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Ring closure metathesis of indole 2-carboxylic acid allylamide derivatives

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Abstract—Ring-closing metathesis of 3-allyl- or 3-vinylindole-2-carboxylic derivatives gave access to fused seven- to eight-membered lactams; 1-allylindole-2-carboxylic homoallylamide afforded the nine-membered lactam. The reactivity of 1,3-disubstituted-2-carboxylic acid derivatives was also investigated.

1. Introduction

In the field of indole chemistry, large fused lactams have been scarcely reported.[1] We can mention Fischer indolisation of hydroxymethylene lactam affording saturated indolactam[2] and cyclic indolic urea.[3] Fused saturated lactams in the 2,3- or 1,2-position have also been described.[4] Recently, ring-closing metathesis (RCM) reactions on indole nucleus were reported to give tripeptide moiety linked through a carbazole[5] or mitosene skeleton.[6]

As reported in the literature, RCM is a highly efficient synthetic method for the construction of functionalised carbocycles and heterocycles.[7] Ring sizes from five through to complex macrocycles have been prepared.[8] Unsaturated lactam derivatives[9,10] or fused bicyclic lactams have been obtained by RCM.[11]

For our part, we became interested in the development of new synthetic routes to fused indolactam derivatives **A** and **B** (Fig. 1). These compounds could constitute innovating scaffolds in medicinal chemistry (i.e. CDK inhibitors).[12] We present, here, a detailed report of our work.

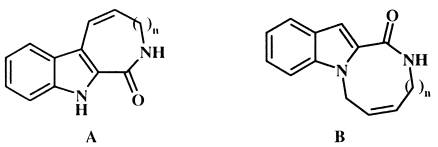

Figure 1.

Keywords: indole; cyclisation; lactam; ruthenium metathesis.

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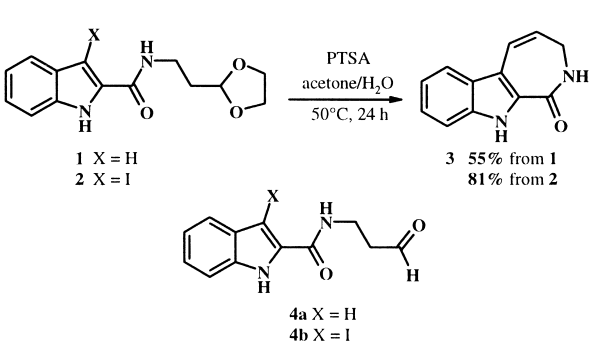
2. Results and discussion

A first efficient synthetic route to indolactam **A** was developed in our laboratory. Thus, the acetal deprotection of compounds **1** or **2** was carried out with *p*-toluenesulfonic acid in a mixture of acetone/water, the lactam derivative **3** was directly obtained in good yield and not the aldehydes **4** (Scheme 1). It should be noted that the isolated aldehydes **4** in the same experimental conditions did not cyclise and were found stable. This behavior was not observed in the pyrrole series.[13]

In order to synthesise both indolactam series **A** and **B**, a second approach based on the ring-closure metathesis of olefin compounds such as **5** or **6** was investigated.

Compound **5** was prepared in four steps from commercially available indole-2-carboxylic acid **7** which was first iodinated in the 3-position with iodine in basic medium (93% yield).[14] Coupling reaction between the iodide derivative and allylamine in the presence of EDCI afforded the 3-iodoindole-2-allylamide in 88% yield. The two nitrogen atoms were protected simultaneously (90% yield)



1 X = H
2 X = I

3 55% from **1**
81% from **2**

4a X = H
4b X = I

Scheme 1.

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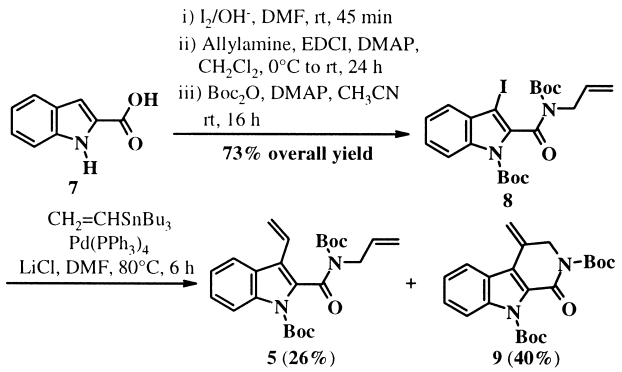


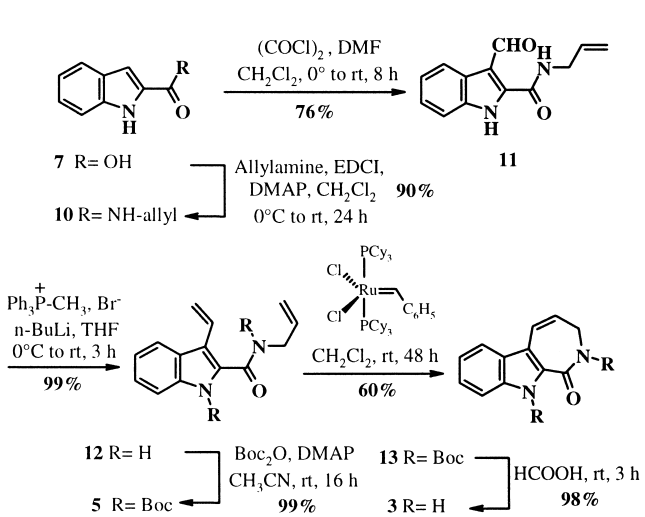
Scheme 2.

to give compound **8**. Attempts of Stille reaction on free nitrogen atom derivative failed. Finally, Stille reaction between **8**, tributylvinyltin and lithium chloride was carried out in DMF at 80°C in the presence of a catalytic amount of *tetrakis*(triphenylphosphine)palladium(0) to afford **5** in only 26% yield. The major compound **9** (40% yield) was obtained from a competitive intramolecular Heck reaction (Scheme 2).

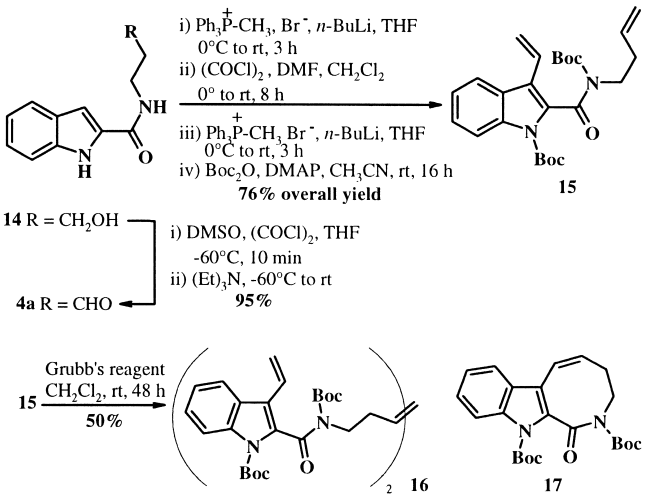
The low yield obtained for **5** led us to investigate an alternative and more effective synthetic route.

Thus, indole-2-allylamide **10** was treated under standard Vilsmeier–Haack conditions ($POCl_3$/DMF) to give aldehyde **11** in only 10% yield.[15] The substitution of $POCl_3$ by oxalyl chloride improved the yield (76%). Preparation of **12** was achieved in 99% yield using methyltriphenyl-phosphonium bromide in the presence of *n*-BuLi. Boc protection of **12** was carried out in the presence of Boc_2O and DMAP in acetonitrile to lead quantitatively to **5**. First attempt of RCM with Grubb's catalyst (10 mol%) in a 0.005 M solution of **5** afforded successfully the desired seven-membered lactam **13** in 60% yield. Formic acid treatment of **13** at room temperature for 3 h afforded **3** in 98% yield (Scheme 3).

Ring-size effects on the RCM was investigated with homoallylamide **15** prepared from alcohol **14**. Swern



Scheme 3.

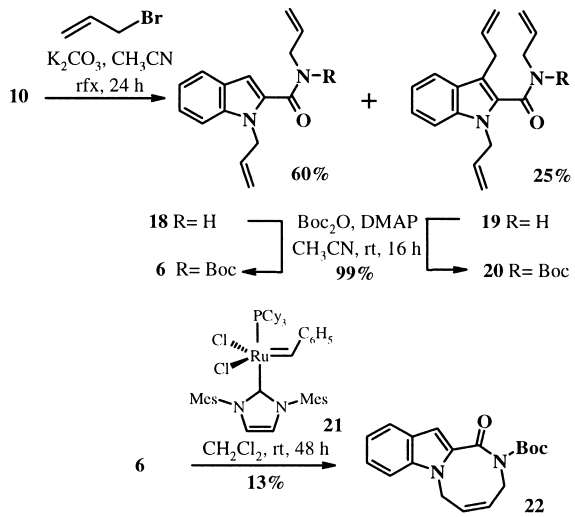


Scheme 4.

oxidation of **14** afforded aldehyde **4a** which was first transformed into the homoallylamide by methylenation with methyltriphenylphosphonium bromide in the presence of *n*-BuLi (99% yield). As previously described, the 3-vinyl group was then introduced in a two-step sequence and the nitrogen atoms were protected to give the derivative **15** in 76% overall yield. The analogous eight-membered compound **17** was not obtained by RCM from **15** with Grubb's catalyst in high dilution (0.005 M). The homo-coupled derivative **16** was only isolated in 25% yield. Higher dilution greatly slows down the reaction without formation of the cyclic derivative **17** (Scheme 4).

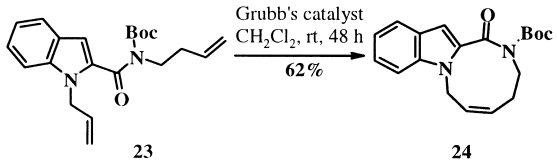
The formation of fused lactams **B** was also achieved (Scheme 5).

2-Allylamide **10** was reacted with allyl bromide in refluxing acetonitrile to afford respectively, **18** in 60% yield and 1,3-diallylindole 2-allylamide derivative **19** in 25% yield. Compounds **18** and **19** were quantitatively transformed into the Boc derivatives **6** and **20**. Diallyl derivative **6** was treated with the Grubb's catalyst, no reaction occurred. Using the more reactive catalyst **21**,[16] the eight-membered



Scheme 5.

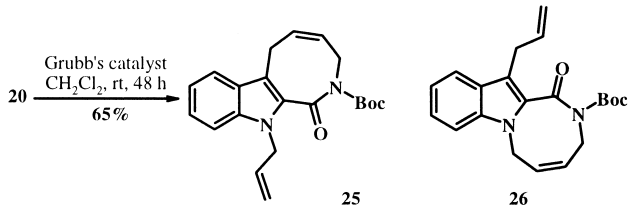
lactam **22** was generated in low yield (13%). In contrast, compound **23**, with an additional methylene unit on the ethylenic amide chain, when subjected to RCM conditions afforded the nine-membered lactam **24** in satisfactory yield (Scheme 6).



23 24

Scheme 6.

Similarly, the triallyl derivative **20** was submitted to RCM reaction (Grubb's catalyst). In this case, two isomeric lactam derivatives may be obtained (**25** or **26**). In our hands, the cyclisation exclusively led to the lactam **25** (64% yield) where the new ring is linked between carbons 2 and 3 of the indolic moiety (Scheme 7). It is interesting to point out that the cyclisation behavior of **6** compared to **20** was totally different.



25 26

Scheme 7.

3. Conclusion

We have obtained in a straightforward manner indolic fused lactams from indole-2-carboxylic acid. The synthetic potential of these compounds are under investigation.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded at 300°K on a Bruker Avance DPX 250 spectrometer. Chemical shifts are reported in parts per million (ppm) and referenced to TMS. Coupling constants are expressed in Hertz (Hz). Melting points were determined using a Büchi SMP-20 melting point apparatus and were uncorrected. IR absorption were recorded on a Perkin–Elmer PARAGON 1000 PC and values are reported in cm^{-1}. MS spectra (Ion Spray) were performed on a Perkin Elmer Sciex PI 300. Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F_{254}). Spots were visualised by UV light at 254 nm. Column chromatography were performed using silica gel 60 (0.063–0.200 mm, Merck). Organic solvents were purified by standard procedures. Anhydrous solvents or reagents were transferred via syringe.

4.1.1. *N*-[2-(1,3-Dioxolan-2-yl)ethyl-1*H*-indole-2-carboxamide (1). DMAP (1.25 g, 10.2 mmol), indole-2-carboxylic acid (1.0 g, 6.2 mmol) and EDCI (1.31 g, 6.8 mmol) were added to a solution of 2-(1,3-dioxolan-2-yl)-1-ethanamine[17] (790 mg, 6.8 mmol) in dichloromethane (50 mL) at 0°C. The mixture was stirred at 0°C for 4 h and then at room temperature for 20 h. After evaporation of the solvent, water (50 mL) was added and a solid was precipitated and filtered. The solid was dissolved in ethyl acetate (50 mL) and stirred for 10 min. in the presence of a few drops of 10% HCl. After extraction, the organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc 1:1) to give **1** (1.20 g, 74%) as a white solid. Mp 178–179°C (EtOAc/petroleum ether); IR (KBr) ν 3366 (NH), 3234 (NH), 1646 (CO) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 1.86–1.94 (m, 2H, CH_2), 3.37–3.43 (m, 2H, CH_2), 3.77–3.94 (m, 4H, OCH_2), 4.90 (t, 1H, CH, J=5.0 Hz), 7.05–7.46 (m, 3H, H_{ar}), 7.45 (d, 1H, H_{ar}, J=7.8 Hz), 7.62 (d, 1H, H_{ar}, J=7.8 Hz), 8.50 (s, 1H, NH), 11.57 (s, 1H, NH); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 34.0 (CH_2), 35.0 (CH_2), 64.9 ($2CH_2$), 102.8 (CH), 103.0 (CH), 112.8 (CH), 120.2 (CH), 122.0 (CH), 123.8 (CH), 127.7 (C), 132.4 (C), 136.9 (C), 161.6 (CO); MS m/z 261 $(M+H)^+$; Anal. calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.28; H, 6.07; N, 10.89.

4.1.2. *N*-[2-(1,3-Dioxolan-2-yl)ethyl]-3-iodo-1*H*-indole-2-carboxamide (2). Following the same procedure, the compound **2** was prepared from 3-iodoindole-2-carboxylic acid[14] in 80% yield. Mp 137–138°C (EtOAc/petroleum ether); IR (KBr) ν 3367 (NH), 3224 (NH), 1638 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.09–2.18 (m, 2H, CH_2), 3.78–3.82 (m, 2H, CH_2), 3.93–4.14 (m, 4H, OCH_2), 5.13 (t, 1H, CH, J=4.1 Hz), 7.21 (t, 1H, H_{ar}, J=7.9 Hz), 7.33 (t, 1H, H_{ar}, J=7.9 Hz), 7.44–7.49 (m, 2H, H_{ar}), 7.69 (s, 1H, NH), 10.22 (s, 1H, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.6 (CH_2), 34.8 (CH_2), 58.2 (C), 65.5 ($2CH_2$), 103.3 (CH), 112.3 (CH), 121.3 (CH), 122.5 (CH), 125.5 (CH), 130.6 (C), 131.0 (C), 135.6 (C), 160.6 (CO); MS m/z 387 $(M+H)^+$; Anal. calcd for $C_{14}H_{15}IN_2O_3$: C, 43.54; H, 3.92; N, 7.25. Found: C, 43.85; H, 4.06; N, 7.34.

4.1.3. 3,10-Dihydroazepino[3,4-*b*]indol-1(2*H*)-one (3). *p*-Toluenesulfonic acid monohydrate (235 mg, 1.24 mmol) was added to a solution of compound **2** (480 mg, 1.24 mmol) in water (3 mL) and acetone (3 mL). The final mixture was stirred at 50°C for 24 h. After evaporation of the solvent, the residue was dissolved in ethyl acetate (10 mL) and washed with a 2% aqueous solution of sodium hydroxide. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent: EtOAc) to give **3** (200 mg, 81%) as a white gum. IR (film) ν 3356 (NH), 3217 (NH), 1644 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.70 (t, 2H, CH_2, J=5.8 Hz), 5.95–6.05 (m, 1H, =CH), 6.84 (t, 1H, NH, J=5.8 Hz), 7.13–7.36 (m, 3H, H_{ar} and =CH), 7.50 (d, 1H, H_{ar}, J=7.9 Hz), 7.73 (d, 1H, H_{ar}, J=7.9 Hz), 10.39 (s, 1H, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.9 (CH_2), 112.1 (CH), 118.3 (C), 120.1 (CH), 120.6 (CH), 124.1 (CH), 124.4 (C), 125.3 (CH), 125.8 (CH), 131.0 (C), 134.8 (C), 163.2 (CO); MS m/z 199 $(M+H)^+$; Anal. calcd for

$C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 73.03; H, 5.20; N, 14.27.

According to the same procedure, compound **1** gave **3** in 51% yield.

4.1.4. 1*H*-Indole-2-carboxylic acid (3-oxopropyl)amide (4a). DMSO (3.19 mL, 41.24 mmol) was added dropwise to a solution of oxalyl chloride (1.81 mL, 20.62 mmol) in THF (30 mL) at −78°C. After stirring for 30 min, the compound **14** (3.0 g, 13.74 mmol) dissolved in THF (20 mL) was added dropwise. The mixture was stirred for 10 min. at −60°C then, triethylamine (4.79 mL, 34.36 mmol) was added and the mixture allowed to return at room temperature. Water was added and the mixture was extracted with ethyl acetate (2×50 mL). The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc 1:1) to afford **4a** (2.82 g, 95%) as a white solid. Mp 139–140°C (EtOAc/petroleum ether); IR (KBr) ν 3401 (NH), 3331 (NH), 1715 (CO), 1620 (CO) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 2.74–2.80 (td, 2H, CH_2, J=1.8, 6.3 Hz), 3.60–3.67 (q, 2H, CH_2, J=6.3 Hz), 7.05–7.26 (m, 3H, H_{ar}), 7.48 (d, 1H, H_{ar}, J=8.2 Hz), 7.66 (d, 1H, H_{ar}, J=8.2 Hz), 8.62 (t, 1H, NH, J=5.3 Hz), 9.77 (d, 1H, CHO, J=1.8 Hz), 11.62 (s, 1H, NH); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 33.9 (CH_2), 44.2 (CH_2), 103.3 (CH), 113.1 (CH), 120.5 (CH), 122.3 (CH), 124,1 (CH), 128.0 (C), 132,4 (C), 137.2 (C), 162.1 (CO), 203.1 (CO); MS *m/z* 217 $(M+H)^+$; Anal. calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.87; H, 5.46; N, 12.79

4.1.5. *tert*-Butyl 2-{[(allyl-*tert*-butoxycarbonyl)amino]-carbonyl}-3-vinyl-1*H*-indole-1-carboxylate (5). A solution of compound **8** (200 mg, 0.58 mmol) and vinyltributyltin (166 μL, 0.87 mmol) in DMF (5 mL) was added to a suspension of freshly prepared *tetrakis*-(triphenylphosphine)palladium(0) (26 mg, 0.03 mmol) and lithium chloride (45 mg, 1.51 mmol) in DMF (5 mL). The mixture was heated at 80°C for 6 h. After evaporation of the solvent, the residue was dissolved in ethyl acetate and washed twice with water. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc 95:5) to afford **5** as a colorless gum (40 mg, 26%) then **9** (60 mg, 40%). IR (film) ν 1755 (CO), 1723 (CO), 1642 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.08 (s, 9H, $C(CH_3)_3$), 1.61 (s, 9H, $C(CH_3)_3$), 4.44 (dd, 1H, CH_2, J=5.7, 15.2 Hz), 4.63 (dd, 1H, CH_2, J=6.0, 15.2 Hz), 5.22–5.42 (m, 3H, =CH_2), 5.77 (dd, 1H, =CH_2, J=1.2, 17.7 Hz), 5.73–5.81 (m, 1H, =CH), 6.58 (dd, 1H, =CH, J=6.2, 11.5 Hz), 7.28–7.39 (m, 2H, H_{ar}), 7.79 (d, 1H, H_{ar}, J=8.0 Hz), 8.16 (d, 1H, H_{ar}, J=8.0 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 27.5 ($3CH_3$), 28.0 ($3CH_3$), 46.5 (CH_2), 83.4 (C), 84.8 (C), 107.4 (CH), 115.6 (CH), 116.5 (C), 117.2 (CH_2), 118.0 (CH_2), 120.5 (CH), 123.4 (CH), 125.4 (CH), 126.3 (CH), 127.4 (C), 132.5 (CH), 135.3 (C), 148.9 (CO), 151.7 (CO), 164.2 (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, 67.92; H, 7.24; N, 6.70.

4.1.6. *tert*-Butyl *N*-allyl-*N*-[(1-allyl-1*H*-indol-2-yl)carbonyl]carbamate (6). According to the procedure for the synthesis of **8** (third step), the compound **6** was prepared from **18** in 99% yield as a colorless gum. IR (film) ν 1737 (CO), 1667 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.18 (s, 9H, $C(CH_3)_3$), 4.37 (dd, 2H, CH_2, J=1.2, 5.6 Hz), 4.99 (dd, 2H, CH_2, J=1.5, 5.6 Hz), 5.00–5.33 (m, 4H, =CH_2), 5.89–6.06 (m, 2H, =CH), 6.80 (s, 1H, H_{ar}), 7.10–7.16 (m, 1H, H_{ar}), 7.24–7.37 (m, 2H, H_{ar}), 7.61 (d, 1H, H_{ar}, J=8.1 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 27.7 ($3CH_3$), 47.0 (CH_2), 48.0 (CH_2), 83.1 (C), 107.4 (CH), 110.6 (CH). 117.1 (CH_2), 117.3 (CH_2), 120.7 (CH), 122.3 (CH), 124.6 (CH), 126.7 (C), 133.2 (CH), 133.5 (C), 133.7 (CH), 138.4 (C), 153.7 (C), 165.9 (CO); MS *m/z* 341 $(M+H)^+$; Anal. calcd for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23. Found: C, 70.34; H, 7.20; N, 8.36.

4.1.7. *tert*-Butyl 2-{[(allyl-*tert*-butoxycarbonyl)amino]-carbonyl}-3-iodo-1*H*-indole-1-carboxylate (8). *3-Iodo-1H-indole-2-carboxylic acid allylamide*. According to the procedure for the synthesis of **1**, the amide was prepared from 3-iodoindole-2-carboxylic acid[14] and allylamine in 88% as a yellow solid (300 mg, 88%). Mp 147–148°C (EtOAc/petroleum ether); IR (KBr) ν 3362 (NH), 3255 (NH), 1622 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.20–4.25 (m, 2H, CH_2), 5.26 (dd, 1H, =CH_2, J=2.5, 12.5 Hz), 5.29 (dd, 1H, =CH_2, J=2.5, 17.5 Hz), 5.97–6.03 (m, 1H, =CH), 7.31–7.49 (m, 5H, NH and H_{ar}), 10.09 (br s, 1H, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 42.6 (CH_2), 59.2 (C), 112.8 (CH), 117.2 (CH_2), 121.9 (CH), 123.0 (C), 126.0 (CH), 130.7 (C), 133.9 (CH), 136.2 (C), 145.1 (CH), 161.1 (CO); MS *m/z* 327 $(M+H)^+$; Anal. calcd for $C_{12}H_{11}IN_2O$: C, 44.19; H, 3.40; N, 8.59. Found: C, 44.46; H, 3.03; N, 8.76.

tert-Butyl 2-{[(allyl-tert-butoxycarbonyl)amino]carbonyl}-3-iodo-1H-indole-1-carboxylate (8). A solution of 3-iodo-1*H*-indole-2-carboxylic acid allyl amide (400 mg, 1.23 mmol), Boc_2O (640 mg, 2.95 mmol) and DMAP (18 mg, 0.12 mmol) in acetonitrile (10 mL) was stirred at room temperature for 16 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc 95:5) to yield **8** as a colorless gum (550 mg, 90%). IR (film) ν 1760 (CO), 1730 (CO), 1662 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.14 (s, 9H, $C(CH_3)_3$), 1.60 (s, 9H, $C(CH_3)_3$), 4.39 (dd, 1H, CH_2, J=5.6, 13.7 Hz), 4.65 (dd, 1H, CH_2, J=6.0, 13.7 Hz), 5.26 (dd, 1H, =CH_2, J=1.1, 10.0 Hz), 5.43 (dd, 1H, =CH_2, J=1.1, 16.9 Hz), 5.90–6.01 (m, 1H, =CH), 7.31–7.40 (m, 3H, H_{ar}), 8.09–8.13 (m, 1H, H_{ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 27.7 ($3CH_3$), 28.1 ($3CH_3$), 46.7 (CH_2), 65.5 (C), 84.7 (C), 85.4 (C), 115.6 (CH), 118.1 (CH_2), 121.8 (CH), 122.8 (C), 123.9 (CH), 126.3 (CH), 131.0 (C), 132.7 (CH), 134.7 (C), 152.5 (CO), 164.0 (2CO); MS *m/z* 527 $(M+H)^+$; Anal. calcd for $C_{22}H_{27}IN_2O_5$: C, 50.20; H, 5.17; N, 5.32. Found: C, 49.87; H, 5.30; N, 5.45.

4.1.8. Di-(*tert*-butyl) 4-methylene-1-oxo-3,4-dihydro-1*H*-β-carboline-2,9-dicarboxylate (9). Colorless gum. IR (film) ν 1760 (CO), 1720 (CO), 1668 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.58 (s, 9H, $C(CH_3)_3$), 1.69 (s, 9H, $C(CH_3)_3$), 4.65 (s, 2H, CH_2), 5.52 (s, 1H, =CH_2), 5.84 (s, 1H, =CH_2), 7.32–7.51 (m, 2H, H_{ar}), 7.85 (d, 1H, H_{ar}, J=7.5 Hz), 7.07 (d, 1H, H_{ar}, J=7.5 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 27.8 ($3CH_3$), 28.2 ($3CH_3$), 51.5

(CH_2), 83.4 (C), 85.0 (C), 114.6 (CH_2), 114.9 (CH), 121.9 (CH), 123.3 (C), 123.9 (CH), 126.9 (C), 128.3 (CH), 129.1 (C), 133.0 (C), 140.1 (C), 149.3 (CO), 152.2 (CO), 156.0 (CO); MS *m/z* 399 $(M+H)^+$; Anal. calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.01; H, 6.43; N, 6.92.

4.1.9. *N*-Allyl 1*H*-indole-2-carboxamide (10). According to the procedure for the synthesis of **8** (second step), the compound **10** was prepared from indole-2-carboxylic acid and allylamine in 90% yield as a solid. Mp 170–171°C (CH_2Cl_2); IR (KBr) ν 3348 (NH), 3237 (NH), 1631 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.14–4.19 (m, 2H, CH_2), 5.24 (dd, 1H, $=CH_2$, J=1.3, 11.2 Hz), 5.30 (dd, 1H, $=CH_2$, J=1.3, 17.2 Hz), 5.90–6.03 (m, 1H, =CH), 6.37 (br s, 1H, NH), 6.88 (d, 1H, H_{ar}, J=1.8 Hz), 7.14 (t, 1H, H_{ar}, J=7.8 Hz), 7.29 (t, 1H, H_{ar}, J=7.8 Hz), 7.46 (d, 1H, H_{ar}, J=7.8 Hz), 7.65 (d, 1H, H_{ar}, J=7.8 Hz), 10.00 (br s, 1H, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 43.9 (CH_2), 103.9 (CH), 114.0 (CH), 118.7 (CH_2), 122.4 (CH), 123.7 (CH), 126.3 (CH), 129.4 (C), 132.3 (C), 135.8 (C), 138.4 (CH), 163.6 (CO); MS *m/z* 201 $(M+H)^+$; Anal. calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.34; H, 5.91; N, 14.10.

4.1.10. *N*-Allyl 3-formyl-1*H*-indole-2-carboxamide (11). Oxalyl chloride (160 μL, 1.85 mmol) was added dropwise to an ice-cooled solution of DMF (2 mL) and dichloromethane (10 mL), then **10** (346 mg, 1.73 mmol) was added and the mixture was stirred at room temperature for 8 h. The solvent was evaporated and the residue was dissolved in ethyl acetate (10 mL) and twice washed with water (5 mL). The organic layer was dried over $MgSO_4$ and evaporated in vacuo.The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc 6:4) to afford **11** (300 mg, 76%) as a solid. Mp 183–184°C (EtOAc/petroleum ether); IR (KBr) ν 3329 (NH), 3212 (NH), 2720 (CHO), 1695 (CHO), 1631 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.30–4.34 (m, 2H, CH_2), 5.31 (dd, 1H, CH_2, J=1.2, 10.0 Hz), 5.45 (dd, 1H, CH_2, J=1.2, 15.2 Hz), 6.05–6.16 (m, 1H, =CH), 7.38–7.49 (m, 2H, H_{ar}), 7.71 (d, 1H, H_{ar}, J=7.5 Hz), 8.07 (d, 1H, H_{ar}, J=7.5 Hz), 10.39 (s, 1H, CHO), 11.23 (br s, 1H, NH), 10.96 (br s, 1H, NH); ^{13}C NMR (62.90 Hz, $CDCl_3$) δ 42.8 (CH_2), 113.2 (C), 113.9 (CH), 117.1 (CH_2), 118.7 (CH), 124.0 (CH), 125.8 (CH), 129.7 (C), 133.7 (CH), 135.1 (C), 135.3 (C), 156.0 (CO), 186.1 (CO); MS *m/z* 229 $(M+H)^+$; Anal. calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.13; H, 5.44; N, 12.36.

4.1.11. *N*-Allyl 3-vinyl-1*H*-indole-2-carboxamide (12). *n*-Butyllithium (2.2 mL, 5.5 mmol, 2.5 M in hexane) was added dropwise to an ice-cooled solution of methyltriphenylphosphonium bromide (1.97 g, 5.52 mmol) in THF (5 mL). The mixture was stirred at 0°C for 1 h then at room temperature for 2 h. Aldehyde **11** (100 mg, 0.44 mmol) in THF (1 mL) was added and the mixture stirred at room temperature for 2 h. The solvent was evaporated. The residue was dissolved in ethyl acetate (20 mL) and washed twice with water. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc 8:2) to afford **12** (100 mg, 99%) as a yellow solid. Mp 105–106°C (EtOAc/petroleum ether); IR (KBr) ν 3332 (NH), 3235 (NH), 1622 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.23–4.44 (m, 2H, CH_2), 5.20–5.35 (m, 2H, CH_2), 5.67 (dd, 1H, $=CH_2$, J=1.9, 11.2 Hz), 5.86 (dd, 1H, $=CH_2$, J=1.9, 17.6 Hz), 5.91–6.07 (m, 1H, =CH), 6.06 (s, 1H, NH), 7.06–7.21 (m, 2H, =CH and H_{ar}), 7.26–7.34 (m, 1H, H_{ar}), 7.46 (d, 1H, H_{ar}, J=8.2 Hz), 7.81 (d, 1H, H_{ar}, J=8.2 Hz), 10.30 (br s, 1H, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 41.2 (CH_2), 111.2 (CH), 114.5 (CH), 115.7 (CH_2), 119.0 (C), 119.4 (CH_2), 119.6 (CH), 119.9 (CH), 126.5 (CH), 129.5 (C), 132.7 (CH), 134.8 (C), 137.7 (C), 161.4 (CO); MS *m/z* 227 $(M+H)^+$; Anal. calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.69; H, 6.28; N, 12.56.

Boc protection, as reported for **8**, of **12** afforded **5** in 99% yield.

4.1.12. Di-(*tert*-butyl) 1-oxo-1,3-dihydroazepino[3,4-*b*]-indole-2,10-dicarboxylate (13). Grubb's catalyst (27 mg, 0.03 mmol) was added, under nitrogen, to a solution of **5** (140 mg, 0.33 mmol) in dichloromethane (7 mL). The solution was stirred at room temperature for 48 h. The solvent was evaporated. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc 9:1) to yield **13** (78 mg, 60%) as a colorless gum. IR (film) ν 1740 (CO), 1715 (CO), 1656 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.55 (s, 9H, $C(CH_3)_3$), 1.64 (s, 9H, $C(CH_3)_3$), 4.29 (br s, 2H, CH_2), 6.55–6.62 (m, 1H, =CH), 7.19 (d, 1H, =CH, J=9.5 Hz), 7.27–7.34 (m, 1H, H_{ar}), 7.44–7.51 (m, 1H, H_{ar}), 7.67 (d, 1H, H_{ar}, J=8.0 Hz), 8.10 (d, 1H, H_{ar}, J=8.0 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 28.3 ($3CH_3$), 28.5 ($3CH_3$), 43.8 (CH_2), 83.8 (C), 85.1 (C), 115.0 (CH), 120.7 (CH), 123.7 (CH), 124.1 (C), 125.7 (CH), 126.2 (C), 128.3 (CH), 131.5 (CH), 132.4 (C), 138.5 (C), 149.7 (CO), 151.7 (CO), 159.6 (CO); MS *m/z* 399 $(M+H)^+$; Anal. calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.67; H, 6.45; N, 7.04.

Compound **13** was stirred in formic acid for 3 h at room temperature to afford **3** in 98% yield.

4.1.13. *N*-(3-Hydroxypropyl)-1*H*-indole-2-carboxamide (14). According to the procedure for the synthesis of **8** (second step), the compound **14** was prepared from indole-2-carboxylic acid and 3-aminopropan-1-ol in 74% yield as a solid. Mp 155–156°C (CH_2Cl_2); IR (KBr) ν 3430–3410 (OH, NH), 1625 (CO) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 1.66–1.77 (m, 2H, CH_2), 3.32–3.40 (m, 2H, CH_2), 3.47–3.54 (m, 2H, CH_2), 4.52 (br s, 1H, OH), 7.03 (t, 3H, H_{ar}, J=8.2 Hz), 7.10 (s, 1H, H_{ar}), 7.43 (d, 1H, H_{ar}, J=8.2 Hz), 7.61 (d, 1H, H_{ar}, J=8.2 Hz), 8.45 (t, 1H, NH, J=5.3 Hz), 12.02 (br s, 1H, NH); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 33.4 (CH_2), 39.4 (CH_2), 59.4 (CH_2), 103.0 (CH), 113.1 (CH), 120.5 (CH), 122.3 (CH), 124,0 (CH), 128.0 (C), 132,7 (C), 137.2 (C), 162.0 (CO); MS *m/z* 219 $(M+H)^+$; Anal. calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.80; H, 6.41; N, 12.73.

4.1.14. *tert*-Butyl 2-{[(but-3-enyl-*tert*-butoxycarbonyl)-amino]carbonyl}-3-vinyl-1*H*-indole-1-carboxylate (15). *1H-indole-2-carboxylic acid (but-3-enyl)amide*. According to the procedure for the synthesis of **12**, the amide was

prepared from **4** in 99% yield as a white solid. Mp 157–158°C (EtOAc/petroleum ether); IR (KBr) ν 3420 (NH), 3257 (NH), 1636 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.41 (q, 2H, CH_2, J=6.8 Hz), 3.58 (q, 2H, CH_2, J=6.8 Hz), 5.16 (dd, 1H, =CH_2, J=1.7, 10.0 Hz), 5.26 (dd, 1H, =CH_2, J=1.0, 18.5 Hz), 5.80–5.87 (m, 1H, =CH), 6.36 (br s, 1H, NH), 6.80 (d, 1H, H_{ar}, J=1.2 Hz), 7.14 (t, 1H, H_{ar}, J=8.0 Hz), 7.30 (t, 1H, H_{ar}, J=8.0 Hz), 7.45 (d, 1H, H_{ar}, J=8.0 Hz), 7.64 (d, 1H, H_{ar}, J=8.0 Hz), 9.42 (br s, 1H, NH); ^{13}C NMR (62,90 MHz, $CDCl_3$) δ 34.2 (CH_2), 38.9 (CH_2), 102.0 (CH), 112.5 (CH), 118.0 (CH_2), 121.0 (CH), 122.2 (CH), 124.8 (CH), 128.0 (C), 131.2 (C), 135.5 (CH), 136.8 (C), 162.1 (CO); MS m/z 215 $(M+H)^+$; Anal. calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.65; H, 6.45; N, 13.22.

3-Formyl-1H-indole-2-carboxylic acid (but-3-enyl)amide. According to the procedure for the synthesis of **11**, the aldehyde was prepared from 1*H*-indole-2-carboxylic acid (but-3-enyl)amide in 76% yield as a solid. Mp 173–174°C (EtOAc/petroleum ether); IR (KBr) ν 3364 (NH), 3258 (NH), 2710 (CHO), 1695 (CHO), 1634 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.52 (q, 2H, CH_2, J=6.7 Hz), 3.60 (q, 2H, CH_2, J=6.2 Hz), 5.15 (dd, 1H, =CH_2, J=1.7, 11.7 Hz), 5.21 (dd, 1H, =CH_2, J=1.7, 17.2 Hz), 5.82–6.01 (m, 1H, =CH), 7.34–7.64 (m, 2H, H_{ar}), 7.65 (d, 1H, H_{ar}, J=8.0 Hz), 8.03 (d, 1H, H_{ar}, J=8.0 Hz), 10.34 (s, 1H, CHO), 11.01 (br s, 1H, NH), 11.49 (br s, 1H, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 33.9 (CH_2), 36.0 (CH_2), 113.1 (C), 114.0 (CH), 117.6 (CH_2), 118.6 (CH), 123.9 (CH), 125.7 (CH), 129.7 (C), 135,3 (CH), 135.4 (C), 135.5 (C), 160.1 (CO), 185.9 (CHO); MS m/z 243 $(M+H)^+$; Anal. calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.60; H, 5.93; N, 11.39.

3-Vinyl-1H-indole-2-carboxylic acid (but-3-enyl)amide. According to the procedure for the synthesis of **12**, the vinyl derivative was prepared from 3-formyl-1*H*-indole-2-carboxylic acid (but-3-enyl)amide in quantitative yield as a solid. Mp 97–98°C (EtOAc/petroleum ether); IR (KBr) ν 3410 (NH), 3258 (NH), 1636 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.40 (q, 2H, CH_2, J=6.7 Hz), 3.60 (q, 2H, CH_2, J=6.2 Hz), 5.14–5.22 (m, 2H, =CH_2), 5.64 (dd, 1H, =CH_2, J=1.7, 11.2 Hz), 5.77–5.86 (m, 2H, =CH_2, =CH), 6.44 (s, 1H, NH), 6.96–7.08 (m, 1H, =CH), 7.17 (td, 1H, H_{ar}, J=1.0, 8.2 Hz), 7.30 (td, 1H. H_{ar}, J=1.0, 8.2 Hz), 7.42 (d, 1H, H_{ar}, J=8.2 Hz), 7.77 (d, 1H, H_{ar}, J=8.2 Hz), 9.40 (br s, 1H, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 33.8 (CH_2), 39.0 (CH_2), 112.1 (CH), 115.3 (C), 117.8 (CH), 120.2 (CH). 120.8 (CH_2), 120.9 (CH_2), 124.8 (CH), 126.9 (C), 127.5 (C), 128.7 (CH), 135.3 (CH), 135.7 (C), 162.3 (CO); MS m/z 241 $(M+H)^+$. Anal. calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.65; H, 6.87; N, 11.79.

*tert-Butyl 2-{[(but-3-enyl-tert-butoxycarbonyl)amino] carbonyl}-3-vinyl-1H-indole-1-carboxylate (**15**)*. According to the procedure for the synthesis of **5** from **12**, compound **15** was prepared from 3-vinyl-1*H*-indole-2-carboxylic acid (but-3-enyl)amide in 98% yield as a gum. IR (film) ν 1748 (CO), 1740 (CO), 1680 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.07 (s, 9H, $C(CH_3)_3$), 1.61 (s, 9H, $C(CH_3)_3$), 2.49 (q, 2H, CH_2, J=6.8 Hz), 3.82–3.88 (m, 1H, CH_2), 4.08–4.14 (m, 1H, CH_2), 5.14 (dd, 1H, CH_2, J=1.7, 11.2 Hz), 5.17 (dd, 1H, CH_2, J=1.7, 17.2 Hz), 5.39 (dd, 1H, CH_2, J=1.2, 11.5 Hz), 5.78 (dd, 1H, CH_2, J=1.2, 17.7 Hz), 5.81–6.02 (m, 1H, CH=), 6.57–6.64 (m, 1H, CH=), 7.27–7.36 (m, 2H, H_{ar}), 7.79 (d, 1H, H_{ar}, J=7.7 Hz), 8.15 (d, 1H, H_{ar}, J=7.7 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 27.5 ($3CH_3$), 28.1 ($3CH_3$), 32.8 (CH_2), 43.9 (CH_2), 83.3 (C), 84.8 (C), 115.6 (CH), 116.4 (C), 117.0 (CH_2), 117.1 (CH_2), 120.6 (CH), 123.5 (CH), 125.5 (CH), 126.6 (CH), 127.5 (C), 132.3 (C), 135.2 (CH), 135.3 (C), 149.0 (CO), 152.0 (CO), 162.3 (CO); MS m/z 441 $(M+H)^+$; Anal. calcd for $C_{25}H_{32}N_2O_5$: C, 68.16; H, 7.32; N, 6.36. Found: C, 68.47; H, 7.21; N, 6.25.

4.1.15. *tert*-Butyl 2-{[((*Z*)-6-[(*tert*-butoxycarbonyl)[(3-vinyl-1*H*-indol-2-yl)carbonyl]amino-3-hexenyl)amino] carbonyl}-3-vinyl-1*H*-indole-1-carboxylate (16). Grubb's catalyst (25 mg, 0.03 mmol) was added, under nitrogen, to a solution of **15** (120 mg, 0.27 mmol) in dichloromethane (6 mL). The final solution was stirred at room temperature for 48 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc 95:5) to afford **16** (58 mg, 50%) as a colorless gum. IR (film) ν 1755 (CO), 1732 (CO), 1672 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.09 (s, 18H, $C(CH_3)_3$), 1.61 (s, 18H, $C(CH_3)_3$), 2.48–2.62 (m, 4H, CH_2), 3.73–3.84 (m, 2H, CH_2), 4.02–4.16 (m, 2H, CH_2), 5.40 (dt, 2H, CH_2, J=1.2, 11.2 Hz), 5.60–5.67 (m, 2H, CH=), 5.78 (dd, 2H, CH_2, J=1.2, 17.9 Hz), 6.56–6.70 (m, 2H, CH=), 7.24–7.36 (m, 4H, H_{ar}), 7.80 (d, 2H, H_{ar}, J=7.7 Hz), 8.15 (d, 2H, H_{ar}, J=7.7 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 27.6 ($6CH_3$), 28.2 ($6CH_3$), 31.7 ($2CH_2$), 44.0 ($2CH_2$), 83.4 (2C), 84.9 (2C), 115.7 (2CH), 116.4 (2C), 117.2 ($2CH_2$), 120.6 (2CH), 123.5 (2CH), 125.5 (2CH), 126.7 (2CH), 127.6 (2C), 128.4 (2CH), 129.3 (2C), 132.4 (2C), 149.1 (2CO), 152.0 (2CO), 164.4 (2CO); MS m/z 854 $(M+H)^+$; Anal. calcd for $C_{48}H_{60}N_4O_{10}$: C, 67.59; H, 7.09; N, 6.57. Found: C, 67.33; H, 7.24; N, 6.48.

4.1.16. *N*-Allyl 1-allyl-1*H*-indole-2-carboxamide (18). A suspension of potassium carbonate (553 mg, 4.00 mmol), allyl bromide (208 μL, 2.40 mmol) and compound **10** (200 mg, 1.00 mmol) in acetonitrile (10 mL) was refluxed for 24 h. After evaporation of the solvent, the residue was dissolved in ethyl acetate (10 mL) and washed twice with water. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc 8:2) to afford **19** (50 mg, 25%) then **18** (120 mg, 60%) as white solids. Mp 92–93°C (EtOAc/petroleum ether); IR (KBr) ν 3242 (NH), 1625 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.07–4.12 (m, 2H, CH_2), 4.97 (dd, 1H, =CH_2, J=1.2, 17.2 Hz), 5.14 (dd, 1H, =CH_2, J=1.2, 10.2 Hz), 5.20–5.35 (m, 4H, =CH), 5.90–6.11 (m, 2H, =CH), 6.57 (br s, 1H, NH), 6.94 (s, 1H, H_{ar}), 7.17–7.23 (m, 1H, H_{ar}), 7.30–7.43 (m, 2H, H_{ar}), 7.66 (d, 1H, H_{ar}, J=7.8 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 41.9 (CH_2), 46.8 (CH_2), 104.4 (CH), 110.7 (CH), 116.0 (CH_2), 116.5 (CH_2), 120.6 (CH), 121.9 (CH), 124.2 (CH), 126.2 (C), 131.5 (C), 134.1 (CH), 134.2 (CH), 138.5 (C), 162.3 (CO); MS m/z 241 $(M+H)^+$; Anal. calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.27; H, 6.62; N, 11.79.

4.1.17. *N*-Allyl 1,3-diallyl-1*H*-indole-2-carboxamide (19). Yield 25%; Mp 73–74°C (EtOAc/petroleum ether); IR (KBr) ν 3274 (NH), 1629 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.70–3.73 (m, 2H, CH_2), 4.05–4.13 (m, 2H, CH_2), 4.89–5.30 (m, 8H, CH_2 and $=CH_2$), 5.88–5.92 (m, 3H, =CH), 6.34 (br s, 1H, NH), 7.12–7.18 (m, 1H, H_{ar}), 7.27–7.37 (m, 2H, H_{ar}), 7.60 (d, 1H, H_{ar}, J=8.0 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 29.1 (CH_2), 42.1 (CH_2), 46.8 (CH_2), 110.5 (CH_2), 113.9 (C), 116.0 (CH), 116.9 (CH), 120.1 (CH_2), 121.9 (C), 124.2 (CH), 127.0 (CH), 130.4 (C), 133.9 (CH), 134.3 (CH), 134.4 (CH), 137.5 (C), 137.8 (CH_2), 162.5 (CO); MS *m/z* 281 $(M+H)^+$; Anal. calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C 76.78; H, 7.35; N, 10.12.

4.1.18. *tert*-Butyl *N*-allyl-*N*-[(1,3-diallyl-1*H*-indol-2-yl) carbonyl]carbamate (20). According to the procedure for the synthesis of **8** (third step), compound **20** was prepared from **19** in quantitative yield as a gum. IR (film) ν 1741 (CO), 1629 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.14 (s, 9H, $C(CH_3)_3$), 3.50–3.56 (m, 2H, CH_2), 4.36–4.41 (m, 2H, CH_2), 4.73–4.81 (m, 2H, $=CH_2$), 4.97–5.19 (m, 6H, CH_2), 5.83–6.05 (m, 3H, =CH), 7.07–7.14 (m, 1H, H_{ar}), 7.22–7.33 (m, 2H, H_{ar}), 7.60 (d, 1H, H_{ar}, J=8.2 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 27.7 ($3CH_3$). 29.1 (CH_2), 47.3 (CH_2), 47.7 (CH_2), 83.4 (C), 110.3 (CH), 114.5 (C), 115.4 (CH_2), 117.4 (CH_2), 117.8 (CH_2), 119.9 (CH), 120,6 (CH), 123.9 (CH), 127.0 (C), 131.9 (C), 133.1 (CH), 133.8 (CH), 136.7 (CH), 137.1 (C), 152.8 (CO), 165.9 (CO); MS *m/z* 381 $(M+H)^+$; Anal. calcd for $C_{23}H_{28}N_2O_3$: C, 72.61; H, 7.42; N, 7.36. Found: C, 72.94; H, 7.29; N, 7.50.

4.1.19. *tert*-Butyl 1-oxo-4,7-dihydro-1*H*-[1,4]diazocino-[1,2-*a*]indole-2(3*H*)-carboxylate (22). A mixture of catalyst **21** (26 mg, 3.14×10^{-5} mol.) and compound **6** (107 mg, 3.14×10^{-4} mol) in dry dichloromethane (6 mL) was stirred under argon at room temperature for 48 h. After evaporation of the solvent, the residue was purified by two successive flash chromatographies (eluent: petroleum ether/EtOAc 9/1 then EtOAc/toluene 3:97) to afford **22** (13 mg, 13%) as a colorless solid. Mp 165–166°C (EtOAc/petroleum ether); IR (KBr) ν 1749 (CO), 1665 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.55 (s, 9H, $C(CH_3)_3$), 4.06 (d, 2H, CH_2, J=5.4 Hz), 4.87 (d, 2H, CH_2, J=5.4 Hz), 5.93 (dt, 1H, =CH, J=5.4, 11.5 Hz), 6.15 (dt, 1H, =CH, J=5.4, 11.5 Hz), 7.13 (s, 1H, H_{ar}), 7.13–7.19 (m, 1H, H_{ar}), 7.29–7.40 (m, 2H, H_{ar}), 7.67 (d, 1H, J=8.5 Hz, H_{ar}); ^{13}C MNR (62.90 MHz, $CDCl_3$) δ 28.1 ($3CH_3$), 41.7 (CH_2), 44.0 (CH_2), 82.2 (C), 108.5 (CH), 109.8 (CH), 120.9 (CH), 122.5 (CH), 125.3 (CH), 126.8 (C), 128.2 (CH), 130.7 (CH), 134.1 (C), 137.4 (C), 152.0 (C), 164.7 (C); MS *m/z* 313 $(M+H)^+$; Anal. calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.47; H, 6.29; N, 9.10.

4.1.20. *tert*-Butyl *N*-[(1-allyl-1*H*-indol-2-yl)carbonyl]-*N*-(but-3-enyl)carbamate (23). *1-Allyl N-(but-3-enyl)-1H-indole-2-carboxamide*. A mixture of potassium carbonate (263 mg, 2.05 mmol), sodium iodide (7 mg, 0.05 mmol), allyl bromide (213 μL, 2.46 mmol) and 1*H*-indole-2-carboxylic acid but-3-enylamide (200 mg, 0.51 mmol) in acetonitrile (10 mL) was refluxed for 48 h. After evaporation of the solvent, the residue was dissolved in ethyl acetate (10 mL) and washed twice with water. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc 8:2) to afford 1-allyl-*N*-(3-butenyl)-1*H*-indole-2-carboxamide (120 mg, 93%) as a white solid. Mp 72–73°C (EtOAc/petroleum ether); IR (KBr) ν 3234 (NH), 1626 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.37 (q, 2H, CH_2, J=6.7 Hz), 3.51 (q, 2H, CH_2, J=6.7 Hz), 4.93 (dd, 1H, $=CH_2$, J=1.2, 17.0 Hz), 5.07–5.22 (m, 5H, CH_2 and $=CH_2$), 5.78–5.89 (m, 1H, =CH), 5.94–6.07 (m, 1H, =CH), 6.26 (br s, 1H, NH), 6.82 (s, 1H, H_{ar}), 7.14 (t, 1H, H_{ar}, J=8.0 Hz), 7.27–7.39 (m, 2H, H_{ar}), 7.63 (d, 1H, H_{ar}, J=8.0 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 35.6 (CH_2), 40.2 (CH_2), 48.5 (CH_2), 105.7 (CH), 112.4 (CH), 115.4 (CH_2), 117.7 (CH_2), 121.7 (CH), 123.5 (CH), 125.8 (CH), 127.9 (C), 133.6 (C), 136.1 (CH), 137.0 (CH), 140.2 (C), 164.1 (CO); MS *m/z* 255 $(M+H)^+$; Anal. calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.88; H, 7.24; N, 11.16.

tert-Butyl N-[(1-allyl-1H-indol-2-yl)carbonyl]-N-(but-3-enyl)carbamate (23). According to the procedure for the synthesis of **8** (third step), the compound **23** was prepared in 99% yield as a colorless gum. IR (film) ν 1742 (CO), 1668 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.16 (s, 9H, $C(CH_3)_3$), 2.47 (q, 2H, CH_2, J=7.0 Hz), 3,86 (t, 2H, CH_2, J=7.0 Hz), 4.96–5.22 (m, 6H, CH_2 and $=CH_2$), 5.80–6.05 (m, 2H, =CH), 7.14 (t, 1H, H_{ar}, J=8.0 Hz), 7.27 (s, 1H, H_{ar}), 7.29–7.38 (m, 2H, H_{ar}), 7.62 (d, 1H, H_{ar}, J=8.0 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 26.6 ($3CH_3$), 32.5 (CH_2), 44.1 (CH_2), 45.9 (CH_2), 81.9 (C), 106.0 (CH), 109.5 (CH), 116.2 (CH_2), 116.3 (CH_2), 119.7 (CH), 121.2 (CH), 123.4 (CH), 125.2 (C), 132.7 (C), 134.1 (CH), 135.6 (C), 137.3 (CH), 153.0 (CO), 165.2 (CO); MS *m/z* 355 $(M+H)^+$; Anal. calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.28; H, 7.50; N, 8.03.

4.1.21. *tert*-Butyl 1-oxo-4,7-dihydro-1*H*-[1,4]diazonino-[1,2-*a*]indole-2(3*H*)-carboxylate (24). According to the procedure for the synthesis of **13**, the compound **24** was prepared from **23** in 62% yield as a colorless gum. IR (film) ν 1734 (CO), 1672 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.00 (s, 9H, $C(CH_3)_3$), 2.80–3.20 (m, 2H, CH_2), 3.90 (t, 2H, CH_2, J=5.5 Hz), 4.68–4.71 (m, 2H, CH_2), 5.57–5.61 (m, 1H, =CH), 5.81–5.85 (m, 1H, =CH), 7.09 (s, 1H, H_{ar}), 7.11–7.17 (m, 1H, H_{ar}), 7.34–7.36 (m, 2H, H_{ar}), 7.65 (d, 1H, H_{ar}, J=7.5 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 25.3 (CH_2), 26.8 ($3CH_3$), 41.3 (CH_2), 45.3 (CH_2), 82.0 (C), 108.7 (CH), 108.9 (CH), 120.1 (CH), 122.0 (CH), 124.3 (CH), 126.7 (C), 128.5 (CH), 130.1 (CH), 134.9 (C), 137.5 (C), 152.5 (CO), 166.7 (CO); MS *m/z* 327 $(M+H)^+$; Anal. calcd for $C_{19}H_{22}NO_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.24; H, 6.63; N, 8.71.

4.1.22. *tert*-Butyl 11-allyl-1-oxo-1,3,6,11-tetrahydro-2*H*-azocino[3,4-*b*]indole-2-carboxylate (25). According to the procedure for the synthesis of **13**, the compound **25** was prepared from **20** in 65% yield as a colorless gum. IR (film) ν 1762 (CO), 1668 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.53 (s, 9H, $C(CH_3)_3$), 3.70 (dd, 2H, CH_2, J=1.5, 6.5 Hz), 4.19–4.29 (m, 2H, CH_2), 4.97–5.60 (m, 4H, CH_2 and $=CH_2$), 5.60–5.68 (m, 1H, =CH), 5.87–6.02 (m, 2H, 2 =CH), 7.13–7.19 (m, 1H, H_{ar}), 7.32–7.37 (m,

2H, H_{ar}), 7.65 (d, 1H, H_{ar}, J=7.9 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 22.0 (CH_2), 28.1 ($3CH_3$), 44.1 (CH_2), 46.1 (CH_2), 82.7 (C), 110.4 (CH), 116.8 (CH), 118.1 (CH_2), 120.4 (CH), 120.5 (CH), 125.5 (CH), 125.9 (C), 127.2 (CH), 127.6 (C), 129.8 (C), 133.9 (CH), 139.0 (C), 153.8 (CO), 162.7 (CO); MS *m/z* 375 $(M+Na)^+$, 353 $(M+H)^+$; Anal. calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.32; H, 6.74; N, 8.07.

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