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# Selective reduction and functionalization of diethyl 1-alkyl-1*H*-indole-2,3-dicarboxylates

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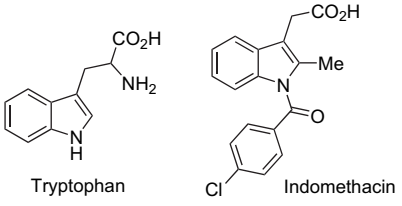
**Abstract**

A convenient and highly selective reduction of easily accessible indole-2,3-dicarboxylates is described. Ten different 1-alkyl-2-formyl-1*H*-indole-3-carboxylates are obtained in high yield and represent interesting building blocks for novel indoles.


## 1. Introduction

Indole and its derivatives have been termed as 'privileged pharmacologic structures' since they bind to many biological receptors with high affinity.[1] In addition, the indole moiety is found in numerous natural products and is an important building block of several families of alkaloids.[2] Many of them have significant biological activity such as Indomethacin[3] (anti-inflammatory), Vincristine[4] (anti-cancer), Fluvastatin[5] (cholesterol-lowering), Vinblastine[6] (anti-cancer), and tryptophan, which is an essential amino acid[7] (Scheme 1).




Scheme 1. Selected biologically active indoles.

Due to their importance as one of the most represented building blocks in natural products and known marketed drugs, there is a continuing interest in the development of improved methods for the synthesis of indoles.[8,9] In recent years especially domino sequences provided efficient complementary access to various indoles.[10] Though, many catalytic methods exist for the preparation of indoles, still the most famous route for the construction of the indole ring constitutes the Fischer indole synthesis.[9]

For some time, we have been interested in the improvement and exploration of methodologies for the synthesis and functionalization of indoles. For example, we developed a titanium-catalyzed as well as zinc-mediated synthesis of functionalized tryptamines and tryptophol derivatives starting from commercially available arylhydrazines and alkynes.[11] More recently, we reported also a transition-metal-free one-pot synthesis of indole-2,3-dicarboxylates **1** from arylhydrazines and acetylene dicarboxylates.[12] Based on this work, we became interested in the selective reduction of indole-2,3-dicarboxylates (Scheme 2). Obviously, such a selective protocol would offer direct access to a variety of novel indole derivatives. Here, we report our results on this project.

Clearly, reduction of carboxylic acids, esters, and amides is an essential tool for the synthesis of aldehydes, alcohols, and amines.[13] Especially, selective reduction to aldehydes is important, as the highly reactive formyl group can be easily employed in numerous C–C-, and C–N-coupling reactions as well as other transformations.

As shown in Scheme 2, chemoselective reduction of 1*H*-indole-2,3-dicarboxylates **1** could provide different functionalized

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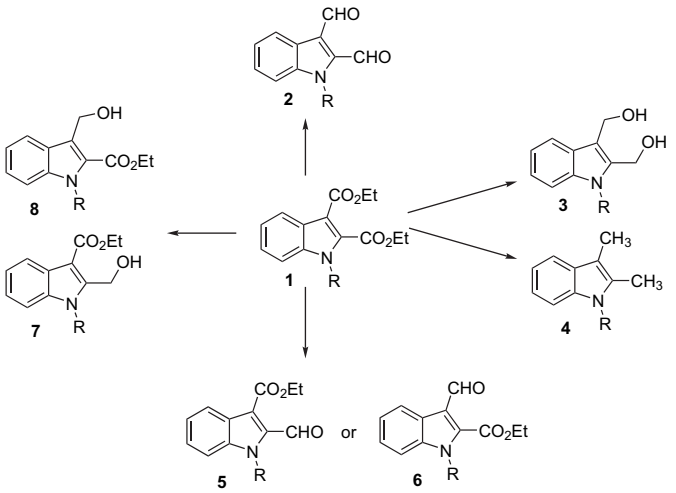


Scheme 2. Potential reductions of the indole-2,3-dicarboxylates.

indoles such as 1-alkyl-1*H*-indole-2,3-dicarbaldehyde **2**, (1-alkyl-1*H*-indole-2,3-diyl)-dimethanol **3**, 1-alkyl-2,3-dimethyl-1*H*-indole **4**, isomeric 2,3-formylindole-carboxylates **5** or **6**, and 2,3-hydroxymethylindole-carboxylates **7** or **8**.

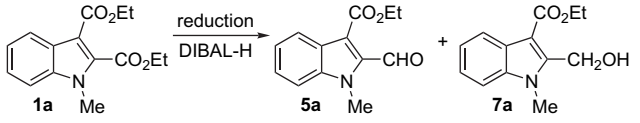
## 2. Results and discussion

At the starting point of our investigations, we studied the reaction of indole 2,3-diester **1a** in the presence of standard metal hydrides at different temperatures. However, in the presence of $NaBH_4$ and $NaCNBH_3$ only the recovered starting material was obtained.

Unfortunately, under more drastic conditions treatment of **1a** with $LiAlH_4$ (reflux temperature) afforded a complex mixture of several products.

As shown in Table 1 reduction using DIBAL-H at room temperature was more selective but also afforded a mixture of products. Here, aldehyde **5a** and alcohol **7a** along with the recovered starting material are observed. When the reduction was carried out in the presence of an excess (2.5 equiv) of DIBAL-H at −78 °C for 5 min, full conversion is seen and the alcohol **7a** is obtained as major product in 60% yield along with some aldehyde **5a**. Reducing the amount of DIBAL-H (2.0 equiv) as well as the reaction time (3 min) afforded the aldehyde **5a** with an excellent yield of 90% as the only product of the reaction. To the best of our knowledge, there is no report on chemoselective reduction of one of the ester group of indole-2,3-dicarboxylates to give 2-formyl-1-alkyl-1*H*-indole-3-carboxylates.

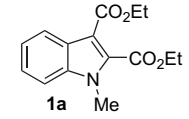
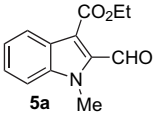
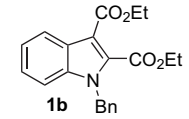
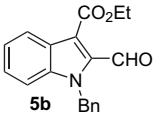
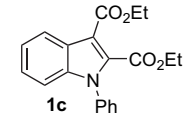
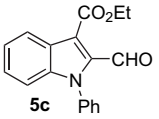
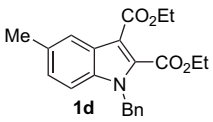
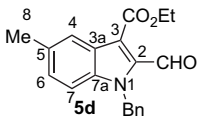
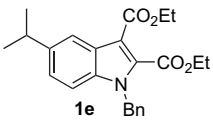
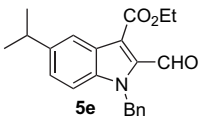
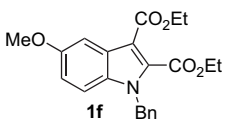
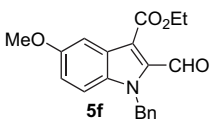
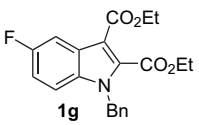
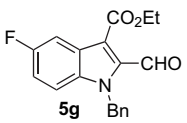
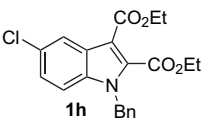
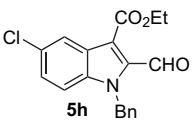
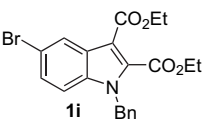
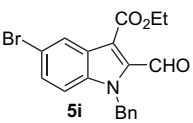
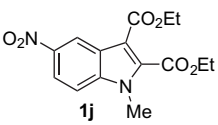
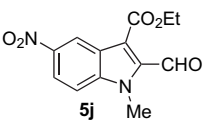
Table 1
Reduction of **1a** under different conditions



| Entry | DIBAL-H (equiv) | Temp (°C) | Time (min) | Yield[a] (%) (**5a**) | Yield[a] (%) (**7a**) | Yield[a] (%) (**1a**) |
|---|---|---|---|---|---|---|
| 1 | 1.5 | 0 | 5 | 23 | 24 | 50 |
| 2 | 2.0 | 0 | 5 | 9 | 40 | 49 |
| 3 | 2.5 | −78 | 5 | 30 | 60 | — |
| 4 | 2.0 | −78 | 5 | 60 | 30 | — |
| 5 | 2.0 | −78 | 3 | 90 | — | — |

[a] Isolated yield.

Table 2
Chemoselective reduction of indole-2,3-dicarboxylates: substrate scope[a]

| Entry | Substrate | Product | Yield[b] (%) |
|---|---|---|---|
| 1 |  **1a** |  **5a** | 90 |
| 2 |  **1b** |  **5b** | 62 |
| 3 |  **1c** |  **5c** | 75 |
| 4 |  **1d** |  **5d** | 75 |
| 5 |  **1e** |  **5e** | 86 |
| 6 |  **1f** |  **5f** | 60 |
| 7 |  **1g** |  **5g** | 90 |
| 8 |  **1h** |  **5h** | 67 |
| 9 |  **1i** |  **5i** | 67 |
| 10 |  **1j** |  **5j** | 60 |

[a] Reaction conditions: indole 2,3-dicarboxylates (1.0 equiv), DIBAL-H (2.0 equiv), $CH_2Cl_2$, −78 °C, 3 min.
[b] Isolated yield.

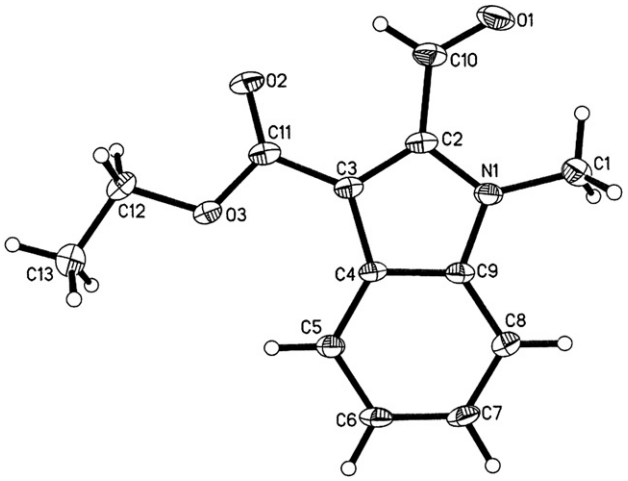



Figure 1. X-ray crystal structure of ethyl 2-formyl-1-methyl-1*H*-indole-3-carboxylate **5a**. The thermal ellipsoids correspond to 30% probability.

At this point, it should be noted that there are only few methods known in the literature for the preparation of 2-formyl-indole-3-carboxylates.[14]

The promising results obtained with the model compound encouraged us to study the general scope and limitations of this protocol for the reduction of different substituted indole-2,3-dicarboxylates (Table 2). Fluoro-, chloro-, and bromo-substituted diethyl indole-2,3-dicarboxylates **1g–1i** readily underwent reduction with DIBAL-H to afford the corresponding aldehydes **5g–5i** in good yield (67–90% yield) with no over-reduction of the halide substituents observed. Likewise, the nitro-substituted indole **1j** gave the corresponding aldehyde **5j** in 60% isolated yield. Previously, the product **1j** has been obtained by nitration of **1a**.[15] Noteworthy, all isolated indole-2-aldehydes are stable solids, which did not oxidize easily in air. In all cases, spectroscopic characterization of the products by NMR revealed the presence of one aldehyde and one ester group. The position of the formyl group is established unambiguously by NOE measurements. For example, in the two-dimensional NOESY spectrum of **5d** correlations are found for the proton H-4 with methyl substituent on the phenyl ring, the $OCH_2$, and the $OCH_2CH_3$ confirming the ester group being placed in C-3 position. In addition, we were able to confirm the regioselective reduction by X-ray crystallographic analysis of **5a** (Fig. 1).[16] Suitable crystals were obtained by recrystallization from dichloromethane.

Obviously, 2-formyl indole-3-carboxylates are versatile building blocks for selective reactions either at the 2- or 3-position of the indole ring. Therefore, we turned our attention to further functionalization reactions of **5a**. In some preliminary studies, the reductive amination with benzylamine in the presence of $NaCNBH_3$ proceeded smoothly at the formyl group to give **10** in 80% yield (Scheme 3). Notably, there is no side reaction at the ester group observed.

Moreover, addition of organometallic reagents progressed highly selectively at the 2-position. Hence, the reaction of the vinyl magnesium bromide with **5a** yielded the corresponding allylic alcohol **9** in 82%. As expected in the NOESY spectrum of compound **9** correlations are found for the proton H-4 with $OCH_2$ and $OCH_2CH_3$ as well as NMe with the protons H-7, H-9, H-10, and H-11 confirming the proposed structure.

## 3. Conclusion

In conclusion, we have developed a convenient and fast reduction of 1*H*-indole-2,3-dicarboxylates. The resulting products **5a–j** are obtained with excellent selectivity in good yield. It is predicted that alkyl 2-formyl-1-alkyl-1*H*-indole-3-carboxylates constitute useful building blocks, which will lead in three easy steps to a variety of novel 2,3-disubstituted indoles from commercially available arylhydrazines and acetylene dicarboxylates.

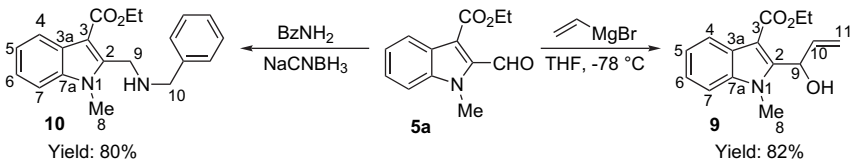
## 4. Experimental

### 4.1. General

All reactions were carried out under an argon atmosphere. Chemicals were purchased from Aldrich, Fluka, Acros, and Strem, and unless otherwise noted were used without further purification. All compounds were characterized by $^1$H NMR, $^{13}$C NMR, MS, HRMS, and IR spectroscopy. $^1$H and $^{13}$C NMR spectra were recorded on Bruker AV 300, AV 400, and AV 500 spectrometers. The $^1$H and $^{13}$C NMR chemical shifts are reported relative to the center of solvent resonance ($CDCl_3$: 7.25 ($^1$H), 77.0 ($^{13}$C)). For compounds **5d**, **9**, and **10**, a complete assignment of the $^1$H- and $^{13}$C-signal is given based on two-dimensional NMR spectra (COSY, NOESY, and C,H-correlation). EI mass spectra were recorded on an AMD 402 spectrometer (70 eV, AMD Intectra GmbH). IR spectra were recorded on an FTIR Nicolet 6700 (Thermo ELECTRON CORPORATION). GC was performed on a Hewlett–Packard HP 6890 chromatograph with a 30 m HP5 column. All yields reported in Tables 1 and 2 refer to isolated yields.

### 4.2. General procedure for the preparation of aldehydes

A solution of diethyl 1-alkyl-1*H*-indole-2,3-dicarboxylate (0.25 mmol) in $CH_2Cl_2$ at −78 °C was treated with DIBAL-H (0.42 ml, 0.5 mmol, 1 M solution in toluene). The reaction




Scheme 3. Potential reduction examples of the indole-2,3-dicarboxylates.

mixture was stirred at −78 °C for 3 min and then quenched with 1 M HCl and MeOH. After warming up to room temperature, $H_2O$ was added and the aqueous layer was extracted three times with $Et_2O$. The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. Chromatography on silica gel with hexane–EtOAc (95:5) as the eluent afforded the aldehydes **5a–j**.

*4.2.1. Ethyl 2-formyl-1-methyl-1H-indole-3-carboxylate (**5a**)*

Isolated yield: 90% (mp: 76–77 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm)=1.47 (t, $J$=7.2 Hz, 3H), 4.05 (s, 3H), 4.45 (q, $J$=7.2 Hz, 2H), 7.26–7.45 (m, 3H), 8.23 (br d, $J$=8.0 Hz, 1H), 10.77 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm)=14.4 ($CH_3$), 32.5 ($CH_3$), 60.8 ($CH_2$), 110.5 (CH), 115.0, 123.2 (CH), 123.8 (CH), 125.5, 126.9 (CH), 136.3, 136.7, 164.3, 186.5 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=231 ($M^+$, 76), 203 (21), 202 (42), 188 (21), 186 (32), 175 (26), 159 (16), 158 (100), 157 (26), 131 (16), 130 (17), 103 (12), 89 (12), 77 (12). HRMS (EI) calcd for $C_{13}H_{13}NO_3$: 231.0890; found: 231.0889. FTIR: (KBr, $cm^{-1}$)= 3077, 3025, 2987, 2906, 1699, 1662, 1612, 1516, 1447, 1396, 1383, 1338, 1267, 1218, 1175, 1160, 1106, 1036, 908, 890, 785, 752, 740, 726, 517.

*4.2.2. Ethyl 1-benzyl-2-formyl-1H-indole-3-carboxylate (**5b**)*

Isolated yield: 62% (mp: 112–113 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm)=1.48 (t, $J$=7.2 Hz, 3H), 4.48 (q, $J$=7.2 Hz, 2H), 5.87 (s, 2H), 7.04 (m, 2H), 7.17–7.42 (m, 6H), 8.31 (br d, $J$=8.0 Hz, 1H), 10.83 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm)=14.4 ($CH_3$), 48.4 ($CH_2$), 60.9 ($CH_2$), 111.2 (CH), 115.9, 123.3 (CH), 123.9 (CH), 125.7, 126.4 (2CH), 127.2 (CH), 127.5 (CH), 128.6 (2CH), 135.8, 136.8, 138.6, 164.2, 186.1 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=307 ($M^+$, 16), 262 (12), 261 (42), 260 (37), 233 (14), 232 (36), 204 (17), 157 (11), 149 (37), 123 (48), 121 (18), 119 (21), 115 (14), 111 (15), 109 (15), 105 (22), 97 (23), 95 (29), 91 (100), 83 (29), 81 (24), 77 (27), 69 (71), 57 (50). HRMS (EI) calcd for $C_{19}H_{17}NO_3$: 307.1208; found: 307.1202. FTIR: (KBr, $cm^{-1}$)=3058, 3030, 2932, 1699, 1671, 1518, 1469, 1450, 1415, 1384, 1338, 1274, 1238, 1175, 1161, 1146, 1026, 913, 868, 785, 747, 730.

*4.2.3. Ethyl 2-formyl-1-phenyl-1H-indole-3-carboxylate (**5c**)*

Isolated yield: 75% (mp: 83–84 °C). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ (ppm)=1.48 (t, $J$=7.2 Hz, 3H), 4.50 (q, $J$=7.2 Hz, 2H), 7.05 (m, 1H), 7.22–7.37 (m, 4H), 7.51 (m, 3H), 8.36 (m, 1H), 10.75 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ (ppm)=14.5 ($CH_3$), 61.0 ($CH_2$), 111.9 (CH), 115.9, 123.6 (CH), 123.6 (CH), 125.4, 127.2 (CH), 127.6 (2CH), 128.8 (CH), 129.3 (2CH), 136.7, 137.4, 139.8, 164.3, 184.3 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=293 ($M^+$, 32), 264 (40), 248 (36), 247 (95), 237 (12), 221 (15), 220 (100), 219 (53), 218 (35), 193 (18), 191 (49), 190 (20), 165 (27), 158 (15), 77 (12), 57 (13), 55 (10). HRMS (EI) calcd for $C_{18}H_{15}NO_3$: 293.1046; found: 293.1044. FTIR: (KBr, $cm^{-1}$)=3054, 2980, 2952, 2899, 1700, 1679, 1597, 1516, 1502, 1482, 1454, 1395, 1381, 1343, 1263, 1241, 1183, 1123, 1065, 1020, 1065, 1020, 940, 773, 753, 698, 562.

*4.2.4. Ethyl 1-benzyl-2-formyl-5-methyl-1H-indole-3-carboxylate (**5d**)*

Isolated yield: 75% (mp: 97–98 °C). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ppm)=1.48 (t, $^3J$=7.2 Hz, 3H, $OCH_2CH_3$), 2.48 (s, 3H, $Me_{(8)}$), 4.49 (q, $^3J$=7.2 Hz, 2H, $OCH_2$), 5.87 (s, 2H, H-8), 7.04 (m, 2H, *o*-Ph), 7.18–7.25 (m, 4H, H-6, *m*-, *p*-Ph), 7.30 (d, $^3J_{6,7}$=8.5 Hz, 1H, H-7), 8.09 (br s, 1H, H-4), 10.79 (s, 1H, CHO). $^{13}$C NMR (125.8 MHz, $CDCl_3$): $\delta$ (ppm)=14.5 ($OCH_2CH_3$), 21.7 ($Me_{(8)}$), 48.5 (C-8), 60.8 ($OCH_2$), 110.9 (C-7), 115.3 (C-3), 123.1 (C-4), 126.0 (C-3), 126.4 (*o*-Ph), 127.5 (*p*-Ph), 128.7 (*m*-Ph), 129.3 (C-6), 133.1 (C-5), 135.7 (C-2), 137.0, 137.2 (C-7a, *i*-Ph), 164.4 (COO), 186.1 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=321 ($M^+$, 28), 276 (18), 275 (71), 274 (62), 256 (57), 247 (20), 218 (15), 111 (14), 97 (20), 95 (16), 91 (100), 83 (20), 71 (20), 69 (22), 57 (31), 55 (28). HRMS (EI) calcd for $C_{20}H_{19}NO_3$: 321.1359; found: 321.1358. FTIR: (KBr, $cm^{-1}$)=3066, 3033, 2985, 2922, 1693, 1669, 1515, 1482, 1452, 1413, 1384, 1351, 1304, 1270, 1234, 1164, 1133, 1030, 1011, 909, 871, 799, 772, 718, 694.

*4.2.5. Ethyl 1-benzyl-2-formyl-5-isopropyl-1H-indole-3-carboxylate (**5e**)*

Isolated yield: 86% (mp: 73–74 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm)=1.31 (d, $J$=7.0 Hz, 6H), 1.49 (t, $J$=7.2 Hz, 3H), 3.05 (sep, $J$=7.0 Hz, 1H), 4.49 (q, $J$=7.2 Hz, 2H), 5.85 (s, 2H), 7.05 (m, 2H), 7.19–7.35 (m, 5H), 8.15 (m, 1H), 10.80 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm)=14.4 ($CH_3$), 24.2 (2 $CH_3$), 34.2 (CH), 48.5 ($CH_2$), 60.8 ($CH_2$), 111.0 (CH), 115.5, 120.3 (CH), 125.9, 126.4 (2CH), 127.0 (CH), 127.4 (CH), 128.6 (2CH), 135.6, 136.9, 137.4, 144.2, 164.3, 186.0 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=349 ($M^+$, 34), 304 (21), 303 (80), 302 (90), 276 (12), 275 (16), 274 (64), 260 (17), 232 (10), 91 (100), 65 (11). HRMS (EI) calcd for $C_{22}H_{23}NO_3$: 349.1672; found: 349.1669. FTIR: (KBr, $cm^{-1}$)=3064, 3033, 2959, 2929, 2870, 1701, 1671, 1621, 1606, 1516, 1482, 1454, 1411, 1383, 1353, 1282, 1235, 1187, 1163, 1130, 1030, 998, 906, 890, 806, 705.

*4.2.6. Ethyl 1-benzyl-2-formyl-5-methoxy-1H-indole-3-carboxylate (**5f**)*

Isolated yield: 60% (mp: 101–102 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm)=1.48 (t, $J$=7.2 Hz, 3H), 3.89 (s, 3H), 4.48 (q, $J$=7.2 Hz, 2H), 5.86 (s, 2H), 7.02–7.09 (m, 3H), 7.22–7.33 (m, 4H), 7.73 (d, $J$=2.0 Hz, 1H), 10.78 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm)=14.4 ($CH_3$), 48.6 ($CH_2$), 55.6 ($CH_3$), 60.8 ($CH_2$), 103.2 (CH), 112.2 (CH), 114.9, 119.3 (CH), 126.4 (2CH), 126.7, 127.5 (CH), 128.7 (2CH), 134.1, 135.6, 136.9, 156.7, 164.4, 185.9 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=337 ($M^+$, 35), 292 (14), 291 (51), 290 (53), 263 (17), 262 (47), 149 (11), 97 (14), 91 (100), 83 (18), 71 (16), 69 (22), 57 (28). HRMS (EI) calcd for $C_{20}H_{19}NO_4$: 337.1308; found:

337.1301. FTIR: (KBr, $cm^{-1}$)=3117, 3030, 3007, 2981, 2927, 2843, 1697, 1661, 1617, 1575, 1509, 1487, 1467, 1408, 1384, 1342, 1303, 1219, 1205, 1179, 1148, 1126, 1081, 1031, 988, 918, 867, 846, 816, 775, 742, 711.

#### 4.2.7. Ethyl 1-benzyl-2-formyl-5-fluoro-1H-indole-3-carboxylate (**5g**)

Isolated yield: 90% (mp: 103–104 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm)=1.49 (t, $J$=7.2 Hz, 3H), 4.49 (q, $J$=7.2 Hz, 2H), 5.87 (s, 2H), 7.03 (m, 2H), 7.16 (dt, $J_{H,F}$=9.0 Hz, $J$=9.0, 2.5 Hz, 1H), 7.22–7.28 (m, 3H), 7.35 (dd, $J$=9.0 Hz, $J_{H,F}$=4.5 Hz, 1H), 7.94 (dd, $J_{H,F}$=9.5 Hz, $J$=2.5 Hz, 1H), 10.84 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm)=14.4 ($CH_3$), 48.7 ($CH_2$), 61.0 ($CH_2$), 108.5 (d, $J_{F,C}$=25.2 Hz, CH), 112.5 (d, $J_{F,C}$=9.5 Hz, CH), 115.5 (d, $J_{F,C}$=5.5 Hz), 116.5 (d, $J_{F,C}$=27.4 Hz, CH), 126.2 (d, $J_{F,C}$=11.0 Hz), 126.4 (2CH), 127.7 (CH), 128.7 (2CH), 135.1, 136.5, 136.8, 159.6 (d, $J_{F,C}$=241.0 Hz), 163.9, 186.1 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=325 ($M^+$, 28), 280 (20), 279 (72), 278 (65), 251 (20), 250 (61), 222 (24), 92 (10), 91 (100), 65 (16). HRMS (EI) calcd for $C_{19}H_{16}FNO_3$: 325.1108; found: 325.1100. FTIR: (KBr, $cm^{-1}$)=3105, 3043, 2982, 2926, 1705, 1657, 1513, 1493, 1461, 1413, 1390, 1260, 1237, 1214, 1176, 1160, 1144, 1126, 1028, 993, 939, 876, 857, 810, 786, 714.

#### 4.2.8. Ethyl 1-benzyl-2-formyl-5-chloro-1H-indole-3-carboxylate (**5h**)

Isolated yield: 67% (mp: 88–89 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm)=1.47 (t, $J$=7.2 Hz, 3H), 4.47 (q, $J$=7.2 Hz, 2H), 5.84 (s, 2H), 7.00 (m, 2H), 7.14–7.33 (m, 5H), 8.27 (br s, 1H), 10.80 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm)=14.4 ($CH_3$), 48.7 ($CH_2$), 61.1 ($CH_2$), 112.4 (CH), 115.2, 123.2 (CH), 126.4 (2CH), 126.5, 127.7 (CH), 127.8 (CH), 128.8 (2CH), 129.4, 136.4, 136.5, 136.9, 163.8, 186.0 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=341 ($M^+$, 20), 297 (16), 296 (28), 295 (46), 294 (48), 267 (20), 266 (37), 204 (10), 91 (100), 65 (13). HRMS (EI) calcd for $C_{19}H_{16}ClNO_3$: 341.0813; found: 341.0811. FTIR: (KBr, $cm^{-1}$)=3101, 3068, 3057, 2958, 2983, 2925, 2856, 1695, 1676, 1515, 1499, 1462, 1453, 1412, 1384, 1347, 1291, 1259, 1233, 1160, 1129, 1069, 1031, 996, 987, 923, 877, 866, 801, 781, 759, 738, 701.

#### 4.2.9. Ethyl 1-benzyl-2-formyl-5-bromo-1H-indole-3-carboxylate (**5i**)

Isolated yield: 67% (mp: 109–110 °C). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ (ppm)=1.48 (t, $J$=7.2 Hz, 3H), 4.49 (q, $J$=7.2 Hz, 2H), 5.85 (s, 2H), 7.01 (m, 2H), 7.20–7.30 (m, 4H), 7.47 (dd, $J$=9.0, 2.0 Hz, 1H), 8.45 (d, $J$=2.0 Hz, 1H), 10.82 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ (ppm)=14.4 ($CH_3$), 48.6 ($CH_2$), 61.1 ($CH_2$), 112.8 (CH), 115.0, 117.1, 126.3 (2CH), 126.4 (CH), 127.0, 127.7, 128.8 (2CH), 130.3, 136.3, 136.4, 137.1, 163.8, 186.0 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=387 ($M^{+2}$, 15), 385 ($M^+$, 15), 341 (39), 340 (39), 339 (39), 338 (28), 312 (28), 310 (22), 304 (12), 91 (100), 65 (10). HRMS (EI) calcd for $C_{19}H_{16}BrNO_3$: 385.0308; found: 385.0302. FTIR: (KBr, $cm^{-1}$)=3100, 3037, 2981, 2923, 1695, 1676, 1515, 1452, 1412, 1383, 1347, 1290, 1259, 1234, 1160, 1130, 1112, 1056, 1030, 987, 921, 878, 865, 799, 781, 732, 698.

#### 4.2.10. Ethyl 1-methyl-2-formyl-5-nitro-1H-indole-3-carboxylate (**5j**)

Isolated yield: 60% (mp: 185–186 °C). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (ppm)=1.49 (t, $J$=7.2 Hz, 3H), 4.20 (s, 3H), 4.50 (q, $J$=7.2 Hz, 2H), 8.16 (dd, $J$=9.0, 2.0 Hz, 1H), 8.40 (d, $J$=9.0 Hz, 1H), 8.42 (d, $J$=2.0 Hz, 1H), 10.87 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (ppm)=14.4 ($CH_3$), 33.0 ($CH_3$), 61.3 ($CH_2$), 107.6 (CH), 114.7, 117.7 (CH), 124.6 (CH), 129.5, 137.3, 139.7, 146.3, 163.4, 186.8 (CHO). MS (EI, 70 eV): *m/z* (relative intensity)=276 ($M^+$, 56), 248 (23), 247 (23), 220 (30), 203 (100), 202 (28), 185 (20), 157 (25), 128 (18), 102 (12), 87 (11). FTIR: (KBr, $cm^{-1}$)=3121, 3091, 1703, 1672, 1515, 1471, 1406, 1397, 1340, 1260, 1218, 1162, 1123, 1070, 1027, 933, 887, 837, 736.

### 4.3. Ethyl 2-(1-hydroxyallyl)-1-methyl-1H-indole-3-carboxylate (**9**)

To a solution of ethyl 2-formyl-1-alkyl-1*H*-indole3-carboxylate (0.151 mmol) in 5 mL dry THF at −78 °C was treated with allyl-magnesium-bromide (0.166 mmol). The reaction mixture was stirred at −78 °C for 30 min. After removal of the solvent and purification by column chromatography (eluent: hexane–EtOAc=80:20) yielded **9** (82%) as colorless oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ppm)=1.48 (t, $^3J$=7.2 Hz, 3H, Me), 3.78 (s, 3H, NMe), 4.38–4.48 (m, 2H, $OCH_2$), 5.15–5.21 (m, 2H, H-11), 5.70 (m, 1H, H-9), 6.17 (ddd, $^3J_{10,11(trans)}$=17.0 Hz, $^3J_{10,11(cis)}$=10.4 Hz, $^3J_{9,10}$=5.7 Hz, 1H, H-10), 6.35 (d, $J$=10.5 Hz, 1H, OH), 7.25–7.31 (m, 2H, H-5,6), 7.34 (m, 1H, H-7), 8.13 (m, 1H, H-4). $^{13}$C NMR (125.8 MHz, $CDCl_3$): $\delta$ (ppm)=14.4 (Me), 30.6 (NMe), 60.6 ($OCH_2$), 68.1 (C-9), 104.1 (C-3), 109.7 (C-7), 115.7 (C-11), 122.0 (C-4), 122.3 (C-5), 122.9 (C-6), 126.3 (C-3a), 136.6 (C-7a), 137.4 (C-10), 149.0 (C-2), 167.7 (CO). MS (EI, 70 eV): *m/z* (relative intensity)=259 ($M^+$, 36), 214 (24), 213 (100), 186 (29), 185 (31), 184 (54), 170 (10), 169 (13), 168 (15), 158 (21), 157 (23), 130 (10). HRMS (EI) calcd for $C_{15}H_{17}NO_3$: 259.1202; found: 259.1200. FTIR: (neat, $cm^{-1}$)=3409, 3054, 2980, 2936, 1689, 1661, 1523, 1472, 1404, 1376, 1351, 1330, 1287, 1219, 1163, 1104, 1032, 990, 928, 878, 790, 753, 741.

### 4.4. Ethyl 2-(benzylamino)methyl-1H-indole-3-carboxylate (**10**)

A solution of ethyl 2-formyl-1-alkyl-1*H*-indole-3-carboxylate (0.216 mmol), benzylamine (0.259 mmol), and $NaCNBH_3$ (0.216 mmol) in 6 mL methanol was stirred for 20 h at room temperature. After removal of the solvent and purification by column chromatography (eluent: EtOAc) yielded **10** (80%) as colorless oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ppm)=1.43 (t, $^3J$=7.2 Hz, 3H), 2.24 (br, 1H, NH), 3.73 (s, 3H, $Me_{(8)}$),

3.89 (s, 2H, H-10), 4.27 (s, 2H, H-9), 4.42 (q, $^3J$=7.2 Hz, 2H, $OCH_2$), 7.26–7.40 (m, 8H, H-5,6,7,Ph), 8.17 (m, 1H, H-4). $^{13}C$ NMR (125.8 MHz, $CDCl_3$): $\delta$ (ppm)=14.5 (Me), 29.8 ($Me_{(8)}$), 42.8 (C-9), 53.5 (C-10), 59.6 ($OCH_2$), 105.0 (C-3), 109.5 (C-7), 121.8 (2), 122.6 (C-4,5,6), 126.2 (C-3a), 127.0 (*p*-Ph), 128.2 (*o*-Ph), 128.3 (*m*-Ph), 136.7 (C-7a), 140.0 (*i*-Ph), 145.9 (C-2), 165.8 (CO). MS (EI, 70 eV): *m/z* (relative intensity)=325 (26), 280 (16), 279 (56), 278 (61), 252 (11), 251 (17), 250 (53), 222 (23), 91 (100), 65 (14). FTIR: (neat, $cm^{-1}$)=3300, 3105, 3042, 3031, 2925, 1704, 1657, 1513, 1492, 1461, 1452, 1412, 1389, 1372, 1351, 1260, 1236, 1214, 1176, 1160, 1143, 1126, 1027, 993, 939, 875, 856, 810, 784, 736, 713.

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16. *X-ray crystallographic study of complex* ***5a***. Data were collected with an STOE-IPDS diffractometer using graphite-monochromated Mo K$\alpha$ radiation. The structures were solved by direct methods [Sheldrick, G. M. *SHELXS-97*; University of Göttingen: Germany, 1997;] and refined by full-matrix least-squares techniques against $F^2$; [Sheldrick, G. M. *SHELXL-97*; University of Göttingen: Germany, 1997;]. XP (BRUKER AXS) was used for structural representations. Space group *P*21/*c*, monoclinic, $a$=14.294(3), $b$=9.846(2), $c$=7.841(2) Å, $\beta$=101.05(3)°, $V$=1130.8(4) $Å^3$, $Z$=4, $\rho_{calcd}$=1.358 g $cm^{-3}$, 3972 reflections measured, 2048 were independent of symmetry, of which 1291 were observed ($I>2\sigma(I)$), $R1$=0.056, $wR2$ (all data)=0.151, 154 parameters. The crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC (**3**). Copies of the data can be obtained free of charge on application to http://www.ccdc.cam.ac.uk/data_request/cif.