Synthesis of Unique Analogues of the Ergoline Skeleton Using Intramolecular [3+2] Cycloaddition

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Abstract: A new methodology is described for the novel and rapid synthesis of unique analogues of the ergoline structure. After introduction of an allyl or alkynyl group in position C-4 on indole-3-carboxaldehyde, an intramolecular 1,3-dipolar cycloaddition using α-amino esters, directly provides novel ergoline-type compounds in good yields.

Key words: intramolecular 1,3-dipolar cycloaddition, Stille reaction, Sonogashira reaction, microwave, ergoline

The ergot alkaloids are derivatives containing the ergoline ring system **1** (Figure 1). They display a large diversity of pharmacological properties, that include central, peripheral, and neurohormonal activity due to binding to adrenergic, dopaminergic and serotonergic receptors.[1] Lysergic acid (**2**) has been a major synthetic target and so have been the analogous derivatives LSD (**3**) or the anti-prolactin drug cabergoline (**4**). Additionally, pergolide **5** is known to act as a partial agonist at the dopamine receptor and has been used for treating Parkinson's disease.[2] Several derivatives in which the D ring is variably substituted are used clinically as labor-inducing agents as well as anti-migraine, analgesic, and anti-Parkinson's therapeutics.[3] Starting from indole-3-carboxaldehyde (**6a**) or 2-methyl-indole-3-carboxaldehyde (**6b**), we report herein the divergent synthesis of novel alkaloid-type derivatives **11** and **12**, that are ergoline analogues, using an intramolecular [3+2] cycloaddition as the key step to form the C and D ring system (Scheme 1).

As outlined in Scheme 2, the synthesis of **7a**,**b** was performed in three steps from indole-3-carboxaldehydes **6a**,**b**. Firstly, the Hollins procedure was found to be the best technique to introduce iodine at C-4 of the indole ring.[4] Thus, the reaction of **6a** or **6b** and thallium(III) trifluoroacetate in trifluoroacetic acid produced the thallium intermediate in position C-4. This intermediate then reacted with potassium iodide to afford compounds **13a** and **13b** as the only regioisomers. Finally, *N*-Boc protection afforded compounds **7a** and **7b** in 93% and 74% overall yields, respectively.[5]

With these two iodo compounds in hand, we chose to first introduce a vinyl or an allyl group at C-4 position by a Stille[6] reaction, using the procedure developed by the

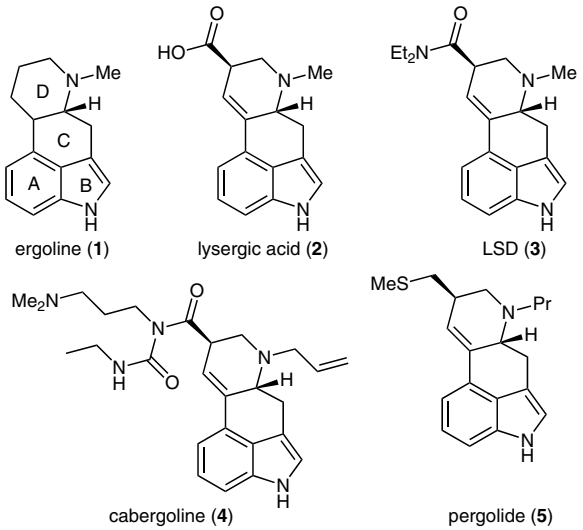
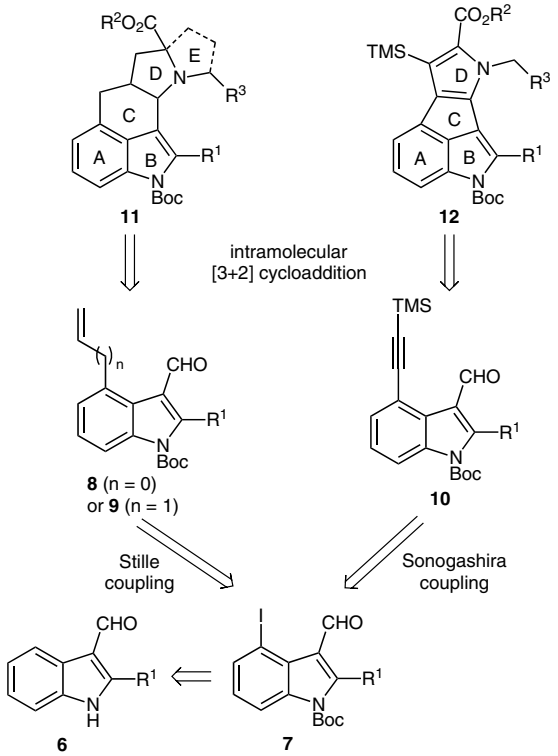


Figure 1 Different ergolines and analogous structures



Scheme 1 Retrosynthetic approach for the synthesis of analogues **11** and **12**

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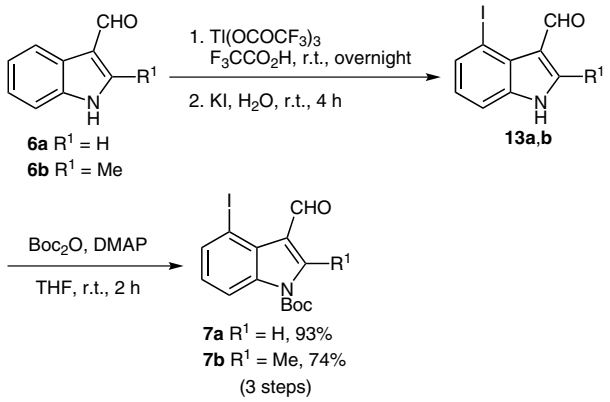
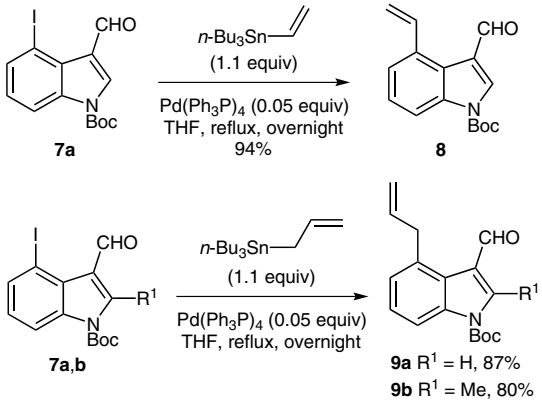


Scheme 2 Iodination and *N*-Boc protection of **6a** and **6b**

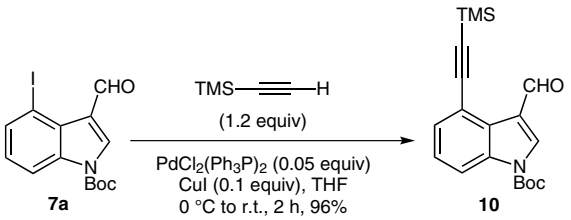
group of Buchwald and co-workers (Scheme 3).[7] Compound **7a** and tributylvinylstannane, in the presence of catalytic amount of $Pd(Ph_3P)_4$, afforded the vinyl precursor **8** in excellent 94% yield. Similarly, the allyl group was introduced by Pd-catalyzed reaction of allyltributylstannane with **7a** or **7b** to afford **9a** or **9b** in 87% and 80% yield, respectively.[8] These compounds were readily isolated after purification by eluting through a short column of silica gel and the resulting white solids were washed with pentane to remove any traces of tin residues.



Scheme 3 Stille reaction with compounds **7a**,**b**

In parallel, a Sonogashira reaction was employed on compound **7a** to synthesize the alkyne precursor **10** (Scheme 4).[9] Inspired by the procedure of Johnson and co-workers,[10] a mixture of compound **7a** and trimethylsilylacetylene in the presence of a catalytic amount of Pd(II)/CuI afforded compound **10** in 96% yield.[11]

Having obtained these precursors, we proceeded to study the 1,3-dipolar cycloaddition between α-amino esters **14a**–**c** (Figure 2) and vinyl derivative **8** (Scheme 5). Contrary to our expectations, in all experiments the formation of desired compounds **15a**–**c** was not observed. The starting material was recovered in up to 60% yield and a mixture of inseparable polar compounds was also observed. We postulate that the vinyl group is either at a great distance or in an unfavorable orientation such that it cannot react with the generated azomethine ylide to achieve cycloaddition.



Scheme 4 Sonogashira reaction with compound **7**

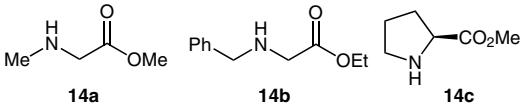
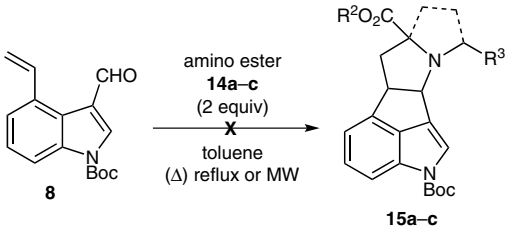
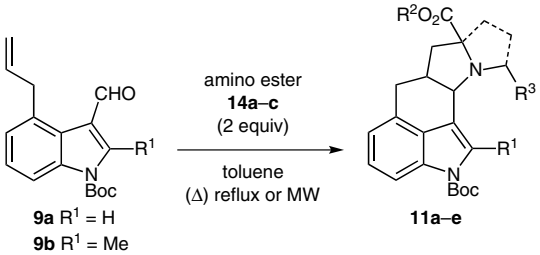


Figure 2 α-Amino esters used in cycloadditions with **8**, **9** and **10**



Scheme 5 [3+2] Cycloaddition between **8** and **14**

However the study was pursued using the allyl derivatives **9a** and **9b** for the 1,3-dipolar cycloaddition (Scheme 6) in the presence of α-amino esters **14a**–**c** (Figure 2). In this case, condensation led directly to the expected novel alkaloids **11**. The cycloaddition reactions were achieved successfully by condensation of **9a** or **9b** and **14a**–**c** in toluene under conventional thermal conditions or under microwave irradiation. Tetracyclic and pentacyclic compounds **11a**–**e** were isolated as a mixture of two diastereomers except for **11b** (Figure 3) in good to excellent yields under both sets of conditions (Table 1).[12]



Scheme 6 [3+2] Cycloaddition between **9a**,**b** and **14**

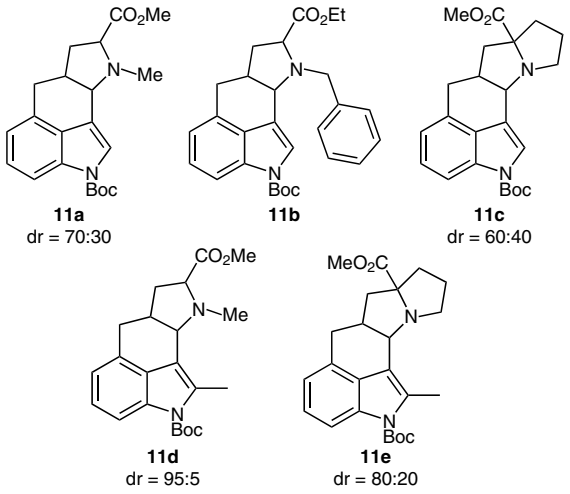


Figure 3 Compounds **11a–e** obtained by [3+2] cycloaddition

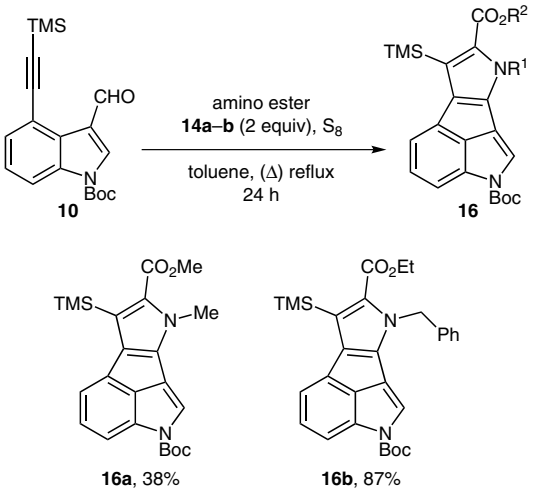
Table 1 Comparative Yield of Cycloaddition Reactions

Entry	Reagents	Product	R^1	Thermal[a]	Microwave[b]	
				Yield (%)	Time (min)	Yield (%)
1	**9a** + **14a**	**11a**	H	95	15	99
2	**9a** + **14b**	**11b**	H	75	45	90
3	**9a** + **14c**	**11c**	H	97	10	98
4	**9b** + **14a**	**11d**	Me	84	20	97
5	**9b** + **14c**	**11e**	Me	90	15	95

[a] All reactions were carried out at reflux in toluene for 24 h.
[b] All reactions were carried out at 110 °C under 100 W irradiation.

Under conventional thermal conditions, the reaction was complete after several hours at reflux. Under microwave irradiation, the reaction was performed using a minimal amount of toluene.[12] Microwave irradiation reduced the time of the reaction and significantly increased the yield, especially for entries 2 and 4 (Table 1). Moreover, an added advantage of using microwave irradiation conditions resided in the observation that the crude reaction mixture was practically devoid of side products, allowing a very simple purification by filtration through a short column of silica gel without prior workup.

The study was pursued further using the alkyne precursor with the hypothesis that the dipole generated should be in the same plane as the azomethine ylide. Indeed, when the aldehyde **10** was condensed with α-amino ester **14a** or **14b**, pyrroles **16a** and **16b** were isolated in 38% and 87% yields, respectively (Scheme 7).[13] These reactions were performed in toluene, under conventional thermal conditions, in the presence of sulfur, following a procedure known in our laboratory to afford directly the expected pyrrole compound in one pot.[14] In the case of **16a**, the reaction also produced a mixture of inseparable polar compounds, similar to the condensation of **8** and **14**, probably due to a secondary polymerization reaction. We also observed that the starting material **10** was completely consumed contrary to the observations with **8**. This suggests that the alkyne function is indeed relatively accessible to react with the azomethine ylide.



Scheme 7 [3+2] Cycloaddition between **10** and **14**

In conclusion, aldehydes **8**–**10** have been prepared from the indole-3-carboxaldehydes **6a**,**b**. Intramolecular [3+2]-cycloadditions with α-amino ester derivatives were achieved efficiently under both thermal or microwave conditions. Thus, we have developed a convenient methodology to access novel alkaloid-type analogues of the ergoline structure, in good to excellent overall yield.

Acknowledgment

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References and Notes

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(5) **General Procedure for the Synthesis of 7a,b**: Under a nitrogen atmosphere, a solution of indole-3-carboxaldehyde (**6a**) or 2-methylindole-3-carboxaldehyde (**6b**; 1 mmol) and thallium trifluoroacetate (1.2 mmol) in trifluoroacetic acid (2 mL/mmol) was stirred overnight at r.t. and the solvent was then removed under reduced pressure. The residue was dissolved in H_2O (4 mL/mmol) and then KI (4 mmol) was added. The reaction mixture was stirred for 4 h at r.t.,

quenched with aq sat. $Na_2S_2O_3$ and then extracted several times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in anhyd THF (10 mL/mmol), and then DMAP (1.5 mmol) was added, followed by the addition of Boc_2O (2 mmol). The reaction mixture was stirred for 2 h at r.t., quenched with an aq sat. NH_4Cl solution, and then extracted with Et_2O several times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography on silica, eluting with pentane–EtOAc (95:5), to give **7a**,**b**.

1-(*tert*-Butoxycarbonyl)-4-iodoindole-3-carboxaldehyde (7a): 93% yield; white powder; mp 108 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67 (s, 9 H), 7.08 (t, *J* = 8.0 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 8.32 (d, *J* = 8.0 Hz, 1 H), 8.38 (s, 1 H), 11.22 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.0, 83.1, 86.0, 115.4, 120.7, 126.2, 130.2, 132.3, 135.6, 136.9, 148.0, 185.8. IR: 3155, 3055, 1752, 1670, 1253, 1149 cm^{-1}. MS (EI): *m*/*z* (%) = 372.1 (47) $[MH]^+$, 338.7 (61), 272.4 (100), 214.4 (48).

1-(*tert*-Butoxycarbonyl)-4-iodo-2-methylindole-3-carboxadehyde (7b): yield: 74%; white powder; mp 109 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67 (s, 9 H), 2.91 (s, 3 H), 6.97 (t, *J* = 8.1 Hz, 1 H), 7.78 (d, *J* = 8.1 Hz, 1 H), 8.14 (d, *J* = 8.1 Hz, 1 H), 11.22 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2, 28.1, 81.8, 86.2, 115.0, 117.5, 125.3, 129.8, 135.8, 136.3, 146.1, 149.1, 187.7. IR: 3136, 3054, 1751, 1665, 1254, 1139 cm^{-1}. HMRS (EI): *m*/*z* calcd for $C_{15}H_{16}INO_3Na$: 408.00727; found: 408.00846.

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(8) **General Procedure for the Synthesis of 8 and 9**: Under a nitrogen atmosphere, a solution of **7** (1 mmol), tetrakis(triphenylphosphine)palladium (0.05 mmol) and allyltributylstannane or tributylvinylstannane (1.1 mmol) in anhyd THF (10 mL/mmol) was heated overnight at reflux. The reaction mixture was quenched with brine and then extracted several times with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica, eluting with pentane–EtOAc (90:10).

1-(*tert*-Butoxycarbonyl)-4-vinylindole-3-carboxaldehyde (8): 94% yield; white powder; mp 90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70 (s, 9 H), 5.42 (d, *J* = 10.9 Hz, 1 H), 5.75 (d, *J* = 17.3 Hz, 1 H), 7.37 (t, *J* = 7.9 Hz, 1 H), 7.54 (d, *J* = 7.9 Hz, 1 H), 7.94 (dd, *J* = 17.3, 10.9 Hz, 1 H), 8.14 (d, *J* = 7.9 Hz, 1 H), 8.27 (s, 1 H), 10.05 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.0, 85.7, 114.4, 115.6, 121.4, 123.0, 123.9, 125.9, 133.0, 136.7, 137.0, 138.6, 148.4, 184.9. IR: 3127, 3092, 1753, 1686, 1255, 1152, 996, 908 cm^{-1}. HMRS (EI): *m*/*z* calcd for $C_{16}H_{17}NO_3Na$: 294.11061; found: 294.11092.

1-(*tert*-Butoxycarbonyl)-4-allylindole-3-carboxaldehyde (9a): 87% yield; white powder; mp 91 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70 (s, 9 H), 4.01 (d, *J* = 6.0 Hz, 2 H), 4.91 (dd, *J* = 17.1, 1.7 Hz, 1 H), 5.04 (dd, *J* = 10.2, 1.7 Hz, 1 H), 6.06 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1 H), 7.19 (d, *J* = 8.0 Hz, 1 H), 7.36 (t, *J* = 8.0 Hz, 1 H), 8.13 (d, *J* = 8.0 Hz, 1 H), 8.30 (s, 1 H), 10.08 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1, 39.4, 85.6, 113.4, 115.6, 122.8, 125.1, 125.8, 126.0, 134.3, 137.0, 137.3, 137.5, 148.6, 185.4. IR: 3115, 3075, 1741, 1686, 1640, 1255, 1149, 1010, 918 cm^{-1}. HMRS (EI): *m*/*z* calcd for $C_{17}H_{19}NO_3Na$: 308.12626; found: 308.12584.

1-(*tert*-Butoxycarbonyl)-4-allyl-2-methylindole-3-carboxaldehyde (9b): 80% yield; white powder; mp 168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71 (s, 9 H), 2.94 (s, 3 H), 3.86 (d, *J* = 5.4 Hz, 2 H), 4.87 (dd, *J* = 17.2, 1.7 Hz, 1 H), 5.07 (dd, *J* = 10.2, 1.7 Hz, 1 H), 6.06 (ddt, *J* = 17.2, 10.2, 5.4 Hz, 1 H), 7.14 (d, *J* = 7.9 Hz, 1 H), 7.27 (t, *J* = 7.9 Hz, 1 H), 8.01 (d, *J* = 7.9 Hz, 1 H), 10.42 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3, 28.6, 40.0, 86.1, 113.7, 116.6, 119.5, 125.0, 125.8, 126.5, 132.4, 136.6, 137.3, 147.3, 150.1, 188.6. IR: 3075, 3011, 1751, 1665, 1272, 1142, 1004, 927 cm^{-1}. MS (EI): *m*/*z* (%) = 300.0 (70) $[MH]^+$, 251.7 (61), 200.4 (56), 176.6 (31), 143.3 (47), 122.8 (100).

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(11) **1-(*tert*-Butoxycarbonyl)-4[(trimethylsilyl)ethynyl]-indole-3-carboxaldehyde (10)**: Under a nitrogen atmosphere, a solution of 1-(*tert*-butoxycarbonyl)-4-iodoindole-3-carboxaldehyde (**7a**; 1 mmol), dichlorobis(triphenylphosphine)palladium (0.05 mmol), copper(I) iodide (0.1 mmol) and trimethylsilylacetylene (1.2 mmol) in anhyd THF (10 mL/mmol) was stirred for 10 min at 0 °C and then Et_3N (3 mmol) was added dropwise. The reaction mixture was stirred for 2 h at r.t., quenched with an aq sat. NH_4Cl solution and then extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by chromatography on silica, eluting with pentane–Et_2O (90:10), to give **10** in 96% yield as a white powder; mp 136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.30 (s, 9 H), 1.68 (s, 9 H), 7.32 (t, *J* = 8.0 Hz, 1 H), 7.50 (dd, *J* = 8.0, 1.0 Hz, 1 H), 8.26 (dd, *J* = 8.0, 1.0 Hz, 1 H), 8.36 (s, 1 H), 10.99 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.3, 28.0, 85.8, 99.4, 104.3, 114.6, 116.3, 121.4, 124.9, 127.7, 129.3, 130.8, 136.0, 148.6, 187.6. IR: 2151, 1749, 1676, 1252, 1149, 859 cm^{-1}. HMRS (EI): *m*/*z* calcd for $C_{19}H_{23}NO_3NaSi$: 364.13499; found: 364.13352.

(12) **General Procedure for the Synthesis of 11**:

Thermal Conditions: A solution of **8** or **9** (1 mmol) and α-amino ester **14** (2 mmol) in toluene (10 mL) was stirred and heated at reflux for 24 h. After evaporation of the solvent under reduced pressure, the crude product was purified by short column chromatography on silica.

Microwave Conditions: In a pyrex tube (2 × 15 mm), **8** or **9** (1 mmol) and α-amino ester **14** (2 mmol) in toluene (0.5 mL) were submitted to microwave irradiation (CEM Discoverer apparatus; 100 W, 110 °C) for 5 min. After cooling, the crude product was purified by short column chromatography on silica gel.

1-(*tert*-Butoxycarbonyl)-8-methyl-9-methyl-6,6a,7,8,9a-pentahydro-9-azaindeno[4,5,6-*cd*]indole-2,8-dicarboxylate (11a): 95% yield (Δ) and 99% yield (MW); yellow oil as a mixture of two diastereomers which were separated by column chromatography. Major diastereomer: yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.68 (s, 9 H), 1.87–2.02 (m, 1 H), 2.13–2.25 (m, 1 H), 2.63 (s, 3 H), 2.81–2.91 (m, 2 H), 3.07 (dd, *J* = 18.2, 7.4 Hz, 1 H), 3.53 (dd, *J* = 9.8, 4.9 Hz, 1 H), 3.74 (s, 3 H), 4.35 (d, *J* = 4.3 Hz, 1 H), 6.98 (d, *J* = 8.0 Hz, 1 H), 7.24 (t, *J* = 8.0 Hz, 1 H), 7.53 (s, 1 H), 7.76 (d, *J* = 8.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2, 30.2, 34.2, 36.2, 38.0, 51.6, 58.9, 63.7, 83.6, 112.6, 115.1, 120.4, 121.7, 125.1, 128.7, 129.4, 133.0, 150.2, 174.8. IR: 3019, 2980, 2951, 1735, 1718, 1439, 1370, 1301, 1281, 1256, 1216, 1149, 1120, 755, 667 cm^{-1}. HMRS (EI):

m/*z* calcd for $C_{21}H_{26}N_2O_4Na$: 393.17903; found: 393.17895. Minor diastereomer: yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.66 (s, 9 H), 1.85–1.96 (m, 1 H), 2.17–2.32 (m, 1 H), 2.43–2.55 (m, 1 H), 2.73 (s, 3 H), 2.87 (dd, *J* = 15.7, 12.0 Hz, 1 H), 3.13 (dd, *J* = 15.7, 3.9 Hz, 1 H), 3.76 (s, 3 H), 3.99 (dd, *J* = 8.7, 2.0 Hz, 1 H), 4.02 (dd, *J* = 8.4, 6.5 Hz, 1 H), 7.00 (d, *J* = 8.0 Hz, 1 H), 7.24 (t, *J* = 8.0 Hz, 1 H), 7.45 (s, 1 H), 7.76 (d, *J* = 8.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2, 32.5, 33.6, 37.3, 43.7, 51.7, 64.0, 65.7, 83.4, 112.9, 117.3, 119.4, 120.5, 125.2, 130.2, 132.0, 133.6, 150.2, 174.6. IR: 3016, 2980, 1740, 1702, 1458, 1440, 1370, 1240, 1216, 1153, 755, 666 cm^{-1}. HMRS (EI): *m*/*z* calcd for $C_{21}H_{26}N_2O_4Na$: 393.17903; found: 393.17801.

1-(*tert*-Butoxycarbonyl)-8-ethyl-9-benzyl-6,6a,7,8,9a-pentahydro-9-azaindeno[4,5,6-*cd*]indole-2,8-dicarboxylate (11b): 75% yield (Δ) and 90% yield (MW); viscous yellow oil as a single diastereomer. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.1 Hz, 3 H), 1.68 (s, 9 H), 1.95–2.08 (m, 1 H), 2.10–2.20 (m, 1 H), 2.71–2.84 (m, 1 H), 2.90–3.00 (m, 2 H), 3.62 (dd, *J* = 9.3, 5.1 Hz, 1 H), 3.96 (d, *J* = 13.6 Hz, 1 H), 4.05 (q, *J* = 7.1 Hz, 2 H), 4.19 (d, *J* = 13.6 Hz, 1 H), 4.48 (d, *J* = 4.7 Hz, 1 H), 7.00 (d, *J* = 7.2 Hz, 1 H), 7.15–7.30 (m, 6 H), 7.53 (s, 1 H), 7.77 (d, *J* = 7.2 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 28.3, 30.6, 34.5, 38.2, 52.3, 57.0, 60.3, 60.8, 83.6, 112.6, 116.1, 120.2, 122.3, 125.7, 126.9, 128.2, 128.5, 130.1, 133.1, 133.2, 139.3, 150.1, 174.8. IR: 3020, 2980, 1725, 1440, 1394, 1371, 1346, 1215, 1152, 1130, 756, 669 cm^{-1}. HMRS (EI): *m*/*z* calcd for $C_{28}H_{32}N_2O_4Na$: 483.22598; found: 483.22678.

2-(*tert*-Butoxycarbonyl)-7a-methyl-6a,9,10,11a-tetrahydro-6*H*-indolo[4,3-*fg*]pyrrolo-[1,2-*a*]indole-2,7a-dicarboxylate (11c): 97% yield (Δ) and 98% (MW); viscous oil, mixture of two inseparable diastereomers (ratio 60:40). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50–3.40 (m, 40 H), 3.78 (s, 6 H), 4.08 (d, *J* = 10.0 Hz, 1 H), 4.59 (d, *J* = 4.9 Hz, 1 H), 7.01 (d, *J* = 7.8 Hz, 2 H), 7.24 (t, *J* = 7.8 Hz, 2 H) 7.49 (s, 1 H), 7.69 (s, 1 H), 7.75–7.90 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.9, 26.7, 28.2, 31.5, 31.6, 37.6, 38.5, 39.7, 41.1, 42.1, 42.2, 51.2, 51.6, 52.5, 52.6, 57.3, 64.5, 76.1, 83.4, 83.6, 112.8, 113.0, 115.4, 117.7, 118.5, 120.3, 120.5, 122.6, 125.0, 125.2, 129.2, 129.9, 130.3, 131.6, 150.0, 177.1, 177.6. IR: 3020, 2980, 2952, 1727, 1439, 1386, 1371, 1297, 1281, 1215, 1152, 1132, 756, 669 cm^{-1}. HMRS (EI): *m*/*z* calcd for $C_{23}H_{28}N_2O_4Na$: 419.19468; found: 419.19534.

1-(*tert*-Butoxycarbonyl)-8-methyl-1,9-methyl-6,6a,7,8,9a-pentahydro-9-azaindeno[4,5,6-*cd*]indole-2,8-dicarboxylate (11d): 84% yield (Δ) and 97% yield (MW); viscous oil as a mixture of two diastereomers which were separated by column chromatography. Major diastereomer: viscous oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.68 (s, 9 H), 2.07–2.16 (m, 1 H), 2.30–2.49 (m, 5 H), 2.62 (s, 3 H), 2.83 (d, *J* = 8.2 Hz, 2 H), 3.76 (s, 3 H), 4.03 (dd, *J* = 8.5, 5.6 Hz, 1 H), 4.21 (d, *J* = 4.1 Hz, 1 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 7.14 (t, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6, 28.3, 31.9, 34.5, 34.8, 38.4, 51.3, 57.1, 63.2, 83.4, 113.1, 114.4, 119.9, 123.9, 127.4, 129.6, 134.1, 134.5, 151.1, 175.1. IR: 3021, 2980, 2950, 1728, 1454, 1370, 1328, 1215, 1145, 1102, 756, 668 cm^{-1}. HMRS (EI): *m*/*z* calcd for $C_{22}H_{28}N_2O_4Na$: 407.19468; found: 407.19663. Minor diastereoisomer: viscous oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.66–1.80 (m, 10 H), 2.30–2.56 (m, 5 H), 2.67–2.80 (m, 4 H), 3.22 (dd, *J* = 15.6, 3.9 Hz, 1 H), 3.69 (dd, *J* = 8.8, 6.3 Hz, 1 H), 3.76 (s, 3 H), 3.95 (d, *J* = 10.8 Hz, 1 H), 6.97 (d, *J* = 8.0 Hz, 1 H), 7.15 (t, *J* = 8.0 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.1, 28.4, 32.0, 33.0, 39.3, 39.6, 52.1, 64.7, 68.5, 83.4, 113.4, 115.4, 120.4, 124.0, 129.2, 130.5, 130.6, 135.0, 151.0, 175.1. IR: 2980, 2929, 1734, 1446, 1370, 1327, 1214, 1146, 1098, 755, 668 cm^{-1}. HMRS (EI): *m*/*z* calcd for $C_{22}H_{28}N_2O_4Na$: 407.19468; found: 407.19622.

2-(*tert*-Butoxycarbonyl)-7a-methyl-1-methyl-6a,9,10,11a-tetrahydro-6*H*-indolo[4,3-*f*,*g*]pyrrolo-[1,2-*a*]indole-2,7a-dicarboxylate 11e: 90% yield (Δ) and 95% yield (MW); viscous oil, mixture of two inseparable diastereoisomers (ratio 80:20). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50–3.20 (m, 46 H), 3.78 (s, 6 H), 4.00 (dd, *J* = 11.5, 2.0 Hz, 1 H), 4.47 (d, *J* = 5.2 Hz, 1 H), 6.96 (d, *J* = 8.0 Hz, 2 H), 7.17 (t, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 14.9, 25.8, 26.4, 28.2, 28.3, 31.4, 32.5, 37.8, 38.5, 40.1, 41.1, 42.8, 43.1, 50.5, 52.2, 52.4, 57.5, 64.5, 71.9, 83.6, 84.7, 113.3, 113.4, 114.0, 120.1, 120.4, 123.7, 123.9, 124.9, 126.6, 128.6, 130.5, 133.8, 134.0, 134.5, 136.8, 150.0, 174.0. IR: 3020, 2980, 1729, 1442, 1385, 1374, 1296, 1281, 1213, 1151, 1132, 755, 670 cm^{-1}. HMRS (EI): *m*/*z* calcd for $C_{24}H_{30}N_2O_4Na$: 433.21033; found: 433.21232.

(13) **General Procedure for the Synthesis of 16**: A solution of **10** (1 mmol), α-amino ester **14** (2 mmol) and sulfur (approx. 100 mg) in toluene (10 mL) was stirred and heated at reflux for 24 h. After evaporation of the solvent under reduced pressure, the crude product was purified by short column chromatography on silica gel.

2-*tert*-Butyl-7-methyl-6-(trimethylsilyl)-8-methylpentaleno[1,2,3-*cd*]indole-2,7-dicarboxylate (16a): 38% yield; white powder; mp 116 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.34 (s, 9 H), 1.64 (s, 9 H), 3.90 (s, 3 H), 4.03 (s, 3 H), 7.14 (s, 1 H), 7.21 (dd, *J* = 8.2, 7.7 Hz, 1 H), 7.32 (dd, *J* = 7.7, 1.0 Hz, 1 H), 7.98 (dd, *J* = 8.2, 1.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.3, 28.2, 38.2, 51.4, 86.1, 97.8, 104.0, 107.9, 114.8, 116.0, 125.7, 134.6, 143.1, 116.4, 117.4, 124.7, 126.3, 150.4, 162.2. IR: 1721, 1710, 1364, 1314, 1250, 1158, 1101, 842 cm^{-1}. MS (EI): *m*/*z* (%) = 425.0 (18) $[MH]^+$, 370 (24), 369.0 (100), 337 (55), 325 (19), 143.1 (27) 122 (65).

2-*tert*-Butyl-7-ethyl-6-(trimethylsilyl)-8-benzylpentaleno[1,2,3-*cd*]indole-2,7-dicarboxylate (16b): 87% yield; white powder; mp 129 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.26 (s, 9 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.64 (s, 9 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 5.56 (s, 2 H), 7.15–7.35 (m, 8 H), 7.98 (d, *J* = 8.2 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.1, 14.3, 28.2, 53.5, 60.4, 83.4, 97.8, 103.8, 107.9, 114.7, 116.2, 125.6, 133.7, 142.9, 115.9, 124.6, 126.1, 127.3, 127.7, 128.7, 116.4, 137.7, 150.1, 161.8. IR: 2973, 2143, 1731, 1715, 1434, 1394, 1366, 1336, 1315, 1265, 1156, 1102, 842 cm^{-1}. HMRS (EI): *m*/*z* calcd for $C_{30}H_{34}N_2O_4NaSi$: 537.21856; found: 537.21889.

(14) Bashiardes, G.; Safir, I.; Mohamed, A. S.; Barbot, F.; Laduranty, J. *Org. Lett.* **2003**, *5*, 4915.

