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Preparation of the 5-substituted azepino[3,4-*b*]indole core structure can be realised through a catalytic Heck reaction. The scope and limitations of this methodology are reported. The reactivity of di-*tert*-butyl 5-ethoxycarbonylmethylene-1,3,4,5-tetrahydro-1-oxoazepino[3,4-*b*]indole-2,10-dicarboxylate (**1**) was investigated in order to prepare the indole analogue of hymenialdisine and derivatives.

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A number of members of the oroidin family containing a pyrrolo[2,3-*c*]azepine structures such as Hymenialdisine, Hymenin and Stevensine have proved to display a large spectrum of biological activities [1]. Recently, two research teams have described the preparation of the same indole analogue of Hymenialdisine (**I**) (Figure 1) with potent kinase inhibition (CDK, GSK-3, Chk 1 and 2) [2] and production inhibition of interleukine-2 and TNF-α [3]. Both synthetic pathways were based on the reaction of easily available azepino[3,4-*b*]indole-1,5-dione (**II**) [4] with 2-aminoimidazole or phenyl oxazolone moiety.

For our part, the retrosynthetic analysis of **I** led us to consider the formation of the seven-membered derivative **1** *via* an intramolecular Heck reaction between the position

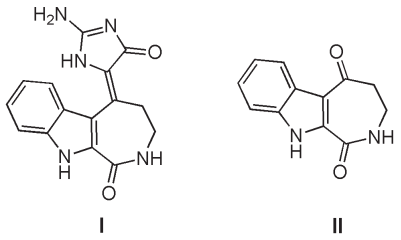
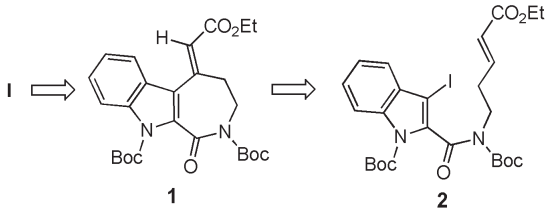


Figure 1

3 of the indole and a conveniently substituted olefin chain (Scheme 1). As described by Annoura for the total synthesis of Hymenialdisine [5], final construction of 2-amino-4-oxo-2-imidazolin-5(*Z*)-disubstituted ylidene ring system will be realised from α-hydroxy- or α-halogenoester derivative prepared from **1**.

We first turned out our attention on the formation of di-*tert*-butyl 5-ethoxycarbonylmethylene-1,3,4,5-tetrahydro-1-oxoazepino[3,4-*b*]indole-2,10-dicarboxylate (**1**). As described in our previous paper [6], we performed the cyclization of **2** in the presence of a stoechiometric amount of palladium acetate, triphenylphosphine (2 equivalents)

Scheme 1

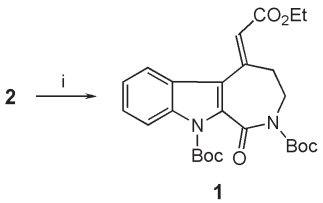


and silver carbonate (2 equivalents) in dry tetrahydrofuran at reflux for 15 hours. Azepino[3,4-*b*]indole derivative **1** was thus obtained in 84% yield.

The synthetic data [2,3] recently disclosed prompted us to report our latest results in this area. Three goals were targeted in this present work. First, a catalytic intramolecular Heck reaction on **2** was developed to obtain derivative **1**. Then, we set out to probe the scope and limitations of this catalytic intramolecular reaction using miscellaneous substrates. Finally, the study of the reactivity of the seven-membered compound **1** was undertaken in order to reach indole analogue of Hymenialdisine (**I**).

The catalytic Heck cyclization was readily achieved by addition of potassium chloride (2 equivalents) in the reaction mixture (Scheme 2). Compound **1** was again obtained, from **2**, in 84% yield. The addition of chloride ions is

Scheme 2

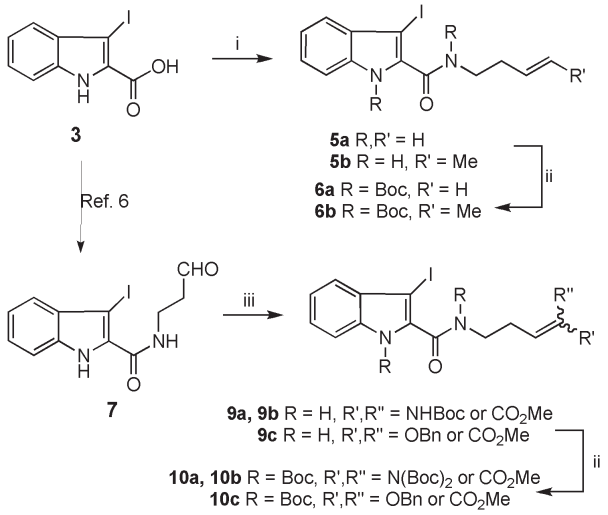


i) $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.2 equiv), Ag_2CO_3 (2 equiv), KCl (2 equiv), THF, reflux, 15 h, 1 = 84%.

known to improve the efficiency of the catalytic cycle involving halide-liganted palladium species [7].

These conditions were then applied to several iodoalkenes **6** and **10** prepared from 3-iodoindole-2-carboxylic acid (**3**) [8]. These substrates were obtained following two synthetic ways (Scheme 3).

Scheme 3



i) CH_2=CH-$(CH_2)_2$-NH_2 (**4a**) or (*E*) CH_3-CH=CH-$(CH_2)_2$-NH_2 (**4b**), EDCI, DMAP, CH_2Cl_2, 0°C to rt, 24 h, **5a** = 79%, **5b** = 84%; ii) Boc_2O, DMAP, CH_3CN, rt, 15 h, **6a** = 90%, **6b** = 90%, **10a** = 83%, **10b** = 83%, **10c** = 84%; iii) $(MeO)_2P(O)CH(NHBoc)CO_2Me$ (**8a**), NaH, THF, rt, 2 h, **9a** = 39%, **9b** = 45% or $Ph_3P^+CH(OBn)CO_2Me$, Br^- (**8b**), NaH, THF, reflux, 3 h, **9c** = 83%.

The first one was based on a simple peptide coupling reaction between **3** and alkenylamines **4** (but-3-enylamine (**4a**), (*E*)-pent-3-enylamine (**4b**) [9]) to lead to the desired alkenes **5** in good yields. The other way required the aldehyde **7** easily obtained from **3** [6]. Horner-Emmons reaction between **7** and (+/-)-Boc-α-phosphonoglycine trimethyl ester (**8a**) afforded two separable isomers **9a** and **9b**, respectively, in 39% and 45% yields (*E* or *Z* configuration of the double bond was not established). Wittig reaction between **7** and [(benzyloxy)(methoxycarbonyl)-methyl]triphenylphosphonium bromide (**8b**) [10] gave **9c** in 83% yield as a lone isomer. Finally, free nitrogen atoms of **5** and **9** were protected, preferentially with Boc groups, to avoid deiodination during the Heck reaction. Protection of **5** and **9** was achieved with *tert*-butyldicarbonate $(Boc_2)O$ in the presence of 4-dimethylaminopyridine (DMAP) in acetonitrile to give **6** and **10** in fair yield.

The expected cyclized products **11** were obtained from **6a** and **6b** in acceptable yields (Figure 2, Table). The major cyclic compounds result from the classical β-elimination process and not from further isomerization as expected by the use of silver salts [11]. It should be noted that disubstituted alkene **10c** give lower yield (32%) and that two bulky groups on the substrates **10a** or **10b** inhibit completely the reaction.

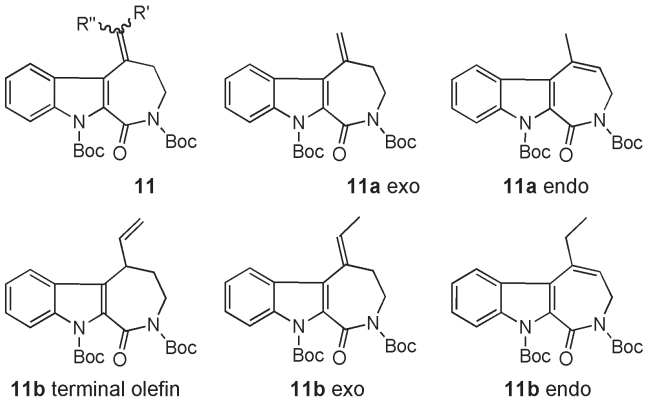


Figure 2

Table

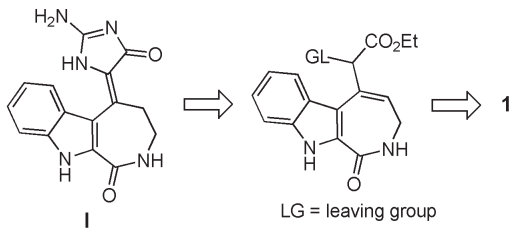
Yield of Compounds **11** Obtained by Heck Coupling Reaction

Cpd	R'	R''	11	Yield (%)
6a	H	/	**11a**	75 [a]
6b	Me	/	**11b**	74 [b]
10a or **10b**	$N(Boc)_2$ or CO_2Me		**11c**	/ [c]
10c	OBn or CO_2Me		**11d**	32

[a] **11a exo/11a endo** ratio 4:1; [b] **11b terminal olefin/11b exo/11b endo** ratio 3:1:1; [c] degradation of the starting material was observed.

Compound **1** in hands, its reactivity was studied in order to prepare the key α-leaving group ester intermediate (Scheme 4). α-Halogenation and α-hydroxylation of **1** were first investigated.

Scheme 4

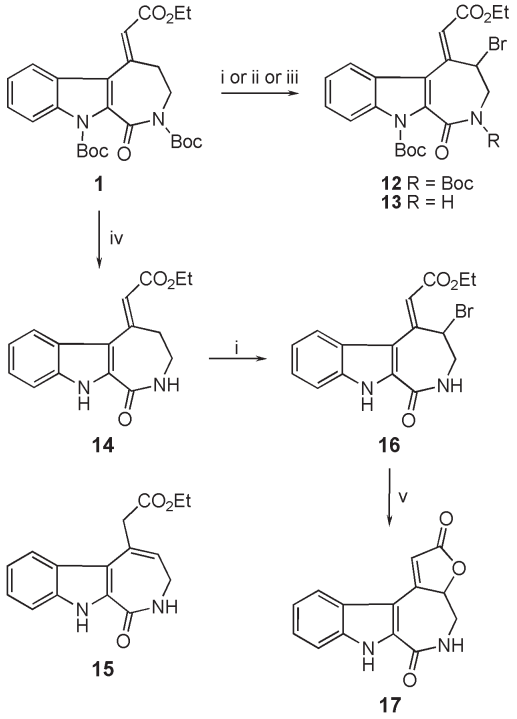


α,β-Dibromination, with respect to the ester, was expected when **1** was treated either by a mixture of potassium bromide and ammonium cerium nitrate [12] or by bromine in carbon tetrachloride, which could lead to the preparation of the α–bromo intermediate after elimination

of hydrobromic acid. Formation of compounds **12** and **13** in which a bromine atom has been introduced in the γ position of the ester was only detected (Scheme 5). The same product was obtained, when **1** was treated by *N*-bromosuccinimide (NBS) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN). Starting from the deprotected compound **14**, prepared by treatment of **1** with formic acid at low temperature (to avoid the isomerization of the double bond and the formation of **15**), the γ-brominated ester **16** was obtained in 90% yield. This compound, in organic solution, was prone to intramolecular nucleophilic substitution to give quantitatively the lactone **17** within few hours.

This chemical behaviour was not favoured with derivative **12** in this case the electron withdrawing property of the Boc group did not allow the internal cyclization.

Scheme 5

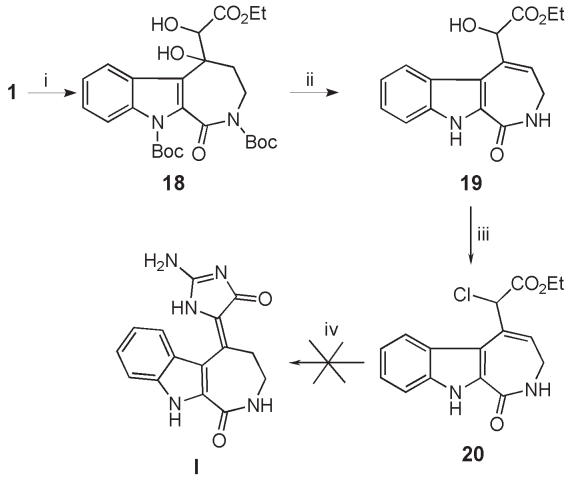


i) NBS, AIBN, CCl_4, reflux, 4 h, **12** = 68%, **16** = 90%; ii) KBr, CAN, CH_2Cl_2/H_2O, rt, 50 min, **12** = 71%; iii) Br_2, CCl_4, rt, 15 h, **12** = 42% and **13** = 43%; iv) formic acid, 0°C, 8 h, **14** = 67%; v) CH_2Cl_2, rt, 3 h, **17** = 100%.

Preferential halogenation occurring in position γ, direct α-hydroxylation was envisaged as an alternative method. First attempt was performed by deprotonation of **14** with lithium hexamethyldisilazide in tetrahydrofuran at –78 °C for 1 hour followed by addition of 2-benzenesulfonyl-3-phenyloxaziridine (Davies reagent) [5]. Despite extensive experimentation, we have not been able to isolate the expected α-hydroxy derivative in fair yield. We further tried the epoxidation of the exocyclic double bond but again without success. Dihydroxylation/dehydration reaction sequence was then explored (Scheme 6). Compound **1** was treated with potassium osmate dihydrate ($K_2OsO_4.2H_2O$), *N*-methylmorpholine oxide (NMO) and citric acid in *tert*-butyl alcohol/water to give dihydroxy derivative **18** in good yield [13]. Dehydration of **18** was carried out in acidic medium (sulfuric acid, ethanol reflux, 5 min) to yield hydroxy ester **19** in 92% yield.

In our hands, transformation of the hydroxy group of **19** into mesylate or triflate was not effective. Transformation of the allylic alcohol into the corresponding halide without rearrangement (leading to γ-halogenation) was conducted. Thus, **19** was treated in the presence of thionyl chloride and triethylamine [14]. α-Chloro derivative **20** was isolated in 35% yield due to the degradation of the starting material (Scheme 6). α-Bromo derivative was also prepared from **19** in low yield (17%) in the presence of triphenylphosphine and carbone tetrabromide [15]. Unfortunately, all attempts to obtain final indole analogue **I** from **20** (or α-bromo derivative) in the presence of guanidine were unsuccessful.

Scheme 6



i) $K_2OsO_4.2\,H_2O$, NMO, citric acid, tert-BuOH/H_2O, rt, 15 h, **18** = 97%.; ii) H_2SO_4, EtOH, reflux, 5 min, **19** = 92%; iii) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C to rt, 15 h, **20** = 35%; iv) guanidine, DMF, 50°C, 5 h.

In conclusion, 5-substituted azepino[3,4-*b*]indole structure was readily prepared through a catalytic palladium cross-coupling Heck reaction. Reactivity studies (halogenation and hydroxylation) of di-tert-butyl 5-ethoxycarbonylmethylene-1,3,4,5-tetrahydro-1-oxoazepino[3,4-*b*]indole-2,10-dicarboxylate (**1**) have allowed the preparation of an unusual lactone derivative and a key intermediate in the synthesis of indole analogue of Hymenialdisine and derivatives.

EXPERIMENTAL

Melting points were obtained on a Büchi capillary instrument and are uncorrected. IR spectra were recorded on a Perkin-Elmer 681 infrared spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance 300 spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C). Chemical shifts are expressed in parts per million (ppm) relative to tetramethylsilane (TMS). Mass spectra were recorded on a Perkin-Elmer SCIEX API spectrometer using ESI mode. Elemental analyses were performed on a Thermoquest Flash 1112 series EA analyser. Thin Layer Chromatographies (TLC) were conducted on precoated silica gel plates (Merck $60F_{254}$) and the spots visualised using an ultraviolet light. Flash chromatographies were carried out on column using flash silica gel 60 Merck (40-63 μm) using the indicated solvents (petroleum ether: boiling range 40-60 °C). All reactions requiring anhydrous conditions were conducted in flame-dried apparatus.

Di-*tert*-butyl 5-Ethoxycarbonylmethylene-1,3,4,5-tetrahydro-1-oxoazepino[3,4-*b*]indole-2,10-dicarboxylate (**1**).

A suspension of triphenylphosphine (42 mg, 0.16 mmole), palladium acetate (18 mg, 0.08 mmole), silver carbonate (436 mg, 1.58 mmoles) and potassium chloride (118 mg, 1.58 mmoles) in dry tetrahydrofuran (20 ml) was stirred at room temperature for 15 min. Iodoalkene **2** (484 mg, 0.79 mmole) in dry tetrahydrofuran (15 ml) was added and the final mixture was heated at reflux for 15 hours. After cooling, the salts were filtered off and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography (petroleum ether/ethyl acetate 85:15) to afford **1** (322 mg, 84%); foam; ir (neat) 1788, 1754, 1722, 1718 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.33 (t, 3H, J = 7.1 Hz, CH_3), 1.57 (s, 9H, 3 CH_3), 1.61 (s, 9H, 3 CH_3), 3.49 (broad s, 2H, CH_2), 4.11-4.16 (m, 2H, CH_2), 4.24 (q, 2H, J = 7.1 Hz, CH_2), 6.37 (t, 1H, J = 2.5 Hz, =CH), 7.33 (t, 1H, *J* = 7.9 Hz, H_{ar}), 7.47 (t, 1H, J = 8.1 Hz, H_{ar}), 7.77 (d, 1H, J = 7.9 Hz, H_{ar}), 8.12 (d, 1H, J = 8.1 Hz, H_{ar}); ^{13}C nmr (deuteriochloroform): δ 14.4 (CH_3), 27.7 (3 CH_3), 28.1 (3 CH_3), 35.0 (CH_2), 42.9 (CH_2), 60.2 (CH_2), 83.7 (C), 85.3 (C), 114.8 (CH), 121.2 (CH), 121.5 (CH), 122.9 (C), 124.0 (CH), 125.2 (C), 127.7 (CH), 131.6 (C), 138.2 (C), 147.4 (C), 148.9 (CO), 151.3 (CO), 161.1 (CO), 166.1 (CO); ms: m/z 485 $(M+H)^+$.

Anal. Calcd. for $C_{26}H_{32}N_2O_7$: C, 64.45; H, 6.66; N, 5.78. Found: C, 64.10; H, 6.48; N, 5.89.

tert-Butyl 2-(*tert*-Butoxycarbonyl)-[(*E*)-5-ethoxy-5-oxo-pent-3-enyl]aminocarbonyl)-3-iodo-1*H*-indole-1-carboxylate (**2**).

Synthesis reported in Ref. [6]; white solid; mp 88-89° (recrystallization from ethyl acetate-hexane); ir (potassium bromide) 1740, 1737, 1718, 1674 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.10 (s, 9H, 3 CH_3), 1.28 (t, 3H, J = 7.1 Hz, CH_3), 1.61 (s, 9H, 3 CH_3), 2.72 (q, 2H, J = 7.1 Hz, CH_2), 3.86-3.96 (m, 1H, CH_2), 4.13-4.22 (m, 3H, CH_2 and CH_2), 6.99 (d, 1H, J = 15.6 Hz, =CH), 6.97-7.08 (m, 1H, =CH), 7.29-7.41 (m, 3H, H_{ar}), 8.08 (d, 1H, J = 8.5 Hz, H_{ar}); ^{13}C nmr (deuteriochloroform): δ 14.2 (CH_3), 27.3 (3 CH_3), 27.8 (3 CH_3), 30.9 (CH_2), 42.7 (CH_2), 60.2 (CH_2), 65.1 (C), 83.5 (C), 85.2 (C), 115.3 (CH), 121.5 (CH), 123.3 (CH), 123.7 (CH), 126.1 (CH), 130.7 (C), 134.3 (C), 136.5 (C), 145.0 (CH), 148.6 (CO), 151.3 (CO), 163.7 (CO), 165.9 (CO); ms: m/z 613 $(M+H)^+$.

Anal. Calcd. for $C_{26}H_{33}IN_2O_7$: C, 50.99; H, 5.43; N, 4.57. Found: C, 51.15; H, 5.52; N, 4.50.

General Procedure for the Preparation of Derivatives **5**.

To a solution of the amine **4** (11 mmoles) in dry dichloromethane (100 ml), were successively added at 0 °C, a catalytic amount of 4-dimethylaminopyridine, **1** (2.87 g, 10 mmoles) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.10 g, 11 mmoles). The solution was stirred at room temperature for 24 hours and the solvent was evaporated *in vacuo*. The residue was taken up in ethyl acetate (50 ml) and 10% hydrochloric acid solution (20 ml) and stirred for 10 min. The two phases were separated, the aqueous phase was extracted with ethyl acetate (2 x 20 ml) and the combined organic layers were successively washed with 1 *M* sodium hydroxide solution (25 ml) and brine solution (25 ml). After drying (magnesium sulfate), the organic phase was evaporated *in vacuo* to give **5** as an oil which crystallized upon addition of diethyl ether.

N-(But-3-enyl)-3-iodo-1*H*-indole-2-carboxamide (**5a**).

5a was prepared from **1** and but-3-enylamine (**4a**); yield: 79%; white solid; mp 146-147 °C (crystallization from diethyl ether); ir (potassium bromide) 3352, 3257, 1612, 1545 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.46 (q, 2H, J = 6.2 Hz, CH_2), 3.67 (q, 2H, J = 6.2 Hz, CH_2), 5.19 (d, 1H, J = 11.3 Hz, $=CH_2$), 5.24 (d, 1H, J = 18.4 Hz, $=CH_2$), 5.82-5.97 (m, 1H, =CH), 7.22 (t, 1H, J = 7.5 Hz, H_{ar}), 7.26 (broad s, 1H, NH), 7.34 (t, 1H, J = 8.3 Hz, H_{ar}), 7.42 (d, 1H, J = 8.3 Hz, H_{ar}), 7.47 (d, 1H, J = 8.1 Hz, H_{ar}), 9.85 (broad s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 33.7 (CH_2), 39.4 (CH_2), 58.6 (C), 112.7 (CH), 118.1 (CH_2), 121.4 (CH), 122.5 (CH), 125.5 (CH), 130.5 (C), 131.0 (C), 135.0 (CH), 136.1 (C), 161.0 (CO); ms: m/z 341 $(M+H)^+$.

Anal. Calcd. for $C_{13}H_{13}IN_2O$: C, 45.90; H, 3.85; N, 8.24. Found: C, 45.62; H, 3.90; N, 8.36.

3-Iodo-*N*-[(*E*)-pent-3-enyl]-1*H*-indole-2-carboxamide (**5b**).

5b was prepared from **1** and (*E*)-pent-3-enylamine (**4b**); yield: 84%; white solid; mp 170-171° (crystallization from diethyl ether); ir (potassium bromide) 3391, 3244, 1630, 1547 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.73 (dd, 3H, J = 1.0, 6.2 Hz, CH_3), 2.38 (q, 2H, J = 6.6 Hz, CH_2), 3.60 (q, 2H, J = 6.6 Hz, CH_2), 5.44-5.55 (m, 1H, =CH), 5.61-5.72 (m, 1H, =CH), 7.22 (t, 1H, J = 8.3 Hz, H_{ar}), 7.26 (broad s, 1H, NH), 7.34 (t, 1H, J = 8.3 Hz, H_{ar}), 7.42 (d, 1H, J = 8.3 Hz, H_{ar}), 7.47 (d, 1H, J = 8.3 Hz, H_{ar}), 9.84 (broad s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 18.3 (CH_3), 32.5 (CH_2), 39.7 (CH_2), 58.4 (C), 112.6 (CH), 121.5 (CH), 122.6 (CH), 125.6 (CH), 127.6 (CH), 129.0 (CH), 130.7 (C), 131.1 (C), 135.9 (C), 160.8 (CO); ms: m/z 355 $(M+H)^+$.

Anal. Calcd. for $C_{14}H_{15}IN_2O$: C, 47.47; H, 4.27; N, 7.91. Found: C, 47.40; H, 4.11; N, 8.00.

General Procedure for the Preparation of Derivatives **6**.

To a solution of **5** (7.7 mmoles) in dry acetonitrile (100 ml) were added *tert*-butyldicarbonate (3.7 g, 16.9 mmoles) and a catalytic amount of 4-dimethylaminopyridine. The solution was stirred at room temperature for 15 hours and the solvent was evaporated *in vacuo*. The residue was then purified by flash chromatography to afford **6**.

tert-Butyl 2-(But-3-enyl-*tert*-butoxycarbonylaminocarbonyl)-3-iodo-1*H*-indole-1-carboxylate (**6a**).

6a was prepared from **5a**; chromatography eluent: petroleum ether/ethyl acetate 95:5; yield: 90%; white solid; mp 90-91 °C (crystallization from *n*-pentane); ir (potassium bromide) 1748, 1732, 1674 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.11 (s, 9H, 3 CH_3), 1.60 (s, 9H, 3 CH_3), 2.57 (q, 2H, J = 7.5 Hz, CH_2), 3.80 (dt, 1H, J = 7.5, 13.2 Hz, CH_2), 4.11 (dt, 1H, J = 7.5, 13.2 Hz, CH_2), 5.09 (d, 1H, J = 10.2 Hz, $=CH_2$), 5.21 (dd, 1H, J = 1.5, 17.3 Hz, $=CH_2$), 5.83-5.97 (m, 1H, =CH), 7.29-7.42 (m, 3H, H_{ar}), 8.11 (d, 1H, J = 7.9 Hz, H_{ar}); ^{13}C nmr (deuteriochloroform): δ 27.6 (3 CH_3), 28.1 (3 CH_3), 32.7 (CH_2), 44.1 (CH_2), 65.2 (C), 83.5 (C), 85.3 (C), 115.6 (CH), 117.1 (CH_2), 121.8 (CH), 123.9 (CH), 126.3 (CH), 131.0 (C), 134.7 (C), 135.1 (CH), 136.8 (C), 148.2 (CO), 151.7 (CO), 163.9 (CO); ms: m/z 541 $(M+H)^+$.

Anal. Calcd. for $C_{23}H_{29}IN_2O_5$: C, 51.12; H, 5.41; N, 5.18. Found: C, 50.87; H, 5.51; N, 5.25.

tert-Butyl 2-[*tert*-Butoxycarbonyl-(*E*)-pent-3-enyl-aminocarbonyl]-3-iodo-1*H*-indole-1-carboxylate (**6b**).

6b was prepared from **5b**; chromatography eluent: petroleum ether/ethyl acetate 9:1; yield: 90%; white solid; mp 114-115 °C (recrystallization from ethyl acetate/*n*-pentane); ir (potassium bromide) 1745, 1732 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.11 (s, 9H, 3 CH_3), 1.59 (s, 9H, 3 CH_3), 1.68 (d, 3H, J = 6.0 Hz, CH_3), 2.57 (q, 2H, J = 7.3 Hz, CH_2), 3.74 (dt, 1H, J = 7.7, 13.2 Hz, CH_2), 4.11 (dt, 1H, J = 7.7, 13.2 Hz, CH_2), 5.44-5.55 (m, 1H, =CH), 5.57-5.69 (m, 1H, =CH), 7.28-7.41 (m, 3H, H_{ar}), 8.11 (d, 1H, J = 8.3 Hz, H_{ar}); ^{13}C nmr (deuteriochloroform): δ 18.2 (CH_3), 27.7 (3 CH_3), 28.1 (3 CH_3), 31.7 (CH_2), 44.6 (CH_2), 65.2 (C), 83.4 (C), 85.3 (C), 115.6 (CH), 121.8 (CH), 123.9 (CH), 126.3 (CH), 127.6 (CH), 127.8 (CH), 131.0 (C), 134.8 (C), 136.9 (C), 148.3 (CO), 151.8 (CO), 164.0 (CO); ms: m/z 555 $(M+H)^+$.

Anal. Calcd. for $C_{24}H_{31}IN_2O_5$: C, 51.99; H, 5.64; N, 5.05. Found: C, 52.26; H, 5.49; N, 4.93.

N-(2-Formylethyl)-3-iodo-1*H*-indole-2-carboxamide (**7**).

To a solution of *N*-(3-hydroxypropyl)-3-iodo-1*H*-indole-2-carboxamide [6] (530 mg, 1.54 mmoles) in dry dimethylsulfoxide (15 ml) was added 2-iodoxybenzoic acid (636 mg, 1.85 mmoles). The reaction mixture was stirred at room temperature for 15 hours and then diluted with water (75 ml). The solution was extracted with ethyl acetate (3 x 25 ml) and the combined organic phases were washed with brine solution (3 x 25 ml), dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 7:3) to afford **7** (450 mg, 85%); white solid; mp 141-142 °C (recrystallization from ethyl acetate-hexane); ir (potassium bromide) 3342, 3251, 1730, 1611 cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 2.92-2.98 (m, 2H, CH_2), 3.78-3.86 (m, 2H, CH_2), 7.32-7.38 (m, 1H, H_{ar}), 7.43-7.50 (m, 1H, H_{ar}), 7.55-7.65 (m, 2H, H_{ar}), 8.27 (t, 1H, J = 5.3 Hz, NH), 9.95 (s, 1H, CHO), 12.19 (s, 1H, NH); ^{13}C nmr (dimethylsulfoxide-d_6): δ 33.2 (CH_2), 43.1 (CH_2), 60.2 (C), 112.6 (CH), 120.9 (CH), 121.8 (CH), 124.7 (CH), 130.3 (C), 131.7 (C), 136.0 (C), 160.7 (CO), 202.4 (CO); ms: m/z 343 $(M+H)^+$.

Anal. Calcd. for $C_{12}H_{11}IN_2O_2$: C, 42.13; H, 3.24; N, 8.19. Found: C, 41.87; H, 3.36; N, 8.26.

Methyl 2-*tert*-Butoxycarbonylamino-5-[(3-iodo-1*H*-indole-2-yl)carbonylamino]pent-2-enoate (**9a**) and (**9b**).

To a suspension of sodium hydride (38 mg, 0.95 mmole, 60% dispersed in oil) in dry tetrahydrofuran (4 ml), was added a solution of methyl (+/-)-Boc-α-phosphonoglycine trimethyl ester (**8a**) (252 mg, 0.85 mmole) in dry tetrahydrofuran (4 ml). The reaction mixture was stirred at room temperature for 45 min and a solution of **7** (290 mg, 0.85 mmole) in dry tetrahydrofuran (6 ml) was added drop by drop. The solution was then stirred for 2 hours, diluted with water (40 ml) and extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 8:2) to afford **9a** (169 mg, 39%) and **9b** (197 mg, 45%).

9a; oil; ir (neat) 3310, 1725, 1610 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.47 (s, 9H, 3 CH_3), 2.96 (q, 2H, J = 6.8 Hz, CH_2), 3.70-3.75 (m, 2H, CH_2), 3.77 (s, 3H, CH_3), 6.73 (s, 1H, NH), 6.83 (broad s, 1H, =CH), 7.21 (t, 1H, J = 7.5 Hz, H_{ar}), 7.30-7.47 (m, 4H, H_{ar}, NH), 9.71 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 28.3 (CH_2), 28.4 (3 CH_3), 39.8 (CH_2), 52.6 (CH_3), 58.8 (C), 80.7 (C), 112.5 (CH), 121.5 (CH), 122.7 (CH), 124.9 (CH), 125.7 (CH), 127.4 (C), 130.7 (C), 131.1 (C), 135.9 (C), 153.3 (CO), 161.0 (CO), 164.6 (CO); ms: m/z *514* $(M+H)^+$.

Anal. Calcd. for $C_{20}H_{24}IN_3O_5$: C, 46.80; H, 4.71; N, 8.19. Found: C, 46.99; H, 4.54; N, 8.17.

9b; oil; ir (neat) 3310, 1730, 1610 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.48 (s, 9H, 3 CH_3), 2.62 (q, 2H, J = 6.9 Hz, CH_2), 3.70-3.75 (m, 2H, CH_2), 3.79 (s, 3H, CH_3), 6.21 (s, 1H, NH), 6.65 (t, 1H, J = 7.5 Hz, =CH), 7.19-7.37 (m, 4H, H_{ar} and NH), 7.48 (d, 1H, J = 7.9 Hz, H_{ar}), 9.69 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 28.3 (3 CH_3), 28.6 (CH_2), 38.8 (CH_2), 52.7 (CH_3), 59.5 (C), 81.1 (C), 112.4 (CH), 121.5 (CH), 122.7 (CH), 125.7 (2 CH), 127.5 (C), 130.3 (C), 131.0 (C), 136.0 (C), 153.7 (CO), 161.1 (CO), 165.2 (CO); ms: m/z 514 $(M+H)^+$.

Anal. Calcd. for $C_{20}H_{24}IN_3O_5$: C, 46.80; H, 4.71; N, 8.19. Found: C, 46.93; H, 4.63; N, 8.29.

Methyl 2-Benzyloxy-5-[(3-iodo-1*H*-indol-2-yl)carbonylamino]-pent-2-enoate (**9c**).

To a solution of [(benzyloxy)(methoxycarbonymethyl)]-triphenylphosphonium bromide (**8b**) [10] (2.1 g, 4.0 mmoles) in dry tetrahydrofuran (30 ml) was added at 0 °C, sodium hydride (160 mg, 4.0 mmoles, 60% dispersed in oil). The reaction mixture was stirred at room temperature for 1 hour and a solution of **7** (684 mg, 2.0 mmoles) in dry tetrahydrofuran (20 ml) was added drop by drop. The solution was heated at reflux for 3 hours and the solvent was evaporated *in vacuo*. The residue was taken up in water (50 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic layers were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was then purified by flash chromatography (petroleum ether/ethyl acetate 7:3) to afford **9c** (840 mg, 83%); foam; ir (neat) 3310, 3260, 1720, 1632 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.52 (q, 2H, J = 7.0 Hz, CH_2), 3.53 (q, 2H, J = 7.0 Hz, CH_2), 3.81 (s, 3H, CH_3), 4.89 (s, 2H, CH_2), 6.36 (t, 1H, J = 7.5 Hz, =CH), 7.19-7.48 (m, 10H, H_{ar}, NH), 10.46 (broad s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 26.0 (CH_2), 38.9 (CH_2), 52.2 (CH_3), 58.9 (C), 74.2 (CH_2), 112.5 (CH), 121.6 (CH), 122.7 (CH), 125.4 (CH), 125.7 (CH), 128.4 (CH), 128.6 (2 CH), 128.7 (2 CH), 130.4 (C), 131.0 (C), 135.9 (C), 136.8 (C), 146.2 (C), 160.9 (CO), 164.1 (CO); ms: m/z 505 $(M+H)^+$.

Anal. Calcd. for $C_{22}H_{21}IN_2O_4$: C, 52.39; H, 4.20; N, 5.55. Found: C, 52.11; H, 4.04; N, 5.43.

Methyl 2-(Di-*tert*-butoxycarbonylamino)-5-[(3-iodo-1*H*-indol-2-yl)carbonylamino]pent-2-enoate (**10a**).

Following the methodology described for the preparation of **6**, **10a** was prepared from **9a**, except that 4 equivalents of *tert*-butyldicarbonate were used. Chromatography eluent: petroleum ether/ethyl acetate 9:1; yield: 83%; oil; ir (neat) 1775, 1720 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.11 (s, 9H, 3 CH_3), 1.48 (s, 18H, 6 CH_3), 1.60 (s, 9H, 3 CH_3), 3.13-3.23 (m, 2H, CH_2), 3.80 (s, 3H, CH_3), 3.82-3.93 (m, 1H, CH_2), 4.13-4.23 (m, 1H, CH_2), 6.29 (t, 1H, J = 7.7 Hz, =CH), 7.34-7.41 (m, 3H, H_{ar}), 8.10 (d, 1H, J = 9.0 Hz, H_{ar}); ms: *m/z* 814 $(M+H)^+$.

Anal. Calcd. for $C_{35}H_{48}IN_3O_{11}$: C, 51.66; H, 5.95; N, 5.16. Found: C, 51.77; H, 6.05; N, 5.09.

Methyl 2-(Di-*tert*-butoxycarbonylamino)-5-[(3-iodo-1*H*-indol-2-yl)carbonylamino]pent-2-enoate (**10b**).

Following the methodology described for the preparation of **6**, **10b** was prepared from **9b**. Chromatography eluent: petroleum ether/ethyl acetate 9:1; yield: 83%; oil; ir (neat) 1775, 1720 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.11 (s, 9H, 3 CH_3), 1.48 (s, 18H, 6 CH_3), 1.59 (s, 9H, 3 CH_3), 2.62-2.72 (m, 2H, CH_2), 3.78 (s, 3H, CH_3), 3.81-3.92 (m, 1H, CH_2), 4.11-4.21 (m, 1H, CH_2), 6.94 (t, 1H, J = 7.4 Hz, =CH), 7.29-7.40 (m, 3H, H_{ar}), 8.08 (d, 1H, J = 8.8 Hz, H_{ar}); ms: m/z 814 $(M+H)^+$.

Anal. Calcd. for $C_{35}H_{48}IN_3O_{11}$: C, 51.66; H, 5.95; N, 5.16. Found: C, 51.60; H, 5.89; N, 5.23.

tert-Butyl 2-[(4-Benzyloxy-4-methoxycarbonyl-but-3-enyl)-*tert*-butoxycarbonylaminocarbonyl]-3-iodo-1*H*-indole-1-carboxylate (**10c**).

Following the methodology described for the preparation of **6**, **10c** was prepared starting from **9c**. Chromatography eluent: petroleum ether/ethyl acetate 8:2; yield: 84%; oil; ir (neat) 1760, 1720 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.10 (s, 9H, 3 CH_3), 1.58 (s, 9H, 3 CH_3), 2.70 (q, 2H, J = 7.5 Hz, CH_2), 3.70-3.79 (m, 1H, CH_2), 3.80 (s, 3H, CH_3), 4.03-4.14 (m, 1H, CH_2), 4.92 (s, 2H, CH_2), 6.42 (t, 1H, J = 7.5 Hz, =CH), 7.27-7.50 (m, 8H, H_{ar}), 8.11 (d, 1H, J = 8.1 Hz, H_{ar}); ^{13}C nmr (deuteriochloroform): δ 25.0 (CH_2), 27.5 (3 CH_3), 27.9 (3 CH_3), 43.0 (CH_2), 51.9 (CH_3), 65.2 (C), 74.3 (CH_2), 83.5 (C), 85.2 (C), 115.4 (CH), 121.7 (CH), 123.8 (CH), 125.7 (CH), 126.2 (CH), 128.1 (CH), 128.4 (2 CH), 128.7 (2 CH), 130.8 (C), 134.6 (C), 136.6 (C), 137.0 (C), 145.7 (C), 148.1 (CO), 151.4 (CO), 163.8 (CO), 164.1 (CO); ms: m/z 705 $(M+H)^+$.

Anal. Calcd. for $C_{32}H_{37}IN_2O_8$: C, 54.55; H, 5.29; N, 3.98. Found: C, 54.33; H, 5.13; N, 4.12.

Di-*tert*-butyl 5-Methylene-1,3,4,5-tetrahydro-1-oxoazepino[3,4-*b*]indole-2,10-dicarboxylate (**11a exo**) and Di-*tert*-butyl 5-Methyl-1,3-dihydro-1-oxoazepino[3,4-*b*]indole-2,10-dicarboxylate (**11a endo**).

Following the methodology described for the preparation of **1**, compounds **11a** were prepared from **6a**. Chromatography eluent: petroleum ether/ethyl acetate 95:5. **11a Exo**; yield: 60%; white solid; mp 128-130° (crystallization from *n*-pentane); ir (potassium bromide) 3080, 1760, 1730, 1670 cm^{-1}; ^1H nmr (acetone-d_6): δ 1.54 (s, 9H, 3 CH_3), 1.60 (s, 9H, 3 CH_3), 3.01 (broad t, 2H, J = 5.6 Hz, CH_2), 4.10 (t, 2H, J = 5.6 Hz, CH_2), 5.58 (s, 2H, =CH_2), 7.34 (t, 1H, J = 7.9 Hz, H_{ar}), 7.51 (t, 1H, J = 8.3 Hz, H_{ar}), 7.80 (d, 1H, J = 7.9 Hz, H_{ar}), 8.09 (d, 1H, J = 8.3 Hz, H_{ar}); ^{13}C nmr (acetone-d_6): δ 27.7 (3 CH_3), 28.2 (3 CH_3), 37.0 (CH_2), 44.1 (CH_2), 83.2 (C), 85.2 (C), 115.0 (CH), 119.5 (CH_2), 122.3 (CH), 124.4 (CH), 125.4 (C), 126.7 (C), 128.4 (CH), 131.1 (C), 137.0 (C), 139.2 (C), 150.0 (CO), 152.7 (CO), 162.0 (CO); ms: m/z 413 $(M+H)^+$, 435 $(M+Na)^+$.

Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 67.23; H, 6.77; N, 6.90.

11a Endo; yield: 15%; oil; ir (neat) 3080, 1760, 1740, 1690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.57 (s, 9H, 3 CH_3), 1.62 (s, 9H, 3 CH_3), 2.44 (s, 3H, CH_3), 3.75 (broad s, 1H, CH_2), 4.66 (broad s, 1H, CH_2), 6.21 (broad t, 1H, J = 5.6 Hz, =CH), 7.28 (t, 1H, J = 8.3 Hz, H_{ar}), 7.45 (t, 1H, J = 8.1 Hz, H_{ar}), 7.84 (d, 1H, J = 8.1 Hz, H_{ar}), 8.18 (d, 1H, J = 8.3 Hz, H_{ar}); ^{13}C nmr (deuteriochloroform): δ 21.5 (CH_3), 27.8 (3 CH_3), 28.2 (3 CH_3), 43.2 (CH_2), 83.5 (C), 84.9 (C), 114.7 (CH), 112.6 (CH), 123.2 (CH), 124.2 (C), 126.1 (C), 126.4 (CH), 127.2 (C), 132.5 (C), 136.3 (C), 138.1 (C), 149.3 (CO), 151.4 (CO), 160.0 (CO); ms: m/z 413 $(M+H)^+$, 435 $(M+Na)^+$.

Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.76; H, 6.97; N, 6.68.

Di-*tert*-butyl 1,3,4,5-Tetrahydro-1-oxo-5-vinylazepino[3,4-*b*]-indole-2,10-dicarboxylate (**11b terminal olefin**), Di-*tert*-butyl 5-Ethylidene-1,3,4,5-tetrahydro-1-oxoazepino[3,4-*b*]indole-2,10-dicarboxylate (**11b exo**) and Di-*tert*-butyl 5-Ethyl-1,3-dihydro-1-oxoazepino[3,4-*b*]indole-2,10-dicarboxylate (**11b endo**).

Following the methodology described for the preparation of **1**, compounds **11b** were prepared from **6b**. Chromatography eluent: petroleum ether/ethyl acetate 95:5. **11b Terminal olefin**; yield: 44%; oil; ir (neat) 1756, 1735, 1675 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.56 (s, 9H, 3 CH_3), 1.61 (s, 9H, 3 CH_3), 2.10-2.45 (m, 2H, CH_2), 3.78 (ddd, 1H, J = 5.1, 10.7, 15.3 Hz, CH), 4.05-4.10 (m, 1H, CH_2), 4.20 (ddd, 1H, J = 3.0, 5.1, 14.9 Hz, CH_2), 4.90 (d, 1H, J = 16.8 Hz, =CH_2), 4.98 (d, 1H, J = 10.2 Hz, =CH_2), 5.96 (ddd, 1H, J = 5.1, 10.2, 16.8 Hz, =CH), 7.27 (t, 1H, J = 7.9 Hz, H_{ar}), 7.44 (t, H, J = 7.2 Hz, H_{ar}), 7.62 (d, 1H, J = 7.9 Hz, H_{ar}), 8.10 (d, 1H, J = 8.5 Hz, H_{ar}); ^{13}C nmr (deuteriochloroform): δ 27.9 (3 CH_3), 28.2 (3 CH_3), 33.0 (CH_2), 36.1 (CH), 44.4 (CH_2), 82.9 (C), 84.6 (C), 114.5 (CH_2), 114.9 (CH), 120.1 (CH), 123.1 (CH), 126.2 (C), 127.3 (C), 127.4 (CH), 130.4 (C), 138.2 (C), 141.0 (CH), 149.3 (CO), 151.9 (CO), 162.0 (CO); ms: m/z 427 $(M+H)^+$.

Anal. Calcd. for $C_{24}H_{30}N_2O_5$: C, 67.59; H, 7.09; N, 6.57. Found: C, 67.33; H, 6.98; N, 6.66.

11b Exo; yield: 14%; oil; ir (neat) 1760, 1740 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.57 (s, 9H, 3 CH_3), 1.60 (s, 9H, 3 CH_3), 1.85 (d, 3H, J = 7.1 Hz, CH_3), 2.83 (s, 2H, CH_2), 4.11 (t, 2H, J = 6.3 Hz, CH_2), 6.10-6.20 (m, 1H, =CH), 7.28 (t, 1H, J = 8.1 Hz, H_{ar}), 7.43 (t, 1H, J = 8.1 Hz, H_{ar}), 7.72 (d, 1H, J = 7.9 Hz, H_{ar}), 8.10 (d, 1H, J = 8.3 Hz, H_{ar}); ms: m/z 427 $(M+H)^+$.

Anal. Calcd. for $C_{24}H_{30}N_2O_5$: C, 67.59; H, 7.09; N, 6.57. Found: C, 67.77; H, 7.19; N, 6.76.

11b Endo; yield: 16%; oil; ir (neat) 1753, 1738, 1682 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.15 (t, 1H, J = 7.5 Hz, CH_3), 1.57 (s, 9H, 3 CH_3), 1.62 (s, 9H, 3 CH_3), 2.75-2.95 (m, 2H, CH_2), 3.65-3.80 (m, 1H, CH_2), 4.60-4.80 (m, 1H, CH_2), 6.22 (t, 1H, J = 7.1 Hz, =CH), 7.28 (t, 1H, J = 8.1 Hz, H_{ar}), 7.45 (t, 1H, J = 8.3 Hz, H_{ar}), 7.82 (d, 1H, J = 8.1 Hz, H_{ar}), 8.18 (d, 1H, J = 8.3 Hz, H_{ar}); ms: m/z 427 $(M+H)^+$.

Anal. Calcd. for $C_{24}H_{30}N_2O_5$: C, 67.59; H, 7.09; N, 6.57. Found: C, 67.50; H, 6.98; N, 6.49.

Di-*tert*-butyl 5-[(Benzyloxy)(methoxycarbonyl)methylene]-1,3,4,5-tetrahydro-1-oxoazepino[3,4-*b*]indole-2,10-dicarboxylate (**11d**).

Following the methodology described for the preparation of **1**, compound **11d** was prepared from **10c**. Chromatography eluent: petroleum ether/ethyl acetate 95:5; yield: 32%; oil; ir (neat) 1760, 1720 cm^{-1}; ^1H NMR (deuteriochloroform): δ 1.58 (s, 9H, 3 CH_3), 1.62 (s, 9H, 3 CH_3), 3.08-3.45 (m, 2H, CH_2), 3.85 (s, 3H, CH_3), 3.96-4.21 (m, 2H, CH_2), 4.35 (s, 2H, CH_2), 6.72 (d, 2H, J = 8.1 Hz, H_{ar}), 7.09 (d, 2H, J = 8.1 Hz, H_{ar}), 7.21 (t, 1H, J = 7.6 Hz, H_{ar}), 7.30-7.39 (m, 1H, H_{ar}), 7.43 (t, 1H, J = 8.0 Hz, H_{ar}), 7.56 (d, 1H, J = 7.6 Hz, H_{ar}), 8.10 (d, 1H, J = 8.0 Hz, H_{ar}); ms: m/z 577 $(M+H)^+$.

Anal. Calcd. for $C_{32}H_{36}N_2O_8$: C, 66.65; H, 6.29; N, 4.86. Found: C, 66.99; H, 6.45; N, 4.97.

Di-*tert*-butyl 4-Bromo-5-ethoxycarbonylmethylene-1,3,4,5-tetrahydro-1-oxoazepino[3,4-*b*]indole-2,10-dicarboxylate (**12**) and *tert*-Butyl 4-Bromo-5-ethoxycarbonylmethylene-2,3,4,5-tetrahydro-1-oxo-1*H*-azepino[3,4-*b*]indole-10-carboxylate (**13**).

Method A: To a solution of **1** (250 mg, 0.52 mmole) and *N*-bromosuccinimide (101 mg, 0.57 mmole) in carbon tetrachloride (10 ml), was added a catalytic amount of azobisisobutyronitrile and the reaction mixture was heated at reflux for 4 hours. After evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether/ethyl acetate 8:2) to afford **12** (198 mg, 68%).

Method B: To a solution of **1** (121 mg, 0.25 mmole) in dichloromethane (3 ml) were successively added potassium bromide (66 mg, 0.55 mmole) and a solution of ammonium cerium nitrate (315 mg, 0.58 mmole) in water (3 ml). The reaction mixture was stirred at room temperature for 50 min and dichloromethane was evaporated *in vacuo*. After dilution with water (15 ml), the aqueous layer was extracted with ethyl acetate (2 x 15 ml), and the combined organic phases were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 8:2) to afford **12** (100 mg, 71%).

Method C: To a solution of **1** (102 mg, 0.21 mmole) in carbon tetrachloride (5 ml) was added a solution of bromine (11.8 µl, 0.23 mmole) in carbon tetrachloride (5 ml). The solution was then stirred at room temperature for 15 hours and concentrated *in vacuo*. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 8:2 then 6:4) to afford **12** (50 mg, 42%) and **13** (42 mg, 43%).

12; foam; ir (neat) 1790-1700 (broad s), 1625 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.35 (t, 3H, J = 7.5 Hz, CH_3), 1.56 (s, 9H, 3 CH_3), 1.62 (s, 9H, 3 CH_3), 3.98-4.09 (m, 1H, CH_2), 4.29 (q, 2H, J = 7.5 Hz, CH_2), 4.58-4.66 (m, 1H, CH_2), 6.26 (s, 1H, =CH), 6.42-6.48 (m, 1H, CH), 7.36 (t, 1H, J = 8.4 Hz, H_{ar}), 7.51 (t, 1H, J = 8.4 Hz, H_{ar}), 7.70 (d, 1H, J = 8.4 Hz, H_{ar}), 8.13 (d, 1H, J = 8.4 Hz, H_{ar}); ^{13}C nmr (deuteriochloroform): δ 14.3 (CH_3), 27.8 (3 CH_3), 28.0 (3 CH_3), 42.7 (CH), 49.4 (CH_2), 61.0 (CH_2), 84.4 (C), 85.6 (C), 115.1 (CH), 120.7 (CH), 121.6 (C), 121.4 (CH), 125.0 (CH), 125.9 (C), 128.4 (CH), 130.8 (C), 138.5 (C), 146.0 (C), 148.7 (CO), 150.6 (CO), 160.4 (CO), 164.7 (CO); ms: m/z 563 $(M+H)^+$ for ^{79}Br, 565 $(M+H)^+$ for ^{81}Br.

Anal. Calcd. for $C_{26}H_{31}BrN_2O_7$: C, 55.42; H, 5.55; N, 4.97. Found: C, 55.13; H, 5.67; N, 5.06.

13; foam; ^1H nmr (deuteriochloroform): δ 1.34 (t, 3H, J = 7.5 Hz, CH_3), 1.63 (s, 9H, 3 CH_3), 3.67-3.77 (m, 1H, CH_2), 3.92-4.04 (m, 1H, CH_2), 4.29 (q, 2H, J = 7.5 Hz, CH_2), 6.24 (s, 1H, =CH), 6.32-6.38 (m, 2H, CH, NH), 7.37 (t, 1H, J = 7.9 Hz, H_{ar}), 7.50 (t, 1H, J = 8.3 Hz, H_{ar}), 7.71 (d, 1H, J = 7.9 Hz, H_{ar}), 8.17 (d, 1H, J = 8.3 Hz, H_{ar}); ^{13}C nmr (deuteriochloroform): δ 14.3 (CH_3), 27.8 (3 CH_3), 45.4 (CH), 46.0 (CH_2), 60.9 (CH_2), 85.3 (C), 115.2 (CH), 120.5 (CH), 121.8 (C), 124.2 (CH), 124.7 (CH), 126.3 (C), 127.8 (CH), 130.1 (C), 138.2 (C), 147.1 (C), 148.8 (CO), 164.9 (2 CO); ms: m/z 463 $(M+H)^+$ for ^{79}Br, 465 $(M+H)^+$ for ^{81}Br.

Anal. Calcd. for $C_{21}H_{23}BrN_2O_5$: C, 54.44; H, 5.00; N, 6.05. Found: C, 54.77; H, 5.13; N, 6.17.

Ethyl (1,3,4,10-Tetrahydro-1-oxo-2*H*-azepino[3,4-*b*]indol-5-ylidene)acetate (**14**).

A solution of **1** (250 mg, 0.52 mmole) in formic acid (10 ml) was stirred for 8 hours at 0 °C. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (petroleum ether/ethyl acetate 3:7) to afford **14** (99 mg, 67%); white solid; mp 160-161 °C (crystallization from diethyl ether); ir (potassium bromide) 3374, 3210, 1700, 1640 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 (t, 3H, J = 7.5 Hz, CH_3), 3.50-3.54 (m, 2H, CH_2), 3.59-3.63 (m, 2H, CH_2), 4.22 (q, 2H, J = 7.5 Hz, CH_2), 6.46 (s, 1H, =CH), 7.16 (t, 1H, J = 5.5 Hz, NH), 7.24 (t, 1H, J = 8.0 Hz, H_{ar}), 7.34 (t, 1H, J = 8.0 Hz, H_{ar}), 7.52 (d, 1H, J = 8.0 Hz, H_{ar}), 7.97 (d, 1H, J = 8.0 Hz, H_{ar}), 10.62 (broad s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 14.8 (CH_3), 35.5 (CH_2), 40.8 (CH_2), 60.2 (CH_2), 113.1 (CH), 116.7 (CH), 119.0 (C), 122.2 (CH), 122.3 (CH), 125.8 (CH), 125.9 (C), 129.6 (C), 137.0 (C), 151.3 (C), 166.4 (CO), 167.4 (CO); ms: m/z 285 $(M+H)^+$.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.79; H, 5.92; N, 9.90.

Ethyl (1,2,3,10-Tetrahydro-1-oxoazepino[3,4-*b*]indol-5-yl)-acetate (**15**).

A solution of **1** (250 mg, 0.52 mmole) in formic acid (10 ml) was stirred for 8 hours at room temperature. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (petroleum ether/ethyl acetate 3:7) to afford **15** (62 mg, 42%) and **14** (54 mg, 37%); white solid; mp 154-155° (crystallization from diethyl ether); ir (potassium bromide) 3350, 3228, 1736, 1628 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.15 (t, 3H, J = 7.5 Hz, CH_3), 3.59 (t, 2H, J = 7.5 Hz, CH_2), 3.78 (s, 2H, CH_2), 4.09 (q, 2H, J = 7.5 Hz, CH_2), 5.90 (t, 1H, J = 7.5 Hz, =CH), 6.94 (t, 1H, J = 5.0 Hz, NH), 7.16 (t, 1H, J = 7.5 Hz, H_{ar}), 7.31 (t, 1H, J = 7.5 Hz, H_{ar}), 7.52 (d, 1H, J = 7.5 Hz, H_{ar}), 7.82 (d, 1H, J = 7.5 Hz, H_{ar}), 10.39 (broad s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 14.4 (CH_3), 39.2 (CH_2), 41.0 (CH_2), 61.3 (CH_2), 113.0 (CH), 118.8 (C), 121.3 (CH), 122.4 (CH), 123.0 (CH), 125.4 (CH), 125.5 (C), 130.4 (C), 134.2 (C), 136.8 (C), 165.5 (CO), 171.6 (CO); ms: m/z 285 $(M+H)^+$.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.33; H, 5.55; N, 9.73.

Ethyl (4-Bromo-1,3,4,10-tetrahydro-1-oxo-2*H*-azepino[3,4-*b*]-indol-5-ylidene)acetate (**16**).

Following the methodology described for the preparation of **12** (Method A), compound **16** was prepared from **14**. Chromatography eluent: petroleum ether/ethyl acetate 6:4); yield: 90%; oil; ir (neat) 3375, 3215, 1720, 1633 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.35 (t, 3H, J = 7.5 Hz, CH_3), 3.72-3.77 (m, 2H, CH_2), 4.28 (q, 2H, J = 7.5 Hz, CH_2), 6.44 (s, 1H, =CH), 6.74-6.78 (m, 1H, CH), 7.22-7.37 (m, 3H, NH, H_{ar}), 7.53 (d,

1H, J = 8.0 Hz, H_{ar}), 7.89 (d, 1H, J = 8.0 Hz, H_{ar}), 10.72 (broad s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 14.5 (CH_3), 45.2 (CH), 46.5 (CH_2), 60.8 (CH_2), 113.0 (CH), 115.5 (C), 119.0 (CH), 121.8 (CH), 122.4 (CH), 125.9 (CH), 126.0 (C), 129.0 (C), 137.0 (C), 149.7 (C), 165.9 (CO), 166.0 (CO); ms: m/z 363 $(M+H)^+$ for ^{79}Br, 365 $(M+H)^+$ for ^{81}Br.

Anal. Calcd. for $C_{16}H_{15}BrN_2O_3$: C, 52.91; H, 4.16; N, 7.71. Found: C, 53.23; H, 4.18; N, 7.88.

4,5-Dihydro-3a*H*,7*H*-3-oxa-5-azaindolo[3,2-*e*]azulene-2,6-dione (**17**).

A solution of bromoester **16** (100 mg, 0.27 mmole) in dichloromethane (10 ml) was stirred at room temperature for 3 hours. After evaporation, the crude residue was purified by flash chromatography (petroleum ether/ethyl acetate 7:3) to afford **17** (70 mg, 100%); oil; ir (neat) 3328, 3230, 1729, 1644 cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 3.56 (broad t, 2H, J = 6.4 Hz, CH_2), 5.53 (broad t, 1H, J = 6.4 Hz, CH), 6.63 (d, 1H, J = 1.3 Hz, =CH), 7.26 (t, 1H, J = 7.2 Hz, H_{ar}), 7.37 (t, 1H, J = 7.2 Hz, H_{ar}), 7.56 (d, 1H, J = 8.1 Hz, H_{ar}), 8.08 (d, 1H, J = 8.1 Hz, H_{ar}), 8.62 (broad t, 1H, J = 4.5 Hz, NH), 12.45 (broad s, 1H, NH); ^{13}C nmr (dimethylsulfoxide-d_6): δ 42.9 (CH_2), 80.2 (CH), 106.5 (C), 108.0 (CH), 113.9 (CH), 122.1 (CH), 123.0 (CH), 125.7 (CH), 125.8 (C), 132.1 (C), 137.2 (C), 161.9 (C), 162.7 (C), 173.6 (CO); ms: m/z 255 $(M+H)^+$.

Anal. Calcd. for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found: C, 66.00; H, 3.85; N, 10.94.

Di-*tert*-butyl 5-[(Ethoxycarbonyl)(hydroxy)methyl]-1,3,4,5-tetrahydro-5-hydroxy-1-oxoazepino[3,4-*b*]indole-2,10-dicarboxylate (**18**).

To a solution of **1** (220 mg, 0.45 mmole) in *tert*-butanol (1 ml), were successively added citric acid (95 mg, 0.45 mmole) in water (1 ml), potassium osmate dihydrate (2 mg), and *N*-methylmorpholine oxide (68 mg, 0.50 mmole). The reaction mixture was stirred at room temperature for 15 hours and then diluted with water (20 ml). The solution was extracted with ethyl acetate (3 x 15 ml) and the combined organic layers were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 6:4) to afford **18** (230 mg, 97%); foam; ir (neat) 3600-3200, 1770-1650 (broad s) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.00 (t, 3H, J = 7.1 Hz, CH_3), 1.56 (s, 9H, 3 CH_3), 1.58 (s, 9H, 3 CH_3), 2.19-2.39 (m, 2H, CH_2), 3.37 (d, 1H, J = 6.0 Hz, OH), 3.54 (s, 1H, OH), 3.82-3.91 (m, 1H, CH_2), 3.98 (q, 2H, J = 7.1 Hz, CH_2), 4.24-4.31 (m, 1H, CH_2), 4.69 (d, 1H, J = 6.0 Hz, CH), 7.26 (t, 1H, J = 8.1 Hz, H_{ar}), 7.41 (t, 1H, J = 7.7 Hz, H_{ar}), 8.01 (d, 1H, J = 8.1 Hz, H_{ar}), 8.08 (d, 1H, J = 8.5 Hz, H_{ar}); ^{13}C nmr (deuteriochloroform): δ 13.5 (CH_3), 27.6 (3 CH_3), 28.1 (3 CH_3), 40.0 (CH_2), 41.0 (CH_2), 62.8 (CH_2), 76.4 (C), 76.9 (CH), 83.6 (C), 84.9 (C), 114.1 (CH), 122.8 (C), 123.1 (CH), 123.6 (CH), 126.5 (C), 126.8 (CH), 130.1 (C), 137.9 (C), 149.4 (CO), 152.0 (CO), 161.2 (CO), 171.8 (CO); ms: m/z 519 $(M+H)^+$.

Anal. Calcd. for $C_{26}H_{34}N_2O_9$: C, 60.22; H, 6.61; N, 5.40. Found: C, 60.44; H, 6.70; N, 5.37.

Ethyl 2-(1,2,3,10-Tetrahydro-1-oxoazepino[3,4-*b*]indol-5-yl)-2-hydroxyacetate (**19**).

To a solution of **18** (225 mg, 0.43 mmole) in ethanol (5 ml) was added sulfuric acid (1 ml). The solution was quickly heated to reflux with a preheated bath and stirred at this temperature for 5 min. The solution was neutralized by adding a saturated aqueous sodium hydrogenocarbonate solution and then extracted with ethyl acetate (3 x 15 ml). The combined organic layers were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate) to afford **19** (120 mg, 92%); foam; ir (neat) 3600-3000, 1729, 1643 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.03 (t, 3H, J = 7.1 Hz, CH_3), 2.57 (s, 1H, OH), 3.59 (broad q, 2H, J = 7.1 Hz, CH_2), 4.06-4.18 (m, 2H, CH_2), 5.50 (s, 1H, CH), 6.06 (t, 1H, J = 6.9 Hz, =CH), 6.95 (broad s, 1H, NH), 7.22 (t, 1H, J = 8.3 Hz, H_{ar}), 7.36 (t, 1H, J = 8.3 Hz, H_{ar}), 7.51 (d, 1H, J = 8.3 Hz, H_{ar}), 8.05 (d, 1H, J = 8.3 Hz, H_{ar}), 10.00 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 13.9 (CH_3), 38.5 (CH_2), 61.9 (CH_2), 71.7 (CH), 112.8 (CH), 117.4 (C), 121.1 (CH), 122.1 (CH), 122.3 (CH), 124.8 (C), 125.3 (CH), 130.3 (C), 136.6 (C), 139.0 (C), 165.7 (CO), 173.8 (CO); ms: m/z 301 $(M+H)^+$.

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.26; H, 5.45; N, 9.50.

Ethyl 2-Chloro-2-(1,2,3,10-tetrahydro-1-oxoazepino[3,4-*b*]-indol-5-yl)acetate (**20**).

To a solution of **19** (60 mg, 0.2 mmole) and triethylamine (140 µl, 1.0 mmole) in dry dichloromethane (2.5 ml), was added at 0 °C, thionyl chloride (58 µl, 0.8 mmole). The solution was then allowed to return to room temperature and was stirred at this temperature for 15 hours. After evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether/ethyl acetate 1:1) to afford **20** (22 mg, 35%); oil; ^{1}H nmr (deuteriochloroform): δ 1.16 (t, 3H, J = 7.5 Hz, CH_3), 3.57-3.74 (m, 2H, CH_2), 4.19 (q, 2H, J = 7.5 Hz, CH_2), 5.73 (s, 1H, CH), 6.44 (t, 1H, J = 7.2 Hz, =CH), 7.08 (t, 1H, J = 4.9 Hz, NH), 7.24 (t, 1H, J = 7.9 Hz, H_{ar}), 7.37 (t, 1H, J = 8.1 Hz, H_{ar}), 7.49 (d, 1H, J = 8.1 Hz, H_{ar}), 7.69 (d, 1H, J = 7.9 Hz, H_{ar}), 10.63 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 14.0 (CH_3), 38.8 (CH_2), 56.9 (CH), 62.7 (CH_2), 113.0 (CH), 116.6 (C), 121.6 (CH), 121.7 (CH), 124.4 (C), 124.8 (CH), 125.7 (CH), 130.3 (C), 136.6 (C), 137.0 (C), 165.1 (CO), 168.2 (CO); ms: *m/z* 319 $(M+H)^+$ for ^{35}Cl, 321 $(M+H)^+$ for ^{37}Cl.

Anal. Calcd. for $C_{16}H_{15}ClN_2O_3$: C, 60.29; H, 4.74; N, 8.79. Found: C, 60.00; H, 4.65; N, 8.67.

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