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Tetrahedron

Tetrahedron 62 (2006) 10815–10820

Synthetic approaches towards an indole alkaloid isolated from the marine sponge *Halichondria melanodocia*

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Received 13 June 2006; revised 14 August 2006; accepted 1 September 2006
Available online 2 October 2006

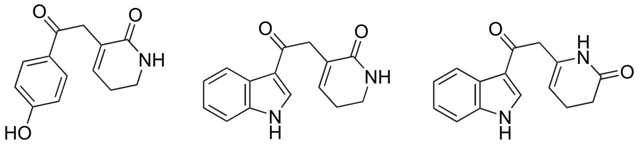
Abstract—The exocyclic analogue of the indole alkaloid isolated from the marine sponge *Halichondria melanodocia* has been prepared via olefination of a phosphonoester derived from 3-(2-bromoacyl)indole. The formation of an unexpected indolylazepine is also discussed.

1. Introduction

Marine organisms, such as sponges and tunicates, constitute a unique and vast resource for the discovery of bioactive molecules with novel structures. Many marine alkaloids have generated interest not only due to their various and often striking pharmacological activities but also as challenging problems for structure elucidation and synthesis.[1]

As far back as in 1979 two lactams were isolated from the isopropanol extracts of an algae-infested Caribbean sponge, *Halichondria melanodocia*.[2] The structures of the lactams were assigned as the related phenol and indole derivatives **1** and **2**, respectively (Fig. 1). Although structure **3** was discussed as an alternative for **2**, it was disregarded since it was incompatible with the chemical shift data.

To the best of our knowledge, the biological activity of the lactams isolated from *H. melanodocia* has not yet been evaluated, neither have their structures been confirmed via synthesis. It also seems to be uncertain whether the alkaloids are produced by the sponge itself or by the associated algae and bacteria.



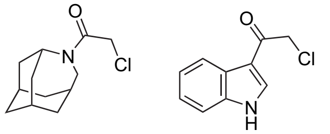
1 **2** **3**

Figure 1.

2. Results and discussion

Our continuous interest in marine indole alkaloids[3] attracted our attention towards compound **2**. Since chloroacetylazahomoadamantane (**4**) (Fig. 2) has been reported to react with triethyl phosphonoacetate at the α-position,[4] we believed that 2-chloro-1-(1*H*-indol-3-yl)-ethanone (**5**)[5] could similarly afford the appropriate building block in our attempts to synthesise **2**. It was conceived that such a phosphonoester building block should provide a possibility to introduce the double bond in the correct position of the lactam.

Hence, triethyl phosphonoacetate was treated with a base (NaH) followed by the Boc-protected chloroacyl indole **6a**. The yields of **7a** were quite modest, under the conditions initially evaluated (NaH, THF), seldom over 30%, largely depending on the co-formation of product **8**[4] together with unreacted starting material (Scheme 1). Other bases were



4 **5**

Figure 2.

Keywords: *Halichondria melanodocia*; Indole alkaloids; Exocyclic; Lactams.

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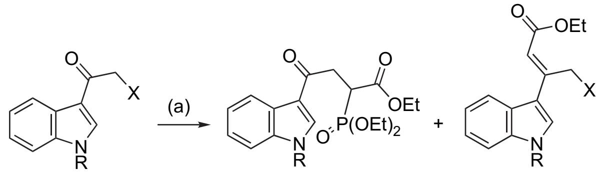
doi:10.1016/j.tet.2006.09.003

tried as well (BuLi, *t*-BuOK, LDA, DBU) with the result of either inferior yields or more by-product formation. Solvent and temperature changes did not improve the yield but, since we noticed that in the presence of a catalyst (NaI or Bu_4NI) the yields improved (less than 10% product without catalyst), we suspected that other 3-(2-haloacyl)indoles could give superior results. As expected, changing the chlorine atom to bromine or iodine (compounds **6b–d**) improved the yields significantly. As a consequence, the formation of **8** was minimised. Changing to a polar aprotic solvent improved the yields even further.



6a X = Cl, R = Boc
6b X = Br, R = Boc
6c X = I, R = Boc
6d X = Br, R = SO_2Ph

7a R = Boc
7b R = SO_2Ph

8 X = Cl, R = Boc

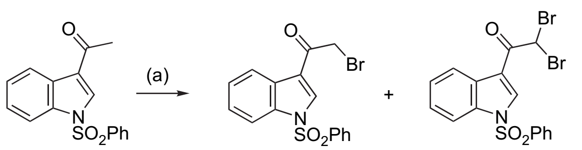
Scheme 1. (a) NaH; other reagents and conditions see Table 1.

Table 1

Indole derivative	Solvent	Other conditions	Yield **7a/7b** (%)	Yield **8** (%)
6a X=Cl, R=Boc	THF	Bu_4NI, rt, 18 h	27	14
6a X=Cl, R=Boc	THF	Bu_4NI, reflux, 4 h	42	n.i
6a X=Cl, R=Boc	THF	Bu_4NI, 0 °C to rt, 18 h	24	n.i
6a X=Cl, R=Boc	Toluene	Bu_4NI, reflux, 3 h	22	n.i
6a X=Cl, R=Boc	DMF	NaI, 60 °C, 36 h	—	—
6a X=Cl, R=Boc	THF	NaI, rt, 18 h	26	26
6d X=Br, R=SO_2Ph	THF	NaI, rt, 1.5 h	72	—
6a X=Cl, R=Boc	THF	rt, 18 h	8	n.i
6c X=I, R=Boc	THF	rt, 18 h	56	n.i
6b X=Br, R=Boc	THF	rt, 18 h	49	n.i
6c X=I, R=Boc	DMF	rt, 18 h	70	—
6d X=Br, R=SO_2Ph	DMF	NaI, rt, 18 h	56	—
6b X=Br, R=Boc	DMF	rt, 18 h	71	—
6d X=Br, R=SO_2Ph	DMF	rt, 18 h	64	—

rt=Room temperature, n.i.=not isolated.

Compound **6d**[6] was synthesised via bromination of 3-(1-benzenesulfonyl-1*H*-indolyl)-ethanone (**9**)[7] using pyridinium hydrobromide perbromide.[8] The minor co-product, the dibromo derivative **10**, could easily be separated from the main product by column chromatography (Scheme 2).



9 **6d** (55%) **10** (10%)

Scheme 2. (a) Py·HBr_3, $CHCl_3$, reflux 30 min.

The Horner–Wadsworth–Emmons olefination of **7a** and **7b** with *N*-Boc-3-aminopropionaldehyde[9] did however only proceed in a very modest yield. Using BuLi as the base afforded compound **11a** and **11b** in low yields, around 20%. Other bases tried (DBU, LDA, *t*-BuOK, [(CH3)$_3$Si]$_2$NK, NaH) failed to give the desired product (Scheme 3).

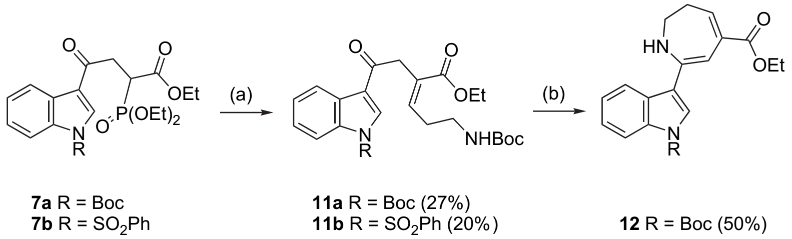
The plan was to remove the Boc-protecting groups and cyclise the amine to the desired lactam. However, treatment of **11a** with 20 equiv TFA and subsequent treatment with $NaHCO_3$ gave the seven-membered heterocycle **12** instead of the expected free amine or the six-membered heterocycle **2**. Also, quite surprisingly, the indole nitrogen remained Boc-protected despite the acid treatment. Due to the rather unstable enamine character of compound **12**, optimal conditions for preparation and isolation are still an issue, as is the deprotection of this compound.

It seems likely that the azepine formation could be induced by the electron withdrawing Boc-protecting group on the indole nitrogen, which would render the carbonyl at the 3-position of the indole more susceptible for attack than the ester functionality. Consequently, removal of the benzenesulfonyl group of **11b** under standard conditions afforded **13**, which was further reacted with *N*-hydroxysuccinimide (HOSu). Surprisingly, during hydrolysis of the ester of **11a** the acidic workup also removed the indole Boc-protecting group, affording compound **13**. This situation is in contrast with the treatment of **11a** with trifluoroacetic acid or formic acid where the amine group is more easily deprotected.

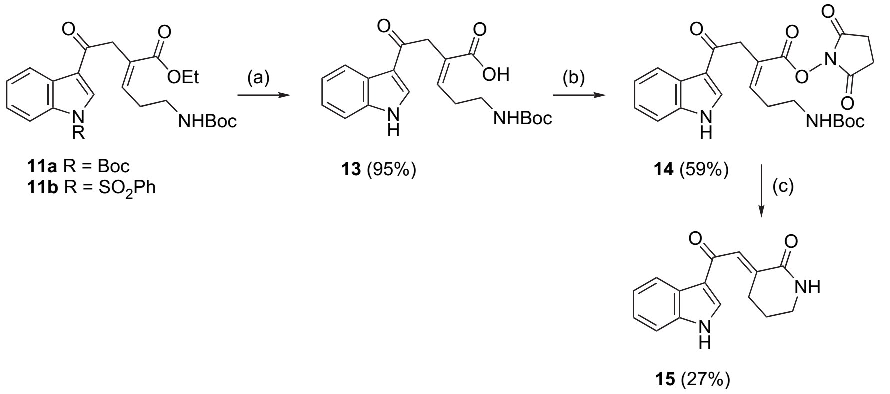
Attempts to accomplish the cyclisation to the lactam under basic conditions, prior to removal of the amine-protecting group were unsuccessful and did not afford the six-membered ring. Instead, treatment of **14** with DBU at −78 °C actually demonstrated the nucleophilic behaviour of DBU, resulting in an *N*-ε-caprolactam derivative.[10]

The *N*-succinimide ester **14** was treated with TFA, and thereafter with a biphasic mixture of aqueous $NaHCO_3$ solution and CH_2Cl_2. A six-membered lactam could thereafter be isolated from the mixture (Scheme 4). However, when comparing the data for this particular lactam with the data reported for the natural compound, it was realised that the exocyclic compound **15** was the product, rather than the endocyclic natural alkaloid. In the ^1H NMR spectrum of compound **15**, it was quite evident that the double bond had migrated, since all three methylenic groups are coupled and one proton *singlet* appears at δ 6.40. For the natural product, a one proton *triplet* appears at δ 6.64, which is coupled with one methylene group, also the methylene bridge appears as a broad singlet. Whether the exocyclic lactam **15** is the kinetic product in this reaction is uncertain, but there are indications from similar examples in the literature.[11]

The exocyclic analogue of the indole alkaloid isolated from the marine sponge *H. melanodocia* has thus been prepared in our laboratory. All attempts to produce the endocyclic lactam and thus to be able to confirm the structure assigned for the natural product to date have been unsuccessful.



Scheme 3. (a) BuLi, *N*-Boc-3-aminopropionaldehyde, THF, −78 °C to rt, 18 h; (b) (i) TFA, CH_2Cl_2, rt, 4 h, (ii) aq satd $NaHCO_3$; (c) TFA.



Scheme 4. (a) (i) 1 M KOH, EtOH, reflux, 1 h, (ii) 1 M HCl; (b) HOSu, EDCI, DMF, rt, 18 h; (c) (i) TFA, CH_2Cl_2, rt, 4 h, (ii) aq $NaHCO_3$, CH_2Cl_2.

3. Experimental

3.1. General

NMR spectra were recorded on a Bruker Avance 300 DPX at 300 MHz for ^{1}H and 75 MHz for ^{13}C. NMR spectra were recorded in DMSO-d_6 or $CDCl_3$, using the solvent signal as reference. δ Values are given in parts per million, coupling constants are given in hertz. The IR spectra were acquired using a ThermoNicolet Avatar 330 FT-IR instrument. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. High-resolution mass spectroscopic (HRMS) analyses were performed by E. Nilsson, University of Lund, Sweden. Melting points were determined on a Büchi B-545, using the capillary method and are uncorrected. All reagents used were purchased from Aldrich, Lancaster, Merck or Biosynth and were used as received. All solvents were purified by distillation or were of analytical grade. THF was distilled from sodium/benzophenone. Chromatographic separations were performed on silica gel 60 (230–400 mesh).

3.1.1. 3-(2-Chloro-acetyl)-indole-1-carboxylic acid *tert*-butyl ester (6a). To a stirred suspension of 2-chloro-1-(1*H*-indol-3-yl)-ethanone[5] (9.65 g, 50 mmol) in CH_3CN (120 mL) was added Boc_2O (12.0 g, 55 mmol), followed by DMAP (37 mg, 0.3 mmol) in small portions. The reaction mixture was stirred for 12 h and the solvent was thereafter evaporated under reduced pressure. The residue was crystallised from EtOH to give 3-(2-chloro-acetyl)-indole-1-carboxylic acid *tert*-butyl ester (**6a**) as a cream coloured amorphous solid (13.1 g, 89%).

Mp 156.0–157.0 °C; IR (neat): 2979, 1730, 1675, 1542, 1447, 1367, 1139, 1108, 836, 747 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.73 (s, 1H), 8.23–8.20 (m, 1H), 8.12–8.10 (m, 1H), 7.47–7.36 (m, 2H), 5.10 (s, 2H), 1.67 (s, 9H); ^{13}C NMR (DMSO-d_6): δ 187.6 (s), 148.4 (s), 134.8 (s), 134.0 (d), 126.8 (s), 125.7 (d), 124.5 (d), 121.7 (d), 116.6 (s), 115.0 (d), 85.7 (s), 47.1 (t), 27.6 (q); MS (ESI) *m*/*z* 294 (M+H)$^+$. Anal. Calcd for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49; N, 4.77. Found: C, 61.31; H, 5.55; N, 4.65.

3.1.2. 3-(2-Bromo-acetyl)-indole-1-carboxylic acid *tert*-butyl ester (6b). 3-(2-Bromo-acetyl)-indole-1-carboxylic acid *tert*-butyl ester (**6b**) was prepared from 2-bromo-1-(1*H*-indol-3-yl)-ethanone[12] as described above. Crystallisation from 2-propanol gave the title compound as a white amorphous solid. Yield: 76%.

Mp 149.0–150.5 °C; IR (neat): 2980, 1730, 1658, 1550, 1448, 1364, 1146, 1093, 837, 750 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.77 (s, 1H), 8.23–8.20 (m, 1H), 8.12–8.09 (m, 1H), 7.46–7.36 (m, 2H), 4.88 (s, 2H), 1.68 (s, 9H); ^{13}C NMR (DMSO-d_6): δ 187.7 (s), 148.4 (s), 134.9 (s), 134.5 (d), 126.9 (s), 125.7 (d), 124.5 (d), 121.7 (d), 116.5 (d), 114.9 (s), 85.7 (s), 34.1 (t), 27.6 (q). Anal. Calcd for $C_{15}H_{16}BrNO_3$: C, 53.27; H, 4.77; N, 4.14. Found: C, 53.31; H, 4.68; N, 4.05.

3.1.3. 3-(2-Iodo-acetyl)-indole-1-carboxylic acid *tert*-butyl ester (6c). 3-(2-Iodo-acetyl)-indole-1-carboxylic acid *tert*-butyl ester (**6c**) was prepared from 2-iodo-1-(1*H*-indol-3-yl)-ethanone[12] as described above. Crystallisation from 2-propanol gave the title compound as a cream coloured amorphous solid. Yield: 79%.

Mp 142.0–144.0 °C; IR (neat): 2980, 1728, 1651, 1547, 1446, 1365, 1145, 1084, 836, 746 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.78 (s, 1H), 8.21–8.18 (m, 1H), 8.11–8.09

(m, 1H), 7.44–7.37 (m, 1H), 4.63 (s, 2H), 1.68 (s, 9H); ^{13}C NMR (DMSO-d_6): δ 189.8 (s), 148.5 (s), 135.0 (s), 134.4 (d), 127.0 (s), 125.6 (d), 124.4 (d), 121.9 (d), 116.0 (s), 114.9 (d), 85.7 (s), 27.6 (q), 6.3 (t). Anal. Calcd for $C_{15}H_{16}INO_3$: C, 46.77; H, 4.19; N, 3.64. Found: C, 46.87; H, 4.27; N, 3.57.

3.1.4. 3-(1-Benzenesulfonyl-1*H*-indol-3-yl)-2-bromo-ethanone (6d) and 3-(1-benzenesulfonyl-1*H*-indol-3-yl)-2,2-dibromo-ethanone (10). 3-(1-Benzenesulfonyl-1*H*-indol-3-yl)-ethanone[7] (**9**) (2.99 g, 10.0 mmol) and pyridinium hydrobromide perbromide (3.84 g, 12.0 mmol) were suspended in chloroform (50 mL) and heated at reflux for 30 min. The reaction mixture was allowed to cool and thereafter transferred to a separatory funnel, washed with H_2O (50 mL), dried over Na_2SO_4 and evaporated to dryness. The residue was subjected to column chromatography using CH_2Cl_2/hexane (80:20) as eluent to give **10** (0.44 g, 10%) followed by **6d** (2.07 g, 55%) as white solids.

3.1.4.1. 3-(1-Benzenesulfonyl-1*H*-indol-3-yl)-2-bromo-ethanone (6d). Mp 119.5–121.5 °C (lit.[6] 130.5–131.0 °C); IR (neat): 3137, 1669, 1536, 1373, 1176, 1134, 989, 749, 726, 589 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 8.36 (s, 1H), 8.31 (d, J=8.2, 1H), 7.98–7.93 (m, 3H), 7.63–7.58 (m, 1H), 7.52–7.47 (m, 2H), 7.42–7.33 (m, 2H), 4.37 (s, 2H); ^{13}C NMR (CDCl$_3$): δ 187.1 (s), 137.4 (s), 135.0 (s), 134.9 (d), 133.0 (d), 129.9 (d), 127.7 (s), 127.3 (d), 126.3 (d), 125.4 (d), 123.2 (d), 118.4 (s), 113.3 (d), 31.6 (t). Anal. Calcd for $C_{16}H_{12}BrNO_3S$: C, 50.81; H, 3.20; N, 3.70. Found: C, 50.79; H, 3.30; N, 3.65.

3.1.4.2. 3-(1-Benzenesulfonyl-1*H*-indol-3-yl)-2,2-dibromo-ethanone (10). Mp 144.0–145.0 °C; IR (neat): 3123, 1682, 1529, 1371, 1176, 1133, 985, 746, 725, 592 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 8.61 (s, 1H), 8.32–8.29 (m, 1H), 7.99–7.95 (m, 3H), 7.61–7.58 (m, 1H), 7.53–7.48 (m, 2H), 7.42–7.37 (m, 2H), 6.51 (s, 1H); ^{13}C NMR (CDCl$_3$): δ 182.4 (s), 137.2 (s), 135.0 (d), 134.8 (s), 133.4 (d), 129.9 (d), 128.0 (s), 127.4 (d), 126.5 (d), 125.5 (d), 123.3 (d), 114.0 (s), 113.3 (d), 40.3 (d). Anal. Calcd for $C_{16}H_{11}Br_2NO_3S$: C, 42.04; H, 2.43; N, 3.06. Found: C, 41.95; H, 2.44; N, 2.89.

3.1.5. 3-[3-(Diethoxy-phosphoryl)-3-ethoxycarbonyl-propionyl]-indole-1-carboxylic acid *tert*-butyl ester (7a).

3.1.5.1. Representative procedure. To a suspension of NaH (88 mg, 2.2 mmol) in DMF (7 mL) at room temperature was added triethyl phosphonoacetate (0.4 mL, 2.0 mmol) in small portions. After 40 min at room temperature compound **6c** (770 mg, 2.0 mmol) dissolved in DMF (5 mL) was added in small portions. After 18 h the reaction mixture was poured into H_2O (15 mL) and extracted with EtOAc (3×10 mL). The combined organic phases were washed with H_2O (25 mL), brine (25 mL), dried over Na_2SO_4 and the solvents were evaporated. The residue was subjected to column chromatography using EtOAc/hexane (70:30) as eluent to give compound **7a** as pale yellow solid (674 mg, 70%).

Mp 119.5–121.0 °C; IR (neat): 2980, 1732, 1664, 1447, 1365, 1255, 1238, 1146, 1136, 1015, 764, 757 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.67 (s, 1H), 8.20 (d, J=7.9, 1H), 8.12 (d, J=7.9, 1H), 7.45–7.33 (m, 2H), 4.16–4.08 (m, 6H), 3.70–3.36 (m, 3H), 1.68 (s, 9H), 1.30–1.17 (m, 9H). Anal. Calcd for $C_{23}H_{32}NO_8P$: C, 57.37; H, 6.70; N, 2.91. Found: C, 57.57; H, 6.81; N, 2.84.

3.1.6. 4-(1-Benzenesulfonyl-1*H*-indol-3-yl)-2-(diethoxy-phosphoryl)-4-oxo-butyric acid ethyl ester (7b). Compound **7b** was prepared from 3-(1-benzenesulfonyl-1*H*-indol-3-yl)-2-bromo-ethanone (**6d**) using the procedure described above. Silica gel column chromatography using hexane/EtOAc (60:40) with increasing amounts of EtOAc as eluent afforded compound **7b** as pale yellow oil. Yield: 64%.

IR (neat): 2982, 1731, 1669, 1538, 1446, 1384, 1250, 1164, 1135, 1018, 750, 727 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.00 (s, 1H), 8.23–8.13 (m, 3H), 7.98 (d, J=8.2, 1H), 7.76–7.63 (m, 3H), 7.43–7.36 (m, 2H), 4.17–4.07 (m, 6H), 3.75–3.46 (m, 3H), 1.30 (dt, J=1.9, 7.0, 6H), 1.20 (t, J=7.1, 3H); HRMS (FAB$^+$) m/z calcd for $C_{24}H_{29}NO_8PS$ (M+H)$^+$ 522.1351, found 522.1350.

3.1.7. 3-(1-Chloromethyl-2-ethoxycarbonyl-vinyl)-indole-1-carboxylic acid *tert*-butyl ester (8). To a suspension of NaH (220 mg, 5.5 mmol) in THF (15 mL) at room temperature was added triethyl phosphonoacetate (0.4 mL, 5.0 mmol) in small portions. After 40 min at room temperature compound **6a** (1.47 g, 5.0 mmol) was added as a solid in small portions together with NaI (75 mg, 0.5 mmol). After 18 h, H_2O (5 mL) was added to the reaction mixture and THF was evaporated. The residue was redissolved in EtOAc (20 mL) and washed with H_2O (2×10 mL), brine (15 mL), dried over Na_2SO_4 and evaporated. The residue was subjected to column chromatography using hexane/EtOAc (90:10) with increasing amounts of EtOAc as eluent to give compound **8** (472 mg, 26%) followed by compound **7a** (637 mg, 26%) as pale yellow solids.

Mp 114–116 °C; IR (neat): 2978, 1735, 1709, 1621, 1450, 1367, 1240, 1146, 1106, 1052, 1035, 742 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 8.23 (d, J=7.9, 1H), 7.96 (s, 1H), 7.84–7.81 (m, 1H), 7.40–7.32 (m, 2H), 6.48 (s, 1H), 5.10 (s, 2H), 4.33 (q, J=7.1, 14.3, 2H), 1.70 (s, 9H), 1.39 (t, J=7.1, 3H); ^{13}C NMR (CDCl$_3$): δ 165.9 (s), 149.4 (s), 146.9 (s), 136.2 (s), 127.8 (s), 126.7 (d), 125.3 (d), 123.7 (d), 120.5 (d), 119.4 (d), 119.3 (s), 115.8 (d), 84.9 (s), 60.7 (t), 40.0 (t), 28.3 (q), 14.5 (q); HRMS (FAB$^+$) m/z calcd for $C_{19}H_{22}ClNO_4$ (M)$^+$ 363.1237, found 363.1253.

3.1.8. 3-(6-*tert*-Butoxycarbonylamino-3-ethoxycarbonyl-hex-3-enoyl)-indole-1-carboxylic acid *tert*-butyl ester (11a). Compound **7a** (2.20 g, 4.57 mmol) was dissolved in THF (20 mL) and cooled to −78 °C under a nitrogen atmosphere. To the solution was added *n*-BuLi (3.14 mL, 5.03 mmol) in a dropwise manner. After the addition the solution was warmed up to 0 °C for 30 min, then again cooled down to −78 °C. A solution of *N*-Boc-3-aminopropionaldehyde[9] (791 mg, 4.57 mmol) in THF (10 mL) was added in small portions and the reaction mixture was thereafter allowed to reach room temperature over night. After 18 h H_2O (2 mL) was added and the solvent was evaporated. The residue was redissolved in EtOAc (20 mL) and washed with H_2O (20 mL). The aqueous phase was extracted with an additional portion of EtOAc (20 mL) and the combined organic phases were washed with brine (20 mL) and dried over Na_2SO_4. After evaporation the oily residue was purified by silica gel column chromatography using hexane/EtOAc (80:20 to 60:40) to give compound **11a** as a yellow oil. Yield: 610 mg (27%).

IR (neat): 3365, 2978, 1742, 1701, 1449, 1364, 1236, 1136, 1100, 749 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.67 (s, 1H), 8.21 (d, J=7.7, 1H), 8.12 (d, J=8.0, 1H), 7.44–7.32 (m, 2H), 6.94–6.89 (m, 2H), 4.11–4.04 (m, 4H), 3.07–3.01 (m, 2H), 2.36–2.29 (m, 2H), 1.67 (s, 9H), 1.35 (s, 9H), 1.14 (t, J=7.1, 3H); ^{13}C NMR (DMSO-d_6): δ 192.7 (s), 166.4 (s), 155.6 (s), 148.5 (s), 142.2 (d), 134.9 (s), 133.3 (d), 127.7 (s), 127.0 (s), 125.4 (d), 124.2 (d), 121.9 (d), 118.9 (s), 114.8 (d), 85.4 (s), 77.5 (s), 60.1 (t), 38.8 (t), 37.6 (t), 29.0 (t), 28.1 (q), 27.5 (q), 14.0 (q); HRMS (FAB^+) *m/z* calcd for $C_{27}H_{37}N_2O_7$ $(M+H)^+$ 501.2601, found 501.2598.

3.1.9. 2-[2-(1-Benzenesulfonyl-1*H*-indol-3-yl)-5-*tert*-butoxycarbonylamino]-pent-2-enoic acid ethyl ester (11b). Compound **11b** was prepared from 4-(1-benzenesulfonyl-1*H*-indol-3-yl)-2-(diethoxy-phosphoryl)-4-oxo-butyric acid ethyl ester (**7b**) using the procedure described above. Column chromatography using hexane/EtOAc (60:40) eluent afforded compound **11b** as pale yellow oil. Yield: 23%.

IR (neat): 2978, 1701, 1536, 1376, 1166, 1135, 748, 727, 592, 571 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.42 (s, 1H), 8.32–8.27 (m, 1H), 7.99–7.92 (m, 4H), 7.63–7.58 (m, 1H), 7.53–7.48 (m, 3H), 7.39–7.29 (m, 2H), 7.08 (t, J=7.8, 1H), 5.11 (br, 1H), 4.20–4.08 (m, 2H), 3.95 (s, 2H), 3.31–3.29 (m, 2H), 2.50–2.42 (m, 2H), 1.39 (s, 9H), 1.31–1.18 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 192.7 (s), 166.9 (s), 156.2 (s), 143.0 (d), 137.8 (s), 135.1 (s), 134.8 (d), 132.6 (d), 129.8 (d), 128.1 (s), 127.9 (s), 127.4 (d), 126.1 (d), 125.1 (d), 123.4 (d), 121.1 (s), 113.2 (d), 77.4 (s), 61.2 (t), 39.6 (t), 38.0 (t), 29.9 (t), 28.5 (q), 14.4 (q); HRMS (FAB^+) *m/z* calcd for $C_{28}H_{33}N_2O_7S$ $(M+H)^+$ 541.2008, found 541.2010.

3.1.10. 5-*tert*-Butoxycarbonylamino-2-[2-(1*H*-indol-3-yl)-2-oxo-ethyl]-pent-2-enoic acid (13). To compound **11a** (429 mg, 0.86 mmol) dissolved in EtOH (10 mL) was added 1 M KOH (5 mL). The reaction mixture was heated to reflux for 1 h and was then allowed to cool. EtOH was evaporated and the residue diluted with H_2O (5 mL). The resulting mixture was cooled on ice and acidified with 1 M HCl until a precipitate appeared. The solid was collected by filtration, washed with water and dried to give **13** as a yellowish solid (302 mg, 95%).

Mp 168–170 °C; IR (neat): 3267, 2978, 1693, 1638, 1515, 1428, 1244, 1154, 1135, 746 cm^{-1}; ^1H NMR (DMSO-d_6): δ 12.18 (s, 1H), 11.94 (s, 1H), 8.40 (d, J=3.1, 1H), 8.15–8.12 (m, 1H), 7.49–7.46 (m, 1H), 7.21–7.16 (m, 2H), 6.91–6.84 (m, 2H), 3.91 (s, 2H), 3.07–3.00 (m, 2H), 2.33–2.26 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (DMSO-d_6): δ 191.6 (s), 168.3 (s), 155.6 (s), 141.2 (d), 136.5 (s), 133.9 (d), 128.8 (s), 125.4 (s), 122.7 (d), 121.6 (d), 121.3 (d), 115.9 (s), 112.1 (d), 77.5 (s), 39.0 (t), 37.0 (t), 29.0 (t), 28.2 (q). Anal. Calcd for $C_{20}H_{24}N_2O_5$: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.37; H, 6.70; N, 7.39.

3.1.11. 5-*tert*-Butoxycarbonylamino-2-[2-(1*H*-indol-3-yl)-2-oxo-ethyl]-pent-2-enoic acid 2,5-dioxo-pyrrolidin-1-yl ester (14). Compound **13** (474 mg, 1.27 mmol) was dissolved in DMF (4 mL). EDCI (269 mg, 1.40 mmol) and HOSu (161 mg, 1.40 mmol) were added and the resulting reaction mixture was kept at room temperature for 18 h. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (3×10 mL). The combined organic phases were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4 and evaporated. The oily residue was purified on column chromatography using EtOAc/hexane (50:50 to 70:30) as eluent to give compound **14** as a light brown oil. Yield: 354 mg (59%).

IR (neat): 3230, 2932, 1733, 1700, 1646, 1521, 1204, 1163, 1067, 749 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.25 (s, 1H), 8.35–8.32 (m, 1H), 7.95 (d, J=3.1, 1H), 7.40–7.37 (m, 1H), 7.30–7.21 (m, 4H), 3.87 (s, 2H), 3.30–3.26 (m, 2H), 2.77 (s, 4H), 2.54–2.47 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (acetone-d_6): δ 190.8 (s), 170.5 (s), 163.2 (s), 148.6 (d), 137.8 (s), 134.0 (d), 126.9 (s), 125.5 (s), 123.6 (d), 122.9 (d), 122.8 (d), 117.6 (s), 112.7 (d), 78.7 (s), 39.8 (t), 38.0 (t), 30.7 (t), 28.6 (q), 26.3 (t), 26.11 (t); HRMS (FAB^+) *m/z* calcd for $C_{24}H_{28}N_3O_7$ $(M+H)^+$ 470.1927, found 470.1927.

3.1.12. 3-(4-Ethoxycarbonyl-6,7-dihydro-1*H*-azepin-2-yl)-indole-1-carboxylic acid *tert*-butyl ester (12). Compound **11a** (378 mg, 0.76 mmol) dissolved in formic acid (15 mL) was stirred at room temperature for 4 h. The acid was evaporated and the residue was dissolved in EtOAc (20 mL) and washed with satd aq $NaHCO_3$ (3×15 mL). The organic phase was washed with H_2O (15 mL) and brine (15 mL), dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography using hexane/EtOAc (60:40) with increasing amounts of EtOAc as eluent to afford the title compound as a yellow oil (144 mg, 50%).

^1H NMR ($CDCl_3$): δ 8.20 (d, J=7.9, 1H), 7.91 (d, J=7.7, 1H), 7.72 (s, 1H), 7.38–7.26 (m, 2H), 6.87 (t, J=6.15, 1H), 5.80 (s, 1H), 4.36 (br s, 1H), 4.29 (q, J=7.1, 14.2, 2H), 3.52–3.51 (m, 2H), 2.75–2.70 (m, 2H), 1.69 (s, 9H), 1.34 (t, J=7.1, 3H); ^{13}C NMR ($CDCl_3$): δ 168.4 (s), 149.4 (s), 140.8 (s), 135.6 (s), 133.5 (d), 130.4 (s), 128.5 (s), 124.6 (d), 123.4 (d), 122.9 (d), 121.6 (s), 120.5 (d), 115.2 (d), 94.5 (d), 83.9 (s), 60.7 (t), 45.2 (t), 35.0 (t), 28.1 (q), 14.2 (q); MS (ESI) *m/z* 383 $(M+H)^+$; HRMS (EI) *m/z* calcd for $C_{22}H_{27}N_2O_4$ $(M+H)^+$ 383.1971, found 383.1948; HRMS (EI) *m/z* calcd for $C_{22}H_{25}N_2O_4$ $(M-H)^-$ 381.1814, found 381.1841.

3.1.13. 3-[2-(1*H*-Indol-3-yl)-2-oxo-ethylidene]-piperidin-2-one (15). To a solution of compound **14** (500 mg, 1.07 mmol) in CH_2Cl_2 (20 mL) was added TFA (1.64 mL, 21.3 mmol) and the resulting solution was stirred at room temperature for 7 h. The solvent was evaporated and the residue was parted between CH_2Cl_2 (25 mL) and H_2O (20 mL), adding $NaHCO_3$ (540 mg, 6.43 mmol) to reach pH ~7–8. After 12 h at room temperature a beige solid was collected by filtration from the biphasic mixture, washed with water and dried to give the title compound. Yield: 72 mg (27%).

Mp 200.0–201.5 °C; IR (neat): 3232, 2938, 1746, 1683, 1642, 1587, 1575, 1523, 1426, 1132, 795, 738 cm^{-1}; ^1H

NMR (DMSO-d_6): δ 11.74 (s, 1H), 8.16–8.13 (m, 1H), 7.84 (d, J=2.7, 1H), 7.56 (br s, 1H), 7.47–7.44 (m, 1H), 7.22–7.14 (m, 2H), 6.40 (s, 1H), 3.24–3.19 (m, 2H), 2.62–2.58 (m, 2H), 1.90–1.84 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 189.8 (s), 163.1 (s), 136.7 (s), 134.8 (d), 133.8 (d), 133.7 (s), 125.3 (s), 122.5 (d), 121.3 (d), 121.2 (d), 116.5 (s), 112.0 (d), 41.41 (t), 30.0 (t), 22.8 (t). HRMS (FAB$^+$) m/z calcd for $C_{15}H_{15}N_2O_2$ $(M+H)^+$ 255.1134, found 255.1141.

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