), 233.1 (63.3), 216.1 (100).

***trans*-(±)-α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-L-tryptophan (15d).** The method was as for **15a** except using L-α-methyl tryptophan: yield 97%; $[\alpha]^{20}_D$ = −18° (c = 1, MeOH); IR (film), 3500–3200, 3200–2400, 2933, 1750–1600 (br), 1505, and 1457 cm^{-1}; NMR (DMSO-d_6) δ 0.87 (1.5 H, d, J = 6.5 Hz), 0.91 (1.5 H, d, J = 6.5 Hz), 0.95–1.30 (4 H, m), 1.27 (1.5 H, s), 1.28 (1.5 H, s), 1.35–1.50 (1 H, m), 1.53–1.63 (1 H, m), 1.65–1.75 (2 H, m), 1.85–2.00 (1 H, m), 3.09 (0.5 H, d, J = 14.3 Hz), 3.13 (0.5 H, d, J = 14.3 Hz), 3.30–3.45 (1 H, m), 4.13–4.28 (1 H, m), 6.80–7.05 (4 H, m), 7.31 (1 H, d, J = 8.0 Hz), 7.45 (1 H, d, J = 7.8 Hz), 10.90 (1 H, s), 12.30–12.45 (1 H, br); MS (FAB) m/e 359.2 (14.8), 269.2 (11.8), 263.1 (24), 244.9 (27.1), 219.1 (93.4), 202.1 (100).

(1*S-trans*)-α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-L-tryptophan, Methyl Ester (17e). The method was as for **17b** except using L-α-methyltryptophan: yield 86%; $[\alpha]^{20}_D$ = −11.3° (c = 1, MeOH); IR (film) 3500–3300, 2937, 1735, 1694, 1502, and 1453 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (3 H, d, J = 6.5 Hz), 1.00–1.80 (8 H, m), 1.65 (3 H, s), 1.98–2.08 (1 H, m), 3.39 (1 H, d, J = 14.4 Hz), 3.45–3.58 (1 H, br d), 3.67 (3 H, s), 4.25–4.38 (1 H, m), 5.30–5.40 (1 H, br s), 6.97 (1 H, s), 7.05–7.20 (2 H, m), 7.34 (1 H, d, J = 8 Hz), 7.54 (1 H, d, J = 8.0 Hz), 8.06 (1 H, s); MS (FAB) m/e 373.2 (60.6), 233.1 (89.7), 216.1 (100).

(1*S-trans*)-α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-L-tryptophan (15e). The method was as for **15b** except using L-α-methyltryptophan: yield 95%; $[\alpha]^{20}_D$ = +6.8° (c = 1, MeOH); IR (film) 400–2800, 1708 (br), 1502, and 1455 cm^{-1}; NMR (DMSO-d_6) δ 0.87 (3 H, d, J = 6.3 Hz), 0.95–1.77 (8 H, m), 1.27 (3 H, s), 1.88–2.00 (1 H, m), 3.10 (1 H, d, J = 14.3 Hz), 3.39 (1 H, d, J = 14.2 Hz), 4.15–4.25 (1 H, m), 6.85–7.06 (4 H, m), 7.31 (1 H, d, J = 8.0 Hz), 7.45 (1 H, d, J = 7.8 Hz), 10.90 (1 H, s), 12.39–12.45 (1 H, br); MS (FAB) m/e 359.0 (48.1), 313.0 (17.1), 263.0 (20.9), 219.2 (87.9), 202.0 (100).

(1*R-trans*)-α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-L-tryptophan, Methyl Ester (17f). The method was as for **17c** except using L-α-methyltryptophan: yield 82%; $[\alpha]^{20}_D$ = −53.9° (c = 1, MeOH); IR (film) 3500, 3300, 2934, 1738, 1697, 1502, and 1457 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (3 H, d, J = 6.4 Hz), 1.00–1.80 (8 H, m), 1.67 (3 H, s), 2.00–2.10 (1 H, m), 3.35 (1 H, d, J = 14.4 Hz), 3.45–3.06 (1 H, m), 3.67 (3 H, s), 4.25–4.40 (1 H, m), 5.30–5.45 (1 H, br s), 6.96 (1 H, d, J = 2.0 Hz), 7.05–7.20 (2 H, m), 7.34 (1 H, d, J = 8.0 Hz), 7.55 (1 H, d, J = 7.7 Hz), 8.09 (1 H, s); MS (FAB) m/e 373.2 (100), 259.1 (9.7), 233.1 (66.1), 216.1 (46.5).

(1*R-trans*)-α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-L-tryptophan (15f). The method was as for **15c** except using *L*-α-methyltryptophan: yield 96%; $[\alpha]^{20}_D$ = −42° (c = 1, MeOH); IR (film) 4000–2800, 1708 br, 1505, and 1475 cm^{-1}; NMR (DMSO-d_6) δ 0.91 (3 H, d, J = 6.4 Hz), 0.97–1.77 (8 H, m), 1.28 (3 H, s), 1.85–1.95 (1 H, m), 3.13 (1 H, d, J = 14.3 Hz), 3.35 (1 H, d, J = 14.8 Hz), 4.15–4.25 (1 H, m), 6.80–7.06 (4 H, m), 7.31 (1 H, d, J = 8 Hz), 7.45 (1 H, d, J = 7.8 Hz), 10.90 (1 H, s), 12.30–12.50 (1 H, br); MS (FAB) m/e 359.0 (45.0), 311.9 (13.8), 263.0 (21.9), 244.9 (12.5), 219.0 (76.9), 202.1 (100).

β-Alanine, *N*-[α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-D-tryptophyl]-L-3-(phenylmethyl)-, Phenylmethyl Ester (ring centers are *trans*-(±)) (27g). A solution of **15a** (1.074 g, 3.00 mmol) and pentafluorophenol (0.552 g, 3.00 mmol) in EtOAc (50 mL) at 0 °C was treated with *N,N'*-dicylohexylcarbodiimide (0.649 g, 3.15 mmol). After 4 h the mixture was filtered and benzyl (*S*)-β-aminobenzenebutanoate (0.888 g, 3.30 mmol) was added to the filtrate. This mixture was left for a further 16 h, filtered, and washed with 1 M HCl (2 × 30 mL), H_2O (30 mL), saturated $NaHCO_3$ solution (2 × 30 mL) and H_2O (30 mL). The dried ($MgSO_4$) organic phase was evaporated to dryness in vacuo and the residue purified by chromatography to give the product **27g**, which was recrystallized from MeOH/H_2O (1.57 g, 86%): $[\alpha]^{20}_D$ = +26° (c = 1, $CHCl_3$);

IR (film) 3500–3200, 2931, 2859, 1723, 1660, 1496, and 1456 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (1.5 H, d, J = 6.6 Hz), 0.91 (1.5 H, d, J = 6.5 Hz), 1.00–1.35 (4 H, m), 1.40–1.50 (1 H, m), 1.45 (3 H, s), 1.55–1.75 (3 H, m), 1.95–2.05 (1 H, m), 2.25–2.45 (2 H, m), 2.64 (1 H, dd, J = 8.3 and 13.5 Hz), 2.82 (1 H, dd, J = 6.4 and 13.6 Hz), 3.25 (0.5 H, d, J = 14.8 Hz), 3.27 (0.5 H, d, J = 14.8 Hz), 3.40 (0.5 H, d, J = 14.7 Hz), 3.41 (0.5 H, d, J = 14.8 Hz), 4.22–4.32 (1 H, m), 4.35–4.50 (1 H, m), 5.02 (1 H, d, J = 12.2 Hz), 5.10 (1 H, d, J = 12.2 Hz), 5.11 (1 H, s), 6.85–7.40 (15 H, m), 7.58 (1 H, d, J = 7.7 Hz), 8.02 (1 H, s); MS (FAB) m/e 610.3 (48.6), 480.3 (28.2), 470.3 (40.6), 452.2 (28.3), 339.2 (27.1), 270.0 (68.5), 220.1 (100).

β-Alanine, *N*-[α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-D-tryptophyl]-L-3-(phenylmethyl)- (ring centers are *trans*-(±)) (28g). A solution of the benzyl ester **27g** (1.1 g, 1.80 mmol) in absolute EtOH (100 mL) was treated with 10% Pd/C (0.11 g, 10% w/w) and put under an atmosphere of hydrogen at 50 psi and 30 °C for 4 h. This mixture was then filtered and evaporated to dryness in vacuo. The residue was purified by chromatography to give product **28g** (0.8 g, 86%) as white needles recrystallized from MeOH. $[\alpha]^{20}_D$ = +15.6° (c = 0.5, MeOH); IR (film) 3500–3200, 2932, 2858, 1711, 1659, 1496, and 1456 cm^{-1}; NMR (DMSO-d_6) δ 0.84 (1.5 H, d, J = 6.5 Hz), 0.90 (1.5 H, d, J = 6.3 Hz), 1.18 (3 H, s), 0.95–1.45 (5 H, m), 1.50–2.85 (2 H, m), 3.05–3.17 (1 H, m), 3.23–3.38 (1 H, m), 4.10–4.30 (2 H, m), 6.07 (1 H, s), 6.75–7.05 (3 H, m), 7.10–7.30 (6 H, m), 7.43 (1 H, d, J = 7.7 Hz), 7.56 (0.5 H, d, J = 8.5 Hz), 7.60 (0.5 H, d, J = 8.5 Hz), 10.80 (1 H, s), 12.20–12.30 (1 H, br s); MS (FAB) m/e 520.3 (100), 390.1 (17.2), 380.1 (27.5), 362.2 (20.6), 201.8 (16.0).

β-Alanine, *N*-[α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-D-tryptophyl]-L-3-(phenylmethyl)-, Phenylmethyl Ester, (1*S*-*trans*)- (27h). The method was as for **27g** except using **15b**: yield 90%; $[\alpha]^{20}_D$ = +37.7° (c = 0.77, $CHCl_3$); IR (film) 2931, 2865, 1721, 1658, 1496, and 1456 cm^{-1}; NMR (DMSO-d_6) δ 0.90 (3 H, d, J = 6.0 Hz), 1.00–1.75 (8 H, m), 1.17 (3 H, s), 1.85–1.95 (1 H, m), 2.41 (1 H, dd, J = 15.7 and 6.5 Hz), 2.47 (0.5 H, d, J = 6.4 Hz), 2.50–2.55 (0.5 H, masked by DMSO peaks), 2.67 (1 H, dd, J = 6.4 and 13.6 Hz), 2.79 (1 H, dd, J = 7.7 and 13.5 Hz), 3.13 (1 H, d, J = 14.4 Hz), 3.29 (1 H, d, J = 14.6 Hz), 4.10–4.20 (1 H, m), 4.25–4.40 (1 H, m), 5.04 (1 H, d, J = 13.0 Hz), 5.08 (1 H, d, J = 12.9 Hz), 6.71 (1 H, s), 6.80 (1 H, s), 6.85–7.05 (2 H, m), 7.10–7.40 (11 H, m), 7.43 (1 H, d, J = 7.8 Hz), 7.66 (1 H, d, J = 8.6 Hz), 10.83 (1 H, s); MS (FAB) m/e 610.0 (8.7), 220.0 (10.3), 173.0 (54.8), 130 (100).

β-Alanine, *N*-[α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-D-tryptophyl]-L-3-(phenylmethyl)-, (1*S*-*trans*)-(28h). The method was as for **28g** except using **27h**: yield 77%; $[\alpha]^{20}_D$ = +30° (c = 0.5, MeOH); IR (film) 3500–3000, 2922, 2855, 1695, 1651, 1494, and 1454 cm^{-1}; NMR (DMSO-d_6), δ 0.90 (3 H, d, J = 6.2 Hz), 1.00–1.75 (8 H, m), 1.18 (3 H, s), 1.85–1.95 (1 H, m), 2.25 (1 H, dd, J = 6.6 and 16.0 Hz), 2.38 (1 H, dd, J = 5.8 and 16.1 Hz), 2.70 (1 H, dd, J = 6.3 and 13.4 Hz), 2.80 (1 H, dd, J = 7.6 and 13.5 Hz), 3.13 (1 H, d, J = 14.4 Hz), 3.29 (1 H, d, J = 14.6 Hz), 4.10–4.33 (2 H, m), 6.70 (1 H, s), 6.80 (1 H, s), 6.85–7.05 (12 H, m), 7.15–7.30 (6 H, m), 7.43 (1 H, d, J = 7.7 Hz), 7.61 (1 H, d, J = 8.6 Hz), 10.80 (1 H, s), 12.10–12.40 (1 H, br).

β-Alanine, *N*-[α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-D-tryptophyl]-L-3-(phenylmethyl)-, Phenylmethyl Ester, (1*R*-*trans*)- (27i). The method was as for **27g** except using **15c**: yield 97%; $[\alpha]^{20}_D$ = 7.6° (c = 1, $CHCl_3$); IR (film) 2933, 2865, 1722, 1659, 1496, and 1456 cm^{-1}; NMR (DMSO-d_6) δ 0.84 (3 H, d, J = 6.4 Hz), 0.90–1.75 (8 H, m), 1.16 (3 H, s), 1.88–1.98 (1 H, m), 2.39 (1 H, dd, J = 6.8 and 15.7 Hz), 2.48 (1 H, dd, J = 6.2 and 16.1 Hz), 2.67 (1 H, dd, J = 6.3 and 13.4 Hz), 2.77 (1 H, dd, J = 7.6 and 13.5 Hz), 3.08 (1 H, d, J = 14.5 Hz), 3.32 (1 H, d, J = 14.6 Hz), 4.12–4.40 (2 H, m), 5.04 (1 H, d, J = 12.7 Hz), 5.08 (1 H, d, J = 13.3 Hz), 6.71 (1 H, s), 6.85–7.40 (14 H, m), 7.45 (1 H, d, J = 7.8 Hz), 7.62 (1 H, d, J = 8.8 Hz), 10.85 (1 H, s); MS (FAB) m/e 610.0 (13.3), 480.0 (10.1), 469.9 (14.2), 220.0 (12.2), 173.0 (68.6), 130.0 (100).

β-Alanine, *N*-[α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-D-tryptophyl]-L-3-(phenylmethyl)-, (1*R*-*trans*)-(28i). The method was as for **28g** except using **27i**: yield 73%; $[\alpha]^{20}_D$ = −5.4° (c = 0.5, MeOH); IR (film) 3500–3000, 2927, 2867, 1704, 1655, 1495, and 1454 cm^{-1}; NMR (DMSO-d_6) δ 0.84 (3 H, d, J = 6.4 Hz), 0.95–1.75 (8 H, m), 1.18 (3 H, s), 1.85–1.95 (1 H, m), 2.24 (1 H, dd, J = 7.0 and 15.9 Hz), 2.36 (1 H, dd, J = 5.6 and 16.1 Hz), 2.70 (1 H, dd, J = 6.4 and 13.6 Hz), 2.78 (1 H, dd, J = 7.5 and 13.6 Hz), 3.09 (1 H, d, J = 14.6 Hz), 3.32 (1 H, d, J = 14.4 Hz), 4.10–4.35 (2 H, m), 6.68 (1 H, s), 6.85 (1 H, s), 6.86–7.05 (2 H, m), 7.10–7.30 (6 H, m), 7.43 (1 H, d, J = 7.8 Hz), 7.56 (1 H, d, J = 8.5 Hz), 10.80 (1 H, s), 12.00–12.40 (1 H, br); MS (FAB) m/e.

β-Alanine, *N*-[α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-L-tryptophyl]-D-3-(phenylmethyl)-, Phenylmethyl Ester (ring centers are *trans*-(±)) (27j). The method was as for **27g** except using **15d** and benzyl (*R*)-β-aminobenzenebutanoate: yield 84%; $[\alpha]^{20}_D$ = −24.8 (c = 0.5, $CHCl_3$); IR (film) 3500–3200, 2925, 1720, 1658, 1495, and 1456 cm^{-1}; NMR ($CHCl_3$) δ 0.89 (1.5 H, d, J = 6.7 Hz), 0.92 (1.5 H, d, J = 6.5 Hz), 1.00–1.35 (4 H, m), 1.40–1.50 (1 H, m), 1.46 (3 H, s), 1.55–1.75 (3 H, s), 1.95–2.05 (1 H, m), 2.25–2.45 (2 H, m), 2.65 (1 H, dd, J = 8.4 and 13.6 Hz), 2.82 (1 H, dd, J = 6.3 and 13.5 Hz), 3.24 (0.5 H, d, J = 14.7 Hz), 3.26 (0.5 H, d, J = 14.6 Hz), 3.40 (0.5 H, d, J = 14.9 Hz), 3.41 (0.5 H, d, J = 14.6 Hz), 4.22–4.32 (1 H, m), 4.35–4.50 (1 H, m), 5.03 (1 H, d, J = 12.2 Hz), 5.10 (1 H, s), 5.11 (1 H, d, J = 12.2 Hz), 6.85–7.40 (15 H, m), 7.58 (1 H, d, J = 7.8 Hz), 8.01 (1 H, s); MS (FAB) m/e 610.3 (29), 480.2 (23.8), 470.2 (29.4), 452.2 (20.4), 339.1 (26.9), 269.8 (61.5), 263.0 (53), 248.1 (37.8), 219.9 (100), 206.1 (49.2).

β-Alanine, *N*-[α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-L-tryptophyl]-D-3-(phenylmethyl)- (ring mixtures are *trans*-(±)) (28j). The method was as for **28g** except using **27j**: yield 78%; $[\alpha]^{20}_D$ = −11.8° (c = 0.5, MeOH); IR (film) 3500–3200, 2931, 1713, 1660, 1496, and 1456 cm^{-1}; NMR (DMSO-d_6) δ 0.84 (1.5 H, d, J = 6.5 Hz), 0.90 (1.5 H, d, J = 6.3 Hz), 0.95–1.45 (5 H, m), 1.18 (3 H, s), 1.50–1.75 (3 H, m), 1.85–1.97 (1 H, m), 2.20–2.40 (2 H, m), 2.65–2.85 (2 H, m), 3.05–3.17 (1 H, m), 3.23–3.38 (1 H, m), 4.10–4.30 (2 H, m), 6.67 (1 H, s), 6.75–7.05 (3 H, m), 7.10–7.30 (6 H, m), 7.43 (1 H, d, J = 7.7 Hz), 7.55 (0.5 H, d, J = 8.7 Hz), 7.59 (0.5 H, d, J = 8.8 Hz), 10.80 (1 H, s), 12.15–12.35 (1 H, br); MS (FAB) m/e 520.3 (100), 380.2 (17.4), 362.1 (12.3), 249.1 (9.9).

β-Alanine, *N*-[α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-L-tryptophyl]-D-3-(phenylmethyl)-, Phenylmethyl Ester, (1*S*-*trans*)- (27k). The method was as for **27i** except using **15e**: yield 91%; $[\alpha]^{20}_D$ = −7.4° (c = 1, $CHCl_3$); IR (film) 2927, 1721, 1657, and 1496 cm^{-1}; NMR (DMSO-d_6) δ 0.84 (3 H, d, J = 6.5 Hz), 0.90–1.75 (8 H, m), 1.15 (3 H, s), 1.85–1.95 (1 H, m), 2.38 (1 H, dd, J = 6.9 and 15.8 Hz), 2.45 (0.5 H, d, J = 6 Hz), 2.47–2.52 (0.5 H, obscured by DMSO peaks), 2.66 (1 H, dd, J = 6.4 and 13.5 Hz), 2.77 (1 H, dd, J = 7.4 and 13.4 Hz), 3.07 (1 H, d, J = 14.5 Hz), 3.31 (1 H, d, J = 14.4 Hz), 4.10–4.40 (2 H, m), 5.04 (1 H, d, J = 12.6 Hz), 5.09 (1 H, d, J = 13.5 Hz), 6.71 (1 H, s), 6.85 (1 H, s), 6.86–740 (13 H, m), 7.43 (1 H, d, J = 7.8 Hz), 7.62 (1 H, d, J = 8.8 Hz), 10.83 (1 H, s); MS (FAB) m/e 610.0 (5.3), 184 (13.8), 173.0 (53.9), 130 (100).

β-Alanine, *N*-[α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-L-tryptophyl]-D-3-(phenylmethyl)-, (1*S*-*trans*)-(28k). The method was as for **28g** except using **27k**: yield 62%; $[\alpha]^{20}_D$ = +5.6° (c = 1, MeOH); IR (film) 3450–3000, 2927, 2857, 1710, 1658, 1495, and 1456 cm^{-1}; NMR (DMSO-d_6) δ 0.84 (3 H, d, J = 6.5 Hz), 0.95–1.75 (8 H, m), 1.18 (3 H, s), 1.85–1.95 (1 H, m), 2.24 (1 H, dd, J = 6.9 and 16 Hz), 2.36 (1 H, dd, J = 5.8 and 15.9 Hz), 2.70 (1 H, dd, J = 6.4 and 13.6 Hz), 2.78 (1 H, dd, J = 7.7 and 13.7 Hz), 3.09 (1 H, d, J = 14.6 Hz), 3.32 (1 H, d, J = 14.4 Hz), 4.10–4.35 (2 H, m), 6.68 (1 H, s), 6.85 (1 H, s), 6.86–7.05 (2 H, m), 7.10–7.30 (6 H, m), 7.43 (1 H, d, J = 7.8 Hz), 7.55 (1 H, d, J = 8.6 Hz), 10.79 (1 H, s), 12.22 (1 H, s).

β-Alanine, *N*-[α-Methyl-*N*-[[(2-methylcyclohexyl)oxy]carbonyl]-L-tryptophyl]-D-3-(phenylmethyl)-, Phenylmethyl Ester, (1*R*-*trans*)- (27l). The method was as for **27j** except using **15f**: yield 96%; $[\alpha]^{20}_D$ = −36.9° (c = 1, $CHCl_3$); IR (film) 2930, 2859, 1722, 1658, 1496, and 1456 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (3 H, d, J = 6.5 Hz), 0.95–1.25 (8 H, m), 1.46 (3 H, s), 1.95–2.05 (1 H, m), 2.27–2.45 (2 H, m), 2.65 (1 H, dd, J = 8.4 and 13.5 Hz), 2.82 (1 H, dd, J = 6.4 and 13.5 Hz), 3.27 (1 H, d, J = 14.8 Hz), 3.40 (1 H, d, J = 14.8 Hz), 4.20–4.50 (2 H, m), 5.02 (1 H, d, J = 12.2 Hz), 5.10 (1 H, s), 5.11 (1 H, d, J = 12.1 Hz), 6.89 (1 H, d, J = 2.3 Hz), 6.92 (1 H, d, J = 8.7 Hz), 7.05–7.40 (13 H, m), 7.59 (1 H, d, J = 7.7 Hz), 7.99 (1 H, s); MS (FAB) m/e 610.0 (21.6), 470.0 (13.9), 173.0 (58), 130.0 (100).

β-Alanine, N-[α-Methyl-N-[[(2-methylcyclohexyl)oxy]carbonyl]-L-tryptophyl]-D-3-(phenylmethyl)-, (1*R-trans*)-(28l). The method was as for **28g** except using **27l**: yield 67%; $[\alpha]^{20}_D = -28.8°$ ($c = 0.5$, MeOH); IR (film) 2922, 1711, 1664, 1515, and 1454 cm^{-1}; NMR (DMSO-d_6) δ 0.90 (3 H, d, $J = 6.2$ Hz), 1.00–1.75 (8 H, m), 1.18 (3 H, s), 1.85–1.95 (1 H, m), 2.27 (1 H, dd, $J = 6.7$ and 15.9 Hz), 2.38 (1 H, dd, $J = 5.7$ and 16 Hz), 2.70 (1 H, dd, $J = 6.4$ and 13.5 Hz), 2.80 (1 H, dd, $J = 7.5$ and 13.5 Hz), 3.13 (1 H, d, $J = 14.6$ Hz), 3.29 (1 H, d, $J = 14.3$ Hz), 4.10–4.30 (2 H, m), 6.70 (1 H, s), 6.80 (1 H, s), 6.85–7.05 (2 H, m), 7.15–7.30 (6 H, m), 7.43 (1 H, d, $J = 7.9$ Hz), 7.61 (1 H, d, $J = 8.6$ Hz), 10.80 (1 H, s), 12.15–12.40 (1 H, br).

β-Alanine, N-[α-Methyl-N-[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophyl]-L-3-(phenylmethyl)-, Phenylmethyl Ester (29m). A solution of [(2-adamantyloxy)carbonyl]-α-methyl-D-tryptophan (2.0 g, 5.05 mmol) and pentafluorophenol (0.93 g, 5.05 mmol) in EtOAc (30 mL) was cooled to 0 °C and treated with *N,N'*-dicyclohexylcarbodiimide (1.09 g, 5.30 mmol). This mixture was stirred at 0 °C for 2 h and filtered and the filtrate treated with benzyl (*S*)-β-aminobenzenebutanoate (1.30 g, 4.8 mmol) and left at room temperature for 16 h. This mixture was then filtered and the filtrate evaporated to dryness in vacuo and the residue purified by chromatography to give the product as a white crystalline solid (2.1 g, 68%): $[\alpha]^{20}_D = +16.3°$ ($c = 0.5$, MeOH); IR (film) 3500–3200, 2911, 2857, 1723 (br), and 1659 cm^{-1}; NMR ($CDCl_3$) δ 1.44 (3 H, s), 1.50 (1 H, s), 1.54 (1 H, s), 1.70–2.05 (12 H, m), 2.40 (2 H, d, $J = 4.8$ Hz), 2.67 (1 H, dd, $J = 8.1$ and 13.5 Hz), 2.82 (1 H, dd, $J = 6.5$ and 13.6 Hz), 3.29 (1 H, d, $J = 14.8$ Hz), 3.34 (1 H, d, $J = 14.8$ Hz), 4.40–4.50 (1 H, m), 4.81 (1 H, s), 5.03 (1 H, d, $J = 12$ Hz), 5.12 (1 H, d, $J = 12$ Hz), 5.14 (1 H, s), 6.87 (1 H, d, $J = 2$ Hz), 6.94 (1 H, d, $J = 8.4$ Hz), 7.05–7.40 (13 H, m), 7.58 (1 H, d, $J = 7.8$ Hz), 8.00 (1 H, s); MS (FAB) *m/e* 648.3 (100), 518.2 (27.6), 452.8 (21.4), 307.1 (22.4), 270.1 (36.8), 220.1 (39.3).

β-Alanine, N-[α-Methyl-N-[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophyl]-L-3-(phenylmethyl)- (30m). A solution of the benzyl ester **29m** (2.0 g, 3.1 mmol) in EtOH (100 mL) was treated with 10% Pd/C (0.2 g, 10% w/w) and put under an atmosphere of hydrogen at a pressure of 50 psi at 30 °C for 8 h. This mixture was filtered, the filtrate evaporated to dryness in vacuo, and the residue purified by chromatography to give the acid **30m** as a white noncrystalline solid (1.5 g, 87%): $[\alpha]^{20}_D = +18.7°$ ($c = 0.15$ $CHCl_3$); IR (film) 3500–3200, 2908, 2856, 1708, and 1658 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (4 H, s), 1.54 (1 H, s), 1.70–2.05 (2 H, m), 2.27–2.34 (2 H, m), 2.70 (1 H, dd, $J = 8.1$ and 13.5 Hz), 2.82 (1 H, dd, $J = 6.3$ and 13.6 Hz), 3.23 (1 H, d, $J = 14.7$ Hz), 3.43 (1 H, d, $J = 14.7$ Hz), 4.42 (1 H, m), 4.81 (1 H, s), 5.41 (1 H, br s), 6.87–7.31 (10 H, m), 7.55 (1 H, d, $J = 7.8$ Hz), 8.50 (1 H, s); MS (FAB) *m/e* 558.4 (100).

β-Alanine, N-[α-Methyl-N-[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophyl]-D-3-(phenylmethyl)-, Phenylmethyl Ester (29n). The method was as for **29m** except using benzyl (*R*)-β-aminobenzenebutanoate: yield 72%; $[\alpha]^{20}_D = +32.6°$ ($c = 1$, MeOH); IR (film) 3500–3200, 2909, 2855, 1723, and 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.49 (4 H, s), 1.59 (1 H, s), 1.65–1.85 (8 H, m), 1.90–2.05 (4 H, m), 2.25 (1 H, dd, $J = 5.6$ and 16.3 Hz), 2.38 (1 H, dd, $J = 4.8$ and 16.3 Hz), 2.68 (1 H, dd, $J = 8$ and 13.6), 2.82 (1 H, dd, $J = 6.3$ and 13.6 Hz), 3.24 (1 H, d, $J = 14.7$ Hz), 3.39 (1 H, d, $J = 14.7$ Hz), 4.35–4.45 (1 H, m), 4.80 (1 H, s), 5.03 (1 H, d, $J = 12.2$ Hz), 5.10 (1 H, d, $J = 12.2$ Hz), 5.29 (1 H, s), 6.83–6.86 (1 H, m), 6.87 (1 H, d, $J = 2.3$ Hz), 7.00–7.40 (13 H, m), 7.57 (1 H, d, $J = 7.8$ Hz), 8.11 (1 H, s); MS (FAB) *m/e* 648.5 (3.7), 270.3 (12.5), 184.1 (30.4), 173.3 (32.7), 135.3 (100).

β-Alanine, N-[α-Methyl-N-[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophyl]-D-3-(phenylmethyl)- (30n). The method was as for **30m** except using **29n**: yield 61%; $[\alpha]^{20}_D = +36.0°$ ($c = 1$, MeOH); 3450–3200, 2908, 2854, 1711, and 1659 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (1 H, s), 1.53 (4 H, s), 1.70–2.00 (12 H, m), 2.25–2.40 (2 H, m), 2.65–2.85 (2 H, m), 3.22 (1 H, d, $J = 14.7$ Hz), 3.40 (1 H, d, $J = 14.6$ Hz), 4.35–4.45 (1 H, m), 4.80 (1 H, s), 5.41 (1 H, s), 6.70–6.80 (1 H, m), 6.91 (1 H, s), 7.05–7.27 (2 H, m), 7.33 (1 H, d, $J = 8.1$ Hz), 7.56 (1 H, d, $J = 7.9$ Hz), 8.28 (1 H, s); MS (FAB) *m/e* 558.3 (22.2), 445.2 (26.7), 444.2 (100), 418.2 (71.9), 307.2 (32.6).

β-Alanine, N-[α-Methyl-N-[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-L-tryptophyl]-L-3-(phenylmethyl)-, Phenylmethyl Ester (29o). The method was as for **29m** except using [(2-adamantyloxy)carbonyl]-α-methyl-L-tryptophan: yield 63%; $[\alpha]^{20}_D = -28.1°$ ($c = 1$, MeOH); IR (film) 3500–3200, 2909, 2855, 1723, and 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.49 (4 H, s), 1.54 (1 H, s), 1.68–1.85 (8 H, m), 1.90–2.05 (4 H, m), 2.25 (1 H, dd, $J = 5.6$ and 16.3 Hz), 2.3 (1 H, dd, $J = 4.8$ and 16.3 Hz), 2.68 (1 H, dd, $J = 8$ and 13.6 Hz), 2.82 (1 H, dd, $J = 6.3$ and 13.6 Hz), 3.24 (1 H, d, $J = 14.7$ Hz), 3.39 (1 H, d, $J = 14.7$ Hz), 4.35–4.45 (1 H, m), 4.80 (1 H, s), 5.03 (1 H, d, $J = 12.2$ Hz), 5.09 (1 H, d, $J = 12.2$ Hz), 5.30 (1 H, s), 6.82–6.90 (2 H, m), 7.00–7.40 (13 H, m), 7.57 (1 H, d, $J = 7.8$ Hz), 8.16 (1 H, s); MS (FAB) *m/e* 648.3 (90.4), 518.2 (60.6), 470.2 (40.9), 452.2 (41.3), 339.2 (45.7), 307.2 (73.6), 270.2 (100), 220.1 (94.5).

β-Alanine, N-[α-Methyl-N-[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-L-tryptophyl]-L-3-(phenylmethyl)- (30o). The method was as for **30m** except using **29o**: yield 76%; $[\alpha]^{20}_D = -36.6°$ ($c = 1$, MeOH); IR (film) 3500–3200, 2919, 2859, 1712, and 1658 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (1 H, s), 1.53 (4 H, s), 1.70–2.00 (12 H, m), 2.27 (1 H, dd, $J = 5.1$ and 16.2 Hz), 2.36 (1 H, dd, $J = 5.5$ and 16.3 Hz), 2.71 (1 H, dd, $J = 7.7$ and 13.7 Hz), 2.81 (1 H, dd, $J = 6.3$ and 13.5 Hz), 3.22 (1 H, d, $J = 14.6$ Hz), 3.40 (1 H, d, $J = 14.7$ Hz), 4.35–4.45 (1 H, m), 4.80 (1 H, s), 5.43 (1 H, s), 6.76 (1 H, d, $J = 8.2$ Hz), 6.91 (1 H, d, $J = 2.3$ Hz), 7.05–7.25 (7 H, m), 7.32 (1 H, d, $J = 8.0$ Hz), 7.56 (1 H, d, $J = 7.7$ Hz), 8.33 (1 H, s); MS (FAB) *m/e* 558.3 (100), 428.1 (41.5), 400.2 (62.6), 362.1 (40.3), 307.2 (29.0).

β-Alanine, N-[α-Methyl-N-[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-L-tryptophyl]-D-3-(phenylmethyl)- (29p). The method was as for **29m** except using [(2-adamantyloxy)carbonyl]-α-methyl-L-tryptophan and benzyl (*R*)-β-aminobenzenebutanoate: yield 69%; $[\alpha]^{20}_D = -15.5°$ ($c = 1$, MeOH); IR (film) 3500–3200, 2907, 2855, 1722, and 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.45 (3 H, s), 1.50–1.58 (2 H, m), 1.70–2.05 (12 H, m), 2.41 (2 H, d, $J = 4.8$ Hz), 2.68 (1 H, dd, $J = 8.1$ and 13.5 Hz), 2.83 (1 H, dd, $J = 6.6$ and 13.6 Hz), 3.30 (1 H, d, $J = 14.8$ Hz), 3.44 (1 H, d, $J = 14.6$ Hz), 4.40–4.50 (1 H, m), 4.82 (1 H, s), 5.04 (1 H, d, $J = 12.1$ Hz), 5.13 (1 H, d, $J = 12.1$ Hz), 5.15 (1 H, s), 6.88 (1 H, d, $J = 2.3$ Hz), 6.98 (1 H, d, $J = 8.6$ Hz), 7.05–7.40 (13 H, m), 7.59 (1 H, d, $J = 7.9$ Hz), 7.99 (1 H, s); MS (FAB) *m/e* 648.3 (100), 518.2 (36.3), 452.2 (33.0), 307.2 (30.4), 270.1 (42.8), 220.1 (34.6).

β-Alanine, N-[α-Methyl-N-[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-L-tryptophyl]-D-3-(phenylmethyl)- (30p). The method was as for **30m** except using **29p**: yield 68%; $[\alpha]^{24}_D = -11.6°$ ($c = 1$, MeOH); IR (film) 3500–3200, 2907, 2856, 1708, and 1657 cm^{-1}; NMR ($CDCl_3$) δ 1.49 (4 H, s), 1.54 (1 H, s), 1.70–205 (12 H, m), 2.40–2.50 (2 H, m), 2.72 (1 H, dd, $J = 8$ and 13.6 Hz), 2.84 (1 H, dd, $J = 6.5$ and 13.6 Hz), 3.24 (1 H, d, $J = 14.7$ Hz), 3.44 (1 H, d, $J = 14.7$ Hz), 4.40–4.50 (1 H, m), 4.81 (1 H, s), 5.30–5.35 (1 H, br s), 6.84 (1 H, d, $J = 7.8$ Hz), 6.93 (1 H, s), 7.04–7.28 (7 H, m), 7.31 (1 H, d, $J = 8$ Hz), 7.56 (1 H, d, $J = 7.7$ Hz), 8.34 (1 H, s); MS (FAB) *m/e* 558.3 (50.0), 428.2 (10.2), 400.3 (10.3), 362.2 (12.2), 323.0 (11.5), 217.0 (100).

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