Synthesis of Conformationally Constrained Tryptophan Derivatives[1]

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Methyl 1,3,4,5-tetrahydro-4-[[(phenylmethoxy)carbonyl]amino]-1*H*-cyclooct[*cd*]indole-4-carboxylate, methyl 3,4,5,6-tetrahydro-6-methylene-4-[[(phenylmethoxy)carbonyl]amino]-1*H*-cyclohept[*cd*]indole-4-carboxylate, and methyl 3,4-dihydro-6-methyl-4-[[(phenylmethoxy)carbonyl]amino]-1*H*-cyclohept-[*cd*]indole-4-carboxylate are three novel 3,4-fused tryptophan analogues which have been designed and synthesized for use in peptide/peptoid conformation elucidation studies. These derivatives have a ring that bridges the α-carbon and the 4-position of the indole ring, thus limiting the conformational flexibility of the side chain while leaving both amine and carboxylic acid groups free for further derivatization. The synthesis proceeded from 4-bromoindole *via* methyl 3-(4-bromo-1*H*-indol-3-yl)-2-(formylamino)-2-propenoate in which the carbon–carbon double bond was selectively reduced in the presence of the aromatic halide and then converted into methyl 4-bromo-*N*-[(phenylmethoxy)carbonyl]-α-2-propenyl-DL-tryptophan. Palladium-catalyzed cyclization of this α-propenyl tryptophan derivative proceeded smoothly under Heck conditions to give the compounds described above, yielding both the seven- and eight-membered constrained ring analogues. Functionalization of these key materials has been demonstrated.

Introduction

The relative spacial orientation of particular α-amino acid side chains is thought to have a major influence on the affinity of a peptide for its receptor as well as on its agonist or antagonist properties.[2] These topographical requirements are controlled by the main chain secondary structural motifs such as α-helices, reverse turns etc., which are stabilized by intramolecular hydrogen bonding.[3] Conformationally restricted amino acid analogues that favor a specific set of side chain conformations result in decreased systemic entropy, often leading to increased binding affinity and selectivity over receptor subtypes.[4] Such derivatives have been prepared as surrogates of tryptophan with cyclization to the 4- and 2-positions of indole (Figure 1).[5,6]

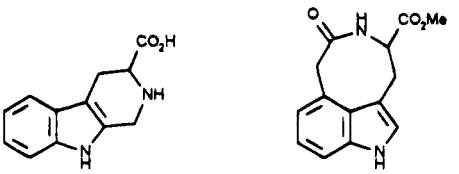
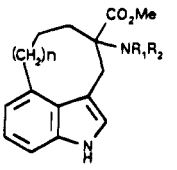


Figure 1.



n = 0,1

Figure 2.

It should be noted that in the examples in Figure 1, the α-nitrogen atom is contained within the framework of the conformational restricting ring and is a consequence of the synthetic methodology used to construct that ring, such as thermal lactamization[4a] and radical-induced cyclizations.[5,7] There is however a penalty to pay for the incorporation of such derivatives into peptides of interest. These compounds when inserted into a strategic position within a peptide, necessarily form a tertiary amide linking group; secondary structure stabilization *via* intramolecular hydrogen bonding is, therefore, not possible. Furthermore, the amide group in such derivatives is more likely to form *cis*- and *trans*-rotamers perturbing the global structure of the peptide.[8] The

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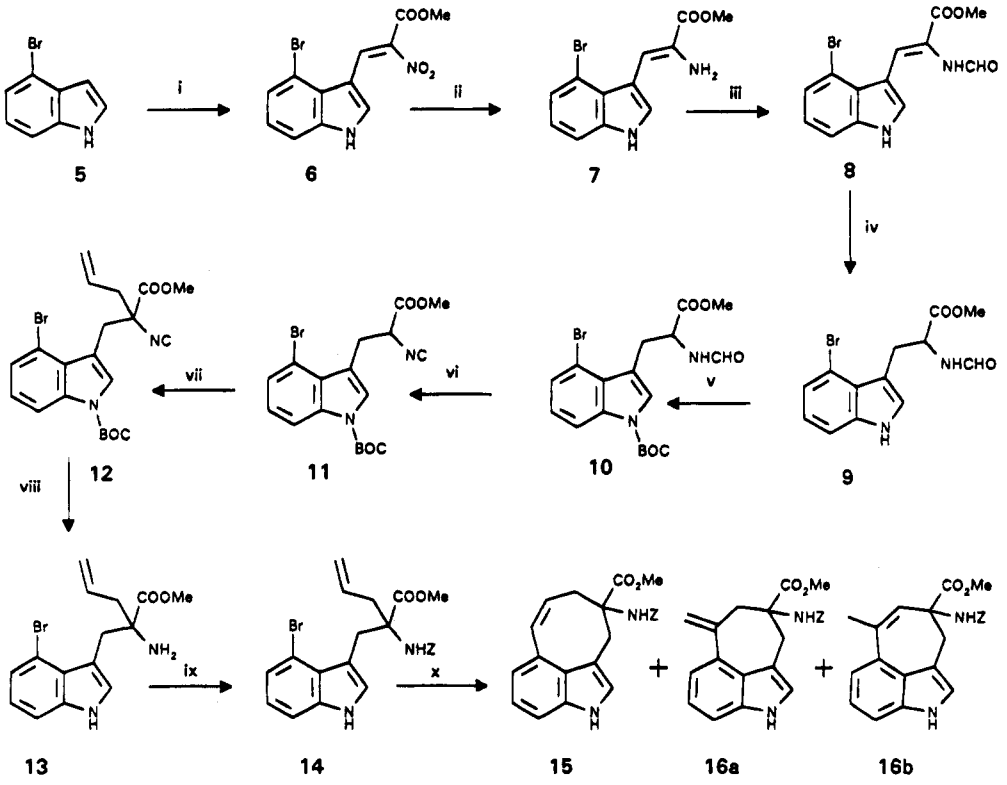
Scheme 1[a]



[a] Reagents and conditions: (i) $EtOCH{=}C(NO_2)CO_2Me$, rt, 18 h, 85%; (ii) 5% Pt/C, H_2, EtOAc, 20 psi, 25 °C; (iii) HCO_2H, Ac_2O, rt 4 h, 63% over two steps; (iv) Wilkinsons catalyst, MeOH, H_2, 65 psi, 20 °C, 48 h, 86%; (v) di-*tert*-butyl carbonate, DMAP, DMF, rt, 18 h, 94%; (vi) Et_3N, triphosgene, CH_2Cl_2, 0 °C, 18 h, 87%; (vii) LDA, THF, −78 °C, allyl bromide, rt, 45%; (viii) MeOH·HCl, 0 °C to rt, 4 h, >95%; (ix) $PhCH_2OCOCl$, THF, pyridine, 18 h, 70%; (x) palladium acetate, Et_3N, tri-*o*-tolylphosphine, acetonitrile, reflux 6 h, 88%.

current strategy attempts to eliminate some of these detrimental effects. Toward this goal the 3,4-cyclized tryptophan analogues were targeted. These have proven difficult to synthesize.[6,9] The target molecules, typified in Figure 2, have not been previously reported.

Moreover, incorporation of such cyclic amino acid derivatives into the peptoid class of compounds have proved useful to the ongoing strategies developed by Horwell *et al.*[10] The amino acid tryptophan has proved pivotal for programs such as those for the development of peptoid antagonists of cholecystokinin (CCK)[10] and tachykinins.[11] In both these cases α-methyltryptophan was incorporated with the objective to increase biostability toward proteinases and reduce the entropy of the system by restricting free rotation about the α-amino acid Cα—Cβ bond.[12]

Results and Discussion

Scheme 1 describes the synthetic route toward the target compounds. 4-Bromoindole (**5**) was prepared by the Leimgruber–Batcho method.[13,14] Functionalization of the 3-indole position was performed using methyl 2-nitro-3-ethoxyacrylate[15] in a Michael-type addition–elimination strategy to **6** in an 85% conversion. Subsequent reduction of the nitro group using 5% Pt/C under an atmosphere of hydrogen gave the enamine **7** which was immediately formylated with formic acid/acetic anhydride giving **8** in 63% yield over two steps. Selective reduction of the double bond to **9** was achieved with Wilkinson's catalyst under an atmosphere of hydrogen (86%). The indole nitrogen was then protected as it's *tert*-butyloxycarbonyl (t-BOC) derivative **10** (94%) and the formamide dehydrated to the isonitrile **11** using triphosgene (87%). The t-BOC-protected **11** was then α-alkylated. This alkylation was carried out in 65% yield using lithium diisopropylamide (LDA) to deprotonate **11**, and allyl bromide as the alkylating agent. In order to circumvent any possible unwanted side reactions of the isonitrile under the organometallic conditions used, the protecting groups were modified accordingly. The isonitrile was hydrolyzed and the t-BOC-group removed in a single step with methanolic hydrogen chloride to **13** in almost quantitative yield. The resulting primary amine was reprotected as it's benzyloxycarbonyl (Z) derivative **14** which gave a suitable substrate to proceed with the cyclization step. The substituted tryptophan **14** cyclized under standard catalytic Heck conditions[16] to give two compounds assigned as **15** and **16** in a 2:1 ratio, respec-

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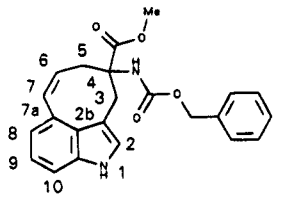
Table 1. NMR Assignments for Compound 15



15

^{1}H NMR (δ, 400 MHz, $CDCl_3$, 323 K)		^{13}C NMR (δ, 400 MHz, $CDCl_3$, 323 K)	
1-H	8.07 (1H, brs)	–	–
2-H	6.87 (1H, s)	C-2	123.81
		C-2a	110.63
		C-2b	137.09
3-H	3.15 (1H, brs)	C-3	31.51 br
		C-4	59.02
5-H	2.53 (1H, br), 2.87	C-5	35.12 br
6-H	5.81 (1H, m)	C-6	126.34
7-H	6.92 (1H, d, J = 12 Hz)	C-7	133.53
		C-7a	129.90
8-H	6.87 (1H, d, J = 9.5 Hz)	C-8	120.73
9-H	7.13 (1H, t, J = 8 Hz)	C-9	122.36
10-H[a]		C-10	110.73
		C-10a	126.60
CON*H*	4.91 (1H, brs)		
		C=O	154.98 (urethane)
O*CH*$_2$Ph	5.10 (2H, m)	OCH_2Ph	66.86
		C=O	173.64 (ester)
O*CH*$_3$	3.73 (3H, brs)	OCH_3	52.34
Ph*	7.24–7.38 (6H, m)	Ph	128.15, 128.48, 136.45

[a] 10-H is part of the multiplet at δ 7.24–7.38.

tively, with a total yield of 88% and were separated by column chromatography.

The NMR data for compound **15** is given in Table 1. All proton and carbon signals were assigned by ^{1}H–^{1}H COSY, 2D heteronuclear multiple quantum coherence (HMQC), and 2D heteronuclear multiple bond coherence (HMBC) experiments. The olefinic 6-H had a characteristic signal at δ_H 5.81. ^{1}H–^{1}H COSY experiments facilitated the assignment of the remaining olefinic proton 7-H as well as differentiated the ring methylene protons 3-H and 5-H. The proton 6-H also exhibited a long range ^{1}H–^{13}C coupling to the indole carbon C-7a at δ_C 129.90 suggesting intramolecular cyclization had taken place between C-7 and C-7a.

Examination of the long range ^{1}H–^{13}C couplings from the benzyloxymethylene group allows assignment of the urethane carbonyl at δ_C 154.98 and the coincident positions of the phenyl carbons at δ_C 128.15 and 128.48. The triplet at δ_H 7.13 (J = 8 Hz) was attributed to 9-H. ^{1}H–^{1}H coupling allowed the assignment of 8-H (J = 9.5 Hz) and 10-H. The position of 8-H was confirmed by long range ^{1}H–^{13}C coupling of 7-H and 8-C. The indole 2-H proton was seen as a singlet at δ_H 6.87. The remaining aromatic carbon signals at 136.45, 123.81, 110.63, 137.09, 120.73, 122.36, 110.73, and 126.60 may be inferred by comparison with literature values.[17] Similarly, all other protons and carbons may be assigned from their relative shifts in the respective proton and carbon spectra in conjunction with ^{1}H–^{13}C coupling experiments.

Fast atom bombardment high resolution mass spectrometry (FAB-HRMS), UV spectra, and elemental analysis also support structure **15**.

The other product (**16**) of the cyclization step was separated by normal phase silica gel chromatography.

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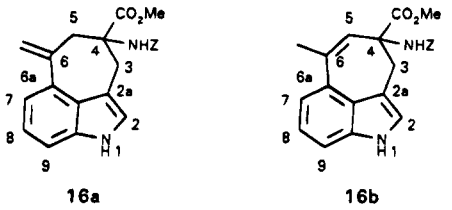


16a **16b**

Figure 3.

This was shown to be a mixture of two compounds **16a** and **16b** in approximately 1:1 ratio by NMR and reverse phase HPLC and could not be separated preparatively. Examination of the mixture by ^{1}H-^{1}H COSY, HMQC and HMBC experiments suggest that the palladium-catalyzed coupling had occurred between C-6 and C-6a (Figure 3) resulting in a seven-membered ring. The characteristic δ_H shifts of **16a** and **16b** are indicated in Figure 3. The exocyclic *methyl* group in **16b** shows a broad singlet at δ_H 2.30 exhibiting long range ^{1}H–^{1}H coupling to 5-H at δ_H 6.40. The methyl group also shows a long range ^{1}H–^{13}C coupling to the indole ring. The exocyclic *methylene* olefinic protons in **16a** show two distinct signals at δ_H 5.16 and 5.57. One of these protons shows a ^{1}H–^{1}H coupling to 5-H$_a$ at δ_H 3.07. 5-H$_a$ is in turn coupled to 5-H$_b$ at δ_H 3.46. The olefinic protons both show a ^{1}H–^{13}C coupling to the same carbon, indicating they are on an olefinic methylene group.

The cyclic products **15** and **16a** are consistent with the cyclization occurring via the standard mechanism proposed for reactions of the Heck type.[16] The isomeric compound **16b** having the double bond within the constraining ring may result from further complexation of **16a** with palladium.

The ester **15** was saponified with lithium hydroxide to the corresponding acid; this acid was derivatized to the α-methylbenzylamide **18** *via* its pentafluorophenyl ester (Scheme 2). Compound **18** was then evaluated in the appropriate tachykinin receptor binding assay as a cyclic analogue of the NK-1 peptoid antagonist, Z-α-methyltryptophan (1-methylbenzyl)amide.[11]

Catalytic hydrogenation of **15** using palladium on carbon as catalyst yielded the saturated analogue **19** as its free amine. Similarly, the isomers of **16** yielded two diastereomeric products **20** and **21** where both the endo- and exo-cyclic double bonds have been reduced and the benzyloxycarbonyl group has been removed to give the free amine. These data may be taken as further evidence for structures **15**, **16a**, and **16b**.

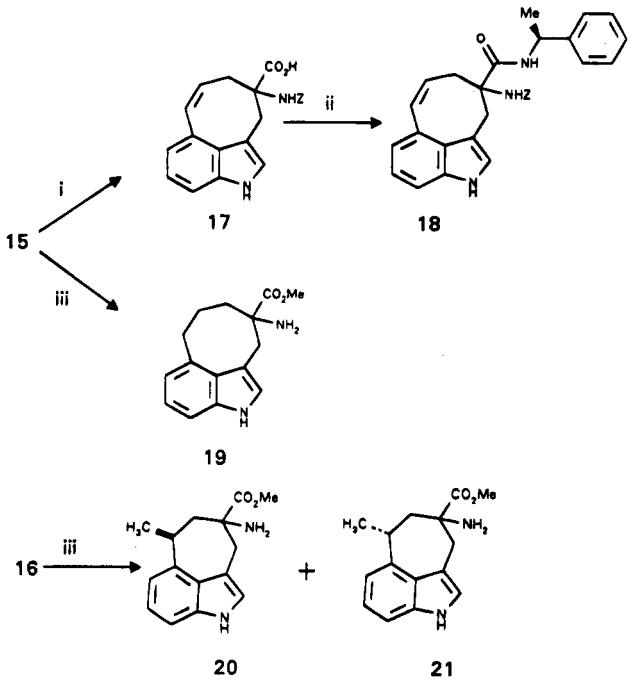
Further examples of novel derivatives and a discussion of biological activity where these novel tryptophan derivatives are incorporated into peptides and peptoids of interest will be disclosed elsewhere.

Experimental Section

General. Preparative chromatography was performed using either a Gilson medium pressure system or a Beckman System Gold HPLC system using Sorbaseal or Lichrosorb RP-18 stationary phase.

Methyl 3-(4-Bromo-1*H*-indol-3-yl)-2-nitro-2-propenoate (6). 4-Bromoindole (**5**)[13,14] (3.00 g,15.3 mmol) and methyl 2-nitro-3-ethoxyacrylate (2.68 g, 15.3 mmol) were stirred under argon at room temperature for 24 h. The resulting orange solid was triturated (Et_2O:*n*-hexane 1:1), filtered, washed with Et_2O, and air-dried to yield the title compound **6** as a pale orange solid (2.50 g, 85%). An analytical sample was prepared by recrystallization from methanol: mp 192–195 °C (MeOH); IR (film) 3275, 1706, 1584, 1287 cm^{-1}; NMR (DMSO-d_6) δ 3.87

Scheme 2[a]



[a] Reagents and conditions: (i) LiOH, aqueous THF, rt, 95%; (ii) DCC, EtOAc, pentafluorophenol, α-methylbenzylamine, 51%; (iii) Pd/C, H_2, 50 psi, 30 °C, 20 h, 48%.

(1.5H, s), 3.97 (1.5H, s), 7.16–7.24 (1H, m), 7.45–7.51 (1H, m), 7.58–7.63 (1H, m), 7.83 (0.5H, s), 8.05 (0.5H, s), 8.86 (0.5H, s), 9.45 (0.5H, s), 12.65 (1H, brs); MS *m/e* (CI) 327(M^+ + 1, (^{81}Br), 13) 326 (M^+, (^{81}Br), 17) 325 (M^+ + 1, (^{79}Br), 14) 324 (M^+, (^{79}Br), 19) 249 (100). Anal. Calcd for $C_{12}H_9BrN_2O_4$: C, 44.33; H, 2.79; N, 8.62%. Found: C, 44.26; H, 2.78; N, 8.56%.

Methyl 3-(4-Bromo-1*H*-indol-3-yl)-2-amino-2-propenoate (7). A mixture of **6** (0.10 g, 0.30 mmol) and 5% platinum on carbon (0.01 g, 10% w/w) in EtOAc (100 mL) was hydrogenated at 25 °C and 20 psi for 3.5 h. The resulting clear yellow solution was filtered through Celite and the solvent removed *in vacuo* to yield a clear yellow oil. The resulting enamine was used without further purification: IR (film) 3333, 2951, 1689 cm^{-1}; NMR (DMSO-d_6) δ 3.77 (3H, s), 4.60 (2H, brs), 7.04 (1H, t, J = 8 Hz), 7.25 (1H, d, J = 7 Hz), 7.43 (1H, d, J = 8 Hz), 7.53 (1H, s), 7.87 (1H, d, J = 2.5 Hz), 11.8 (1H, brs).

Methyl 3-(4-Bromo-1*H*-indol-3-yl)-2-(formylamino)-2-propenoate (8). To a solution of the indole derivative (**7**) (0.10 g, 0.34 mmol) in formic acid (5 mL) was added dropwise acetic anhydride (0.10 g, 1.0 mmol). The resulting solution was then stirred for 2 h at rt. The excess formic acid and acetic anhydride were removed *in vacuo* and the residue was triturated with EtOAc. The precipitate was filtered and air-dried to yield the title compound as an off-white solid (0.042 g, 39%): mp 242-245 °C (EtOAc); IR (film) 3242, 1694, 1634 cm^{-1}; NMR (DMSO-d_6) δ 3.72 (2.25H, s), 3.78 (0.75H, s), 7.07–7.12 (1H, m), 7.34–7.38 (1H, m), 7.50–7.55 (1H, m), 8.02 (0.25H, s), 8.07 (1H, s), 8.24 (0.75H, s), 8.59 (0.75H, s), 8.75 (0.25H, s), 9.11 (0.25H d, J = 11 Hz), 9.15 (0.75H, brs), 12.15 (1H, brs); MS *m/e* (CI) 325 (M^+ + 1 (^{81}Br), 27), 324 (M^+ (^{81}Br), 40), 323 (M^+ + 1 (^{79}Br), 29), 322 (M^+ (^{79}Br), 39), 291 (100). Anal. Calcd for $C_{13}H_{11}BrN_2O_3 \cdot 0.1H_2O$: C, 48.05; H, 3.41; N, 8.62%. Found: C, 47.94; H, 3.41; N, 8.47%.

Methyl 4-Bromo-*N*-formyl-DL-tryptophan (9). A mixture of **8** (0.15 g, 0.46 mmol) and Wilkinson's catalyst (0.20 g, 0.22 mmol) in MeOH (100 mL) was hydrogenated at 20 °C and 65 psi for 48 h. The resulting dark yellow suspension was filtered through Celite and the solvent removed *in vacuo*. The residue was chromatographed over silica gel eluting with 5% MeOH in CH_2Cl_2 to yield pure **9** (0.11 g, 74%): mp 160–169 °C (MeOH); IR (film) 3348, 3260, 1740, 1673 cm^{-1}; NMR (DMSO-d_6) δ 3.13 (1H, dd, J = 10, 15 Hz), 3.50 (1H, dd, J = 5, 15 Hz), 3.61 (3H, s), 4.71 (1H, m), 6.97 (1H, t, J = 8 Hz), 7.18 (1H, d, J = 7.5 Hz), 7.23 (1H, s), 7.37 (1H, d, J = 8 Hz), 7.98 (1H, s), 8.52 (1H, d, J = 8 Hz), 11.25 (1H, brs); MS *m/e* (CI) 327 (M^+ + 1 (^{81}Br), 5), 326 (M^+ (^{81}Br), 5), 325 (M^+ + 1 (^{79}Br), 10), 324 (M^+ (^{79}Br), 6), 210 (100). Anal. Calcd for $C_{13}H_{13}BrN_2O_3$: C, 48.02; H, 4.03; N, 8.62%. Found: C, 48.02; H, 4.00; N, 8.54%.

Methyl 4-Bromo-1-[(1,1-dimethylethoxy)carbonyl]-*N*-formyl-DL-tryptophan (10). The tryptophan derivative **9** (0.10 g, 0.31 mmol) was suspended in dry DMF (5 mL) under an atmosphere of argon. DMAP (0.01 g) in DMF (1 mL) was injected *via* a septum. Di-*tert*-butyl carbonate (0.07 g, 0.31 mmol) in DMF (1 mL) was added dropwise. The mixture was left stirring at rt for 24 h. The solution was evaporated to dryness *in vacuo* and the residue was taken up in EtOAc (50 mL). The solution was washed with 10% aqueous citric acid solution (2 × 50 mL), brine (50 mL), dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. The residue was then chromatographed over silica gel eluting with 1% MeOH in CH_2Cl_2. The required product was isolated as a white solid (0.07 g, 62%): mp 149–150 °C (MeOH); IR (film) 3355, 2978, 1739, 1683 cm^{-1}; NMR (DMSO-d_6) δ 1.62 (9H, s), 3.09 (1H, dd, J = 10, 15 Hz), 3.55 (1H, dd, J = 5, 14 Hz), 3.65 (3H, s), 4.81 (1H, m), 7.24 (1H, t, J = 8 Hz) 7.46 (1H, d, J = 8 Hz), 7.63 (1H, s), 8.02 (1H, s), 8.11 (1H, d, J = 8 Hz), 8.58 (1H, d, J = 8 Hz); MS *m/e* (CI) 427 (M^+ + 1 (^{81}Br), 3), 426 (M^+ (^{81}Br), 12), 425 (M^+ + 1 (^{79}Br), 4), 424 (M^+ (^{79}Br), 12), 208 (100). Anal. Calcd for $C_{18}H_{21}BrN_2O_5$: C, 50.84; H, 4.98; N, 6.59%. Found: C, 50.97; H, 5.00; N, 6.45%.

4-Bromo-3-[2-isocyano-2-(methoxycarbonyl)ethyl]indole-1-carboxylic Acid *tert*-Butyl Ester (11). The protected indole **10** (0.05 g, 0.14 mmol) was suspended in dry CH_2Cl_2 (3 mL) under argon and the solution cooled to below 0 °C using an ice/salt bath. Triethylamine (0.09 g, 0.86 mmol) was then added via a septum followed by the dropwise addition of triphosgene (0.014 g, 0.05 mmol) in CH_2Cl_2 (1 mL). The solution was then allowed to warm to rt before stirring for a further 18 h. The solvent was removed *in vacuo* and the residue taken up in Et_2O (50 mL). The resulting precipitate was removed by filtration and the filtrate evaporated to dryness *in vacuo*. Flash chromatography, eluting with 30% Et_2O in *n*-hexane yielded the title compound **11** as a white gum (0.05 g, 75%): IR (film) 2981, 2148, 1739 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (9H, s), 3.21 (1H, dd, J = 10, 15 Hz), 3.85 (3.5H, brs), 3.90 (0.5H, d, J = 5 Hz), 4.79 (1H, dd, J = 5, 10 Hz), 7.16 (1H, t, J = 8 Hz), 7.40 (1H, d, J = 8 Hz), 7.60 (1H, s), 8.21 (1H, d, J = 8 Hz); MS *m/e* (CI) 409 (M^+ + 1 (^{81}Br), 17), 408 (M^+ (^{81}Br), 50), 407 (M^+ + 1 (^{79}Br), 17), 406 (M^+ (^{79}Br), 52), 307 (100). Anal. Calcd for $C_{18}H_{19}BrN_2O_4$: C, 53.09; H, 4.70; N, 6.88%. Found: C, 53.20; H, 4.70; N, 6.73%.

4-Bromo-3-[2-isocyano-2-(methoxycarbonyl)pent-4-enyl]indole-1-carboxylic Acid *tert*-Butyl Ester (12). Lithium diisopropylamide (LDA) was prepared *in situ*. To a cooled (−20 °C) solution of diisopropylamine (0.55 g, 1.48 mmol) in THF (10 mL) under argon was added dropwise *via* a septum *n*-butyllithium (5.40 mmol, 3.38 mL used as a 1.6 M solution in hexanes). The solution was stirred at this temperature for 20 min and then allowed to warm to rt before cooling to −78 °C. This cooled solution was then added to the indole isonitrile **11** (2.00 g, 4.90 mmol) as a solution in THF (10 mL) at −78 °C. The mixture was stirred for 30 min and then allyl bromide (0.71 g, 5.90 mmol) was added dropwise *via* a septum. The solution was stirred for 3 h at −78 °C and then allowed to warm to rt. The solvent was removed *in vacuo* and the residue taken up in EtOAc (100 mL). The organic phase was washed with water (50 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude product was then chromatographed over silica gel eluting with 20% Et_2O in *n*-hexane to yield the title compound as a white foam (1.30 g, 65%): IR (film) 2980, 2137, 1743 cm^{-1}; NMR ($CDCl_3$) δ 1.66 (9H, s), 2.59 (1H, dd, J = 7, 14 Hz), 2.90 (1H, dd, J = 7.5, 14 Hz), 3.56 (1H, d, J = 15 Hz), 3.78 (3H, s), 3.98 (1H, d, J = 15 Hz), 5.22 (1H, d, J = 8 Hz), 5.27 (1H, s), 5.77–5.91 (1H, m), 7.14 (1H, t, J = 8 Hz), 7.40 (1H, d), 7.64 (1H, s), 8.20 (1H, d, J = 8 Hz); MS *m/e* (CI) 449 (M^+ + 1, (^{81}Br), 16), 448 (M + (^{81}Br), 38), 447 (M^+ + 1, (^{79}Br), 17), 446 (M^+, (^{79}Br), 40), 208 (100). Anal. Calcd for

$C_{21}H_{23}BrN_2O_4 \cdot 0.8H_2O$: C, 54.62; H, 5.37; N, 6.06%. Found: C, 54.70; H, 5.12; N, 5.79%.

Methyl 4-Bromo-α-2-propenyl-DL-tryptophan (13). To a cooled (0 °C) solution of the indole isonitrile 12 (0.12 g, 0.27 mmol) in MeOH (2 mL) was added dropwise methanolic hydrogen chloride (5 mL). Water (100 μL) was added and the resulting solution allowed to warm to rt and stirred for a further 4 h. The solvent was removed *in vacuo* and the residue taken up in EtOAc (50 mL). The organic phase was washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and filtered and the solvent removed *in vacuo*. The residue was chromatographed over silica gel eluting with 3% MeOH in CH_2Cl_2 to yield the free amine 13 in almost quantitative yield (90 mg): mp 129–131 °C (MeOH); IR (film) 3364, 2950, 1731 cm^{-1}; NMR ($CDCl_3$) δ 1.74 (2H, brs), 2.38 (1H, dd, J = 8, 14 Hz), 2.77 (1H, dd, J = 7, 14 Hz), 3.49 (1H, d, J = 15 Hz), 3.66 (1H, d, J = 15 Hz), 3.71 (3H, s), 5.13 (1H, s), 5.18 (1H, d, J = 5 Hz), 5.73–5.87 (1H, m), 6.97 (1H, t, J = 8 Hz), 7.06 (1H, d, J = 2 Hz), 7.25–7.27 (2H, m), 8.39 (1H, brs); MS m/e (CI) 340 ($M^+ + 1$ (^{81}Br), 34), 339 (M^+ (^{81}Br), 36), 338 ($M^+ + 1$ (^{79}Br), 7), 337 (M^+ (^{79}Br), 36), 128 (100). Anal. Calcd for $C_{15}H_{17}BrN_2O_2$: C, 53.43; H, 5.08; N, 8.31%. Found: C, 53.43; H, 5.06; N, 8.15%.

Methyl 4-Bromo-*N*-[(phenylmethoxy)carbonyl]-α-2-propenyl-DL-tryptophan (14). To a cooled solution (0 °C) of the indole substrate **13** in THF (3 mL) and under an atmosphere of argon was added pyridine (20 μL, 0.25 mmol). Benzyl chloroformate (33 μL, 0.23 mmol) was added dropwise via a septum. The solution was stirred for 1 h and allowed to warm to rt with stirring for 12 h. NMR analysis of the crude mixture indicated that the reaction was only 50% complete. A further quantity of benzyl chloroformate was added (33 μL, 0.23 mmol) under identical conditions and the reaction mixture stirred for 3 h at rt. The solution was evaporated to dryness *in vacuo* and the residue taken up in EtOAc (50 mL). The organic phase was washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and filtered and the solvent removed *in vacuo*. The residue was chromatographed over silica gel eluting with 3% MeOH in CH_2Cl_2 to yield the title compound as a white foam (0.063 g, 63%): mp 141 °C (MeOH); IR (film) 3419, 3347, 2960, 1706 cm^{-1}; NMR ($CDCl_3$) δ 2.79–2.86 (1H, m), 3.08–3.15 (1H, m), 3.57 (3H, s), 3.85 (1H, d, J = 15 Hz), 4.00 (1H, d, J = 15 Hz), 5.03–5.08 (4H, m), 5.59–5.73 (1H, m), 5.81 (1H, brs), 6.89–6.95 (2H, m), 7.21–7.39 (7H, m), 8.25 (1H, brs); MS m/e (CI) 473 ($M^+ + 1$ (^{81}Br), 6), 472 (M^+ (^{81}Br), 9), 471 ($M^+ + 1$ (^{79}Br), 6), 470 (M^+ (^{79}Br), 7), 91 (100). Anal. Calcd for $C_{23}H_{23}BrN_2O_4$: C, 58.61; H, 4.92; N, 5.94%. Found: C, 58.51; H, 4.93; N, 5.71%.

Methyl 1,3,4,5-Tetrahydro-4-[[(phenylmethoxy)carbonyl]amino]-1*H*-cyclooct[*cd*]indole-4-carboxylate (15), Methyl 3,4,5,6-Tetrahydro-6-methylene-4-[[(phenylmethoxy)carbonyl]amino]-1*H*-cyclohept[*cd*]indole-4-carboxylate (16a), Methyl 3,4-Dihydro-6-methyl-4-[[(phenylmethoxy)carbonyl]amino]-1*H*-cyclohept[*cd*]indole-4-carboxylate (16b). A 100 mL flask fitted with a reflux condenser capped with a rubber septum was charged with the indole substrate **14** (0.56 g, 1.2 mmol), triethylamine (333 μL, 2.4 mmol), tri-*o*-tolylphosphine (0.05 g, 0.16 mmol), palladium acetate (0.014 g, 5 mol %), and dry acetonitrile (100 mL). The flask was flushed with argon and heated at 85 °C for 3 h. After cooling, another 0.014 g of palladium acetate was added and refluxing continued for a further 3 h. After cooling, the solvent was removed *in vacuo*. The residue was chromatographed over silica gel eluting with 1% MeOH in CH_2Cl_2 to yield a 2:1 mixture of isomers (**15**) and (**16a,b**), respectively. The mixture was then separated by chromatography over silica gel using 25% EtOAc in *n*-hexane as eluant to yield the isomers as white solids.

Data for methyl 1,3,4,5-tetrahydro-4-[[(phenylmethoxy)carbonyl]amino]-1*H*-cyclooct[*cd*]indole-4-carboxylate (**15**) (0.138 g, 30%): mp 72–74 °C (EtOAc); UV (MeOH) λ_{max} 207 (ε = 34 000), 234 (ε = 35 300), 305 (ε = 9700); IR (film) 3365, 1713 cm^{-1}; NMR (see Table 1); MS (EI) m/e 391 ($M^+ + 1$, 100), $C_{23}H_{22}N_2O_4 + H^+$ requires 391.1658, found 391.1658. Anal. Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.17%. Found: C, 70.54; H, 5.77; N, 7.00%.

Data for methyl 3,4,5,6-tetrahydro-6-methylene-4-[[(phenylmethoxy)carbonyl]amino]-1*H*-cyclohept[*cd*]indole-4-carboxylate (**16a**) and methyl 3,4-dihydro-6-methyl-4-[[(phenylmethoxy)carbonyl]amino]-1*H*-cyclohept[*cd*]indole-4-carboxylate (**16b**) (0.07 g, 15%, 1:1 mixture of isomers): mp 65–70 °C; UV (MeOH) λ_{max} 207 (ε = 34 000), 238 (ε = 27 300), 310 (ε = 9650); IR (film) 3402, 1713br cm^{-1}; NMR ($CDCl_3$) δ 2.30 (1.5H, s), 3.07 (0.5H, d, J = 13 Hz), 3.46 (0.5H, d, J = 13 Hz), 3.32–3.67 (2H, m), 3.81 (3H, s), 4.91–5.26 (3H, m), 5.16 (0.5H, s), 5.57 (0.5H, s), 6.40 (0.5H, s), 6.98 (0.5H, s), 7.05 (0.5H, s), 7.13–7.34 (8H, m), 8.12 (0.5H, brs), 8.17 (0.5H, brs); MS (CI) m/e 391 ($M^+ + 1$, 10), 240 ($M^+ - 150$, 100) $C_{23}H_{22}N_2O_4 + H^+$ requires 391.1658, found 391.1658. Anal. Calcd for $C_{23}H_{22}N_2O_4 \cdot 0.1H_2O$: C, 70.43; H, 5.71; N, 7.17%. Found: C, 70.13; H, 5.67; N, 7.04%.

1,3,4,5-Tetrahydro-4-[[(phenylmethoxy)carbonyl]amino]cyclooct[*cd*]indole-4-carboxylic Acid (17). The indole substrate **15** (0.12 g, 0.31 mmol) was dissolved in MeOH (2 mL)/THF (3 mL) and to the resulting solution was added lithium hydroxide (1 N, 1 mL). The reaction mixture was heated at 70 °C for 3 h, and cooled to rt, and the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate (50 mL) and the organic phase washed with 2 N HCl (50 mL), filtered, and dried ($MgSO_4$). The solvent was removed *in vacuo*. The residue was chromatographed on silica gel eluting with 10% MeOH in CH_2Cl_2 as eluent to yield the title compound (0.115 g, 95%) as an off-white solid: mp 92–95 °C (MeOH), IR (film) 3401, 1714 cm^{-1}; NMR ($CDCl_3$, 323 K) δ 2.55 (1H, m), 2.92 (1H, m), 3.20 (1H, m), 3.65 (1H, m), 4.98 (1H, brs), 5.13 (2H, m), 5.85 (1H, m), 6.87–6.95 (3H, m), 7.15 (1H, t, J = 7 Hz), 7.24–7.35 (6H, m), 7.97 (1H, brs); MS m/e (EI) 376 (M^+, 14) and 91($M^+ - 285$, 100) $C_{22}H_{20}N_2O_4 + H^+$ requires 377.1501, found 377.1501.

Phenylmethyl [1,3,4,5-Tetrahydro-4-[[(1-phenylethyl)amino]carbonyl]cyclooct[*cd*]indol-4-yl]carbamate (18). The indole acid **17** (0.10 g, 0.27 mmol) was taken up in EtOAc (20 mL). To the resulting solution was added DCC (0.06 g, 0.29 mmol) and pentafluorophenol (0.05 g, 0.29 mmol). The reaction was stirred at rt for 2 h and then the resulting precipitate of dicyclohexylurea filtered. To the filtrate was added (*S*)-(−)-α-methylbenzylamine (0.04 g, 0.32 mmol) and the reaction stirred for a further 12 h. The organic phase was then washed with 2 N HCl (20 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel with 1% MeOH in CH_2Cl_2 as the eluent. Further purification was achieved by column chromatography on silica gel with 25% EtOAc in *n*-hexane as the eluent to yield the title compound as a white solid (0.065 g, 51%): mp 81 °C (EtOAc); IR (film) 3325, 1713, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.31–1.49 (4H, m), 2.38 (1H, m), 2.81 (1H, m), 3.20 (1H, m), 3.69 (1H, m), 4.80 (1H, brs), 5.02–5.15 (3H, m), 5.86 (1H, m), 6.75 (1H, s), 6.88 (2H, m), 7.13 (1H, t, J = 8 Hz), 7.22–7.34 (11H, m), 7.90 (1H, m); MS m/e (FAB) 480 (M^+, 100). Anal. Calcd for $C_{30}H_{29}N_3O_3 \cdot 0.15H_2O$: C, 74.71; H, 6.12; N, 8.71%. Found: C, 74.69; H, 6.27; N, 8.48%.

Methyl 9-Amino-2,6,7,8,9,10-hexahydro-2-azacyclooct[*cd*]indene-9-carboxylate (19). The indole substrate **15** (0.10 g, 0.26 mmol) was dissolved in MeOH (30 mL) and 10% palladium on carbon (0.01 g) added. The mixture was hydrogenated at 30 °C and 50 psi for 20 h. The mixture was filtered through Celite and then the solvent evaporated *in vacuo*. The residue was chromatographed over silica gel using 2% MeOH in CH_2Cl_2 as eluent to yield **20** as a white amorphous solid which was recrystallized from acetonitrile (0.06 g, 90%): mp 199–200 °C (CH_3CN); IR (film) 1727 cm^{-1}; NMR (DMSO-d_6, 393 K) δ 1.35–1.41 (1H, m), 1.65 (1H, m), 1.82 (1H, m), 1.92 (1H, m), 2.87–3.02 (2H, m), 3.13–3.23 (1H, m), 3.51 (1H, m), 3.67 (3H, s), 6.68 (1H, m), 6.95 (2H, m), 7.19 (1H, m),10.36 (1H, brs); MS (CI) m/z 259 ($M^+ + 1$, 100) $C_{15}H_{18}N_2O_2$ requires 258.1368, found 258.1380. Anal. Calcd for $C_{15}H_{18}N_2O_2 \cdot 0.15H_2O$: C, 69.0; H, 7.0; N, 10.7%. Found: C, 69.1; H, 7.1; N, 10.6%.

***cis*- and *trans*-Methyl 8-Amino-6-methyl-6,7,8,9-tetrahydro-2*H*-2-azabenzo[*cd*]azulene-8-carboxylate (20 and 21).** The indole substrates (**16a,b**) (0.11 g, 0.28 mmol) were

dissolved in MeOH (30 mL) and 10% palladium on carbon (0.01 g) was added. The mixture was hydrogenated at 30 °C and 50 psi for 20 h. The mixture was filtered through Celite and then the solvent evaporated *in vacuo*. The residue was chromatographed over silica gel using 2% MeOH in CH_2Cl_2 as eluent to yield the diastereoisomeric compounds **20** and **21** as clear syrups.

Isomer 1 (24 mg, 32%): IR (film) 3402, 3289, 1727 cm^{-1}; NMR ($CDCl_3$) δ_H 1.48 (3H, d, J = 7 Hz), 1.86 (2H, brs), 1.93 (1H, dd, J = 2, 15 Hz), 2.44 (1H, dd, J = 10, 15 Hz), 3.23 (1H, d, J = 15 Hz), 3.28 (1H, d, J =15 Hz); NMR ($CDCl_3$) δ_c 21.11, 30.96, 36.60, 48.08, 52.25, 61.63, 109.10, 112.97, 115.51, 121.08, 122.21, 126.53, 136.28, 140.38, 177.88; MS (CI) m/z 259 (M^+ + 1, 100), $C_{15}H_{18}N_2O_2$ requires 258.1368, found 258.1368. Anal. Calcd for $C_{15}H_{18}N_2O_2 \cdot 0.15H_2O$: C, 69.0; H, 7.0; N, 10.7%. Found: C, 69.3; H, 7.1; N, 10.4%.

Isomer 2 (12 mg, 16%): IR (film) 3393, 3234, 2934 cm^{-1}; NMR ($CDCl_3$) δ_H 1.42 (3H, d, J = 7 Hz), 1.77–1.83 (4H, m), 2.39 (1H, d, J = 14 Hz), 2.76 (1H, d, J = 15 Hz), 3.74–3.81 (4H, m), 6.83 (1H, d, J = 7 Hz), 6.93 (1H, s), 7.09 (1H, t, J = 8 Hz), 7.15 (1H, d, J = 8 Hz), 8.07 (1H, brs); NMR ($CDCl_3$) δ_c 19.43, 32.20, 36.38, 50.25, 52.48, 62.02, 109.17, 112.86, 114.20, 121.63, 122.48, 126.92, 136.00, 141.37, 177.70; MS (CI) m/z 259 (M^+ + 1, 100), $C_{15}H_{18}N_2O_2$ requires 258.1368, found 258.1368. Anal. Calcd for $C_{15}H_{18}N_2O_2.0.15H_2O$: C, 69.0; H, 7.0; N, 10.7%. Found: C, 69.2; H, 7.1; N, 10.4%.