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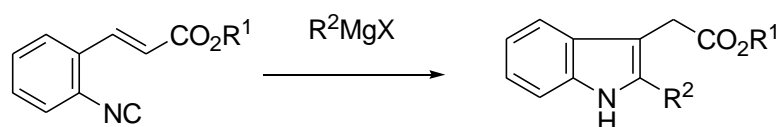
## SYNTHESIS OF 2,3-DISUBSTITUTED INDOLES BY ALKYLATIVE AND ARYLATIVE CYCLIZATION OF 2-ALKENYLPHENYLISOCYANIDES WITH GRIGNARD REAGENTS

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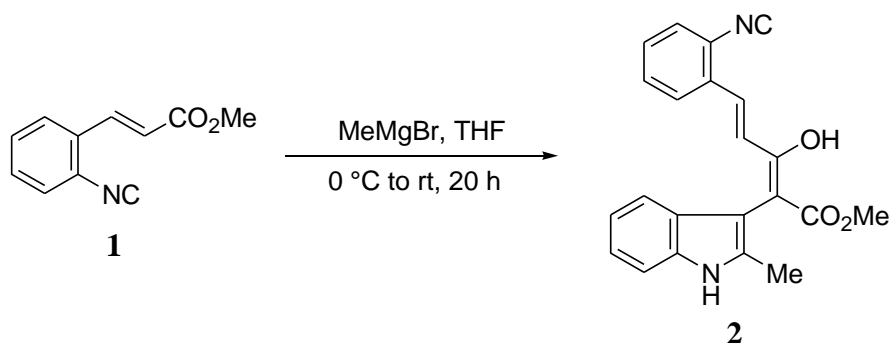
**Abstract** – Alkylative cyclization of 3-(2-isocyanophenyl)propenoic acid *tert*-butyl ester with Grignard reagents proceeds smoothly to form 2-alkyl-indole-3-acetic acid derivatives in moderate-to-good yields. Substituted 3-(2-isocyanophenyl)propenoic acid *tert*-butyl esters undergo a similar reaction when phenylmagnesium bromide is used to render 2-phenylindole-3-acetic acid derivatives in moderate-to-good yields.

Indoles have received special attention in heterocyclic chemistry, and various methods for their synthesis have been reported.<sup>1</sup> Isocyanides are versatile synthetic intermediates, and are particularly useful for the synthesis of heterocycles, such as pyrroles and oxazoles.<sup>2</sup> The use of isocyanides has also been reported for the synthesis of various indoles.<sup>2,3</sup> On the other hand, Kobayashi and coworkers reported the synthesis of 3-substituted 3*H*-indol-3-ols from the reaction of 2-isocyanophenyl ketones with Grignard reagents.<sup>4</sup> Interestingly, in this reaction, the Grignard reagent reacts with the isocyanide prior to the ketone. We envisaged the application of this reaction to 3-(2-isocyanophenyl)propenoic acid derivatives as an appropriate method for the construction of indole ring systems. Herein, we report the synthesis of 2,3-disubstituted indoles from the reaction of 3-(2-isocyanophenyl)propenoic acid derivatives and Grignard reagents (Scheme 1).



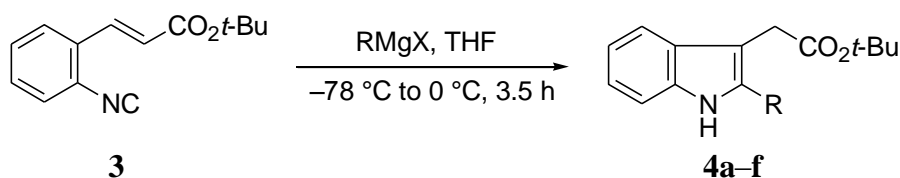
Scheme 1

In an initial study, we examined the reaction of isocyanide (**1**) with MeMgBr in THF from 0 °C to rt, and compound (**2**) was obtained as the major product possibly via alkylative cyclization followed by Claisen condensation of the resulting ester enolate to the unreacted starting material (**1**) (Scheme 2).



Scheme 2

In order to avoid the Claisen condensation, the reaction was performed using *tert*-butyl ester (**3**). Thus, treatment of *tert*-butyl ester (**3**) with MeMgBr afforded the 2-methylindole-3-acetic acid derivative (**4a**) in 71% yield. The dimeric product analogous to **2** was not observed. Various Grignard reagents were well tolerated in the cyclization reaction and furnished functionalized indoles (**4b–f**) in 53–80% yields (Scheme 3).

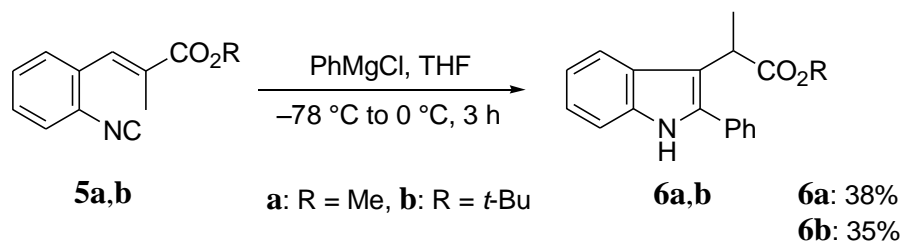


**a:** R = Me, **b:** R = Ph, **c:** R = *i*-Pr, **d:** R = cyclohexyl, **e:** R = 4-ClC<sub>6</sub>H<sub>4</sub>, **f:** R = 4-MeOC<sub>6</sub>H<sub>4</sub>

**4a:** 71% (X = Br)  
**4b:** 72% (X = Br), 80% (X = Cl)  
**4c:** 69% (X = Br), 77% (X = Cl)  
**4d:** 71% (X = Br)  
**4e:** 53% (X = Br)  
**4f:** 59% (X = Br)

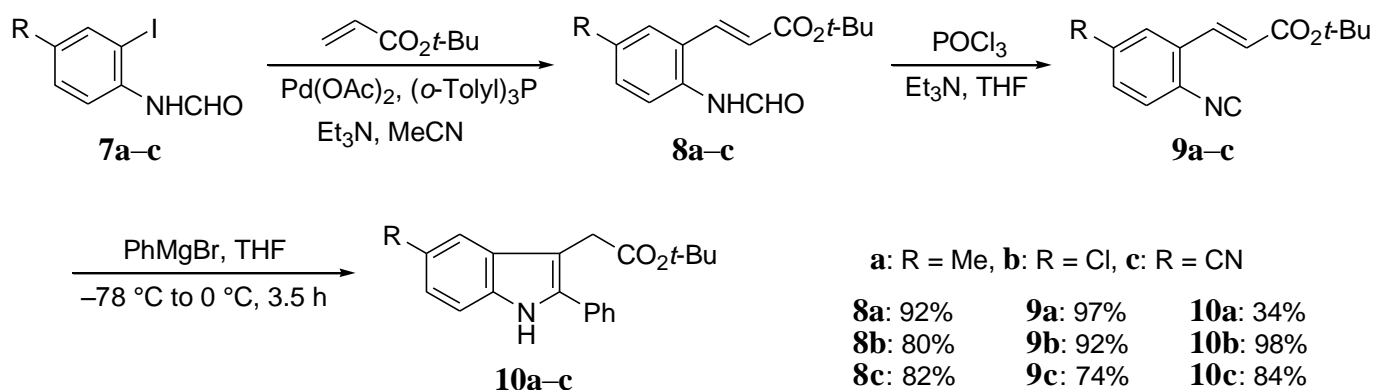
Scheme 3

With the optimized reaction conditions in hand, we then examined other Michael acceptors (**5a,b**). The reaction of methyl ester (**5a**) with PhMgCl afforded the expected indole (**6a**) in 38% yield. A similar result was obtained using *tert*-butyl ester (**5b**) (Scheme 4). Claisen condensation was unfavorable for **5a** owing to a sterically congested environment on the  $\alpha$ -carbon of the ester group.



Scheme 4

Finally, we examined substituted 3-(2-isocyanophenyl)propenoic acid derivatives (**9a–c**) as Michael acceptors which were prepared as shown in Scheme 5. Thus, Heck reaction of **7a–c** with *tert*-butyl acrylate afforded substituted 3-(2-formylaminophenyl)propenoic acid derivatives (**8a–c**), which were subsequently dehydrated with POCl<sub>3</sub> in the presence of Et<sub>3</sub>N to afford substituted 3-(2-isocyanophenyl)propenoic acid derivatives (**9a–c**). Treatment of **9a–c** with PhMgBr afforded 2-phenylindole derivatives (**10a–c**) respectively. The yield of the reaction was moderate for substrate **9a** bearing a methyl group at the para position of the isocyanato group, instead substrates **9b** and **9c**, with electron-withdrawing substituents at the para position of the isocyanato group, furnished the corresponding indoles **10b**, and **10c** in high yields.



Scheme 5

In conclusion, we have demonstrated that 2-substituted indole-3-acetic acid derivatives can be prepared via an addition / cyclization reaction of 3-(2-isocyanophenyl)propenoic acid derivatives with Grignard reagents. This methodology offers the possibility to introduce substituents on the 2-position of the indole ring and on the benzene ring, thus enabling the synthesis of structural diverse indole-3-acetic acid derivatives.

## EXPERIMENTAL

**General Notes.** All melting points were taken on a Yamato MP-21 capillary melting point apparatus.

Flash chromatography was carried out by using Merck silica gel 60 (No. 9385). The ratios of solvents in mixtures are shown in v/v. Spectra reported herein were recorded on a JEOL JMS-700 mass spectrometer, a Perkin-Elmer Spectrum 100 FT-IR spectrometer, or a JEOL JNM-ECA500 ( $^1\text{H}$  500 MHz,  $^{13}\text{C}$  125 MHz) NMR spectrometer. Chemical shifts are reported in  $\delta$  values relative to internal  $\text{Me}_4\text{Si}$ . Rotational isomers based on formamide were observed in NMR for compounds **8a**, **8b** and **8c**.

**(Z,E)- $\alpha$ -[1-Hydroxy-3-(2-isocyanophenyl)-2-propenylidene]-2-methyl-1H-indole-3-acetic acid methyl ester (2).**

To a stirred solution of **1**<sup>3b,5</sup> (187 mg, 1.0 mmol) in THF (5 mL) at 0 °C was added dropwise  $\text{MeMgBr}$  (1.0 mL, 1.1 mmol; 1.1 M in THF). The mixture was gradually warmed to rt, stirred at rt for 20 h, and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (15 mL). The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and evaporated. The residue was purified by flash chromatography (AcOEt-Hexane; 1:4) to give **2** (89 mg, 50%) as a yellow amorphous powder. IR (ATR)  $\nu$ ,  $\text{cm}^{-1}$ : 3377 (OH), 2116 (NC), 1621 (CO);  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.29 (3H, s, CMe), 3.72 (3H, s, OMe), 6.59 (1H, dd,  $J = 15.9, 1.6$  Hz, ArCH=CH), 7.07–7.35 (8H, m, two Ar's), 7.78 (1H, d,  $J = 15.9$  Hz, ArCH=CH), 8.03 (1H, s, NH), 13.10 (1H, d,  $J = 1.6$  Hz, OH);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 12.5 ( $\text{CH}_3$ ), 52.2 ( $\text{CH}_3$ ), 98.1 (C), 105.6 (C), 110.4 (CH), 119.1 (CH), 120.0 (CH), 121.5 (CH), 124.8 (CH), 126.6 (CH), 127.6 (CH), 129.38 (CH), 129.42 (CH), 129.6 (C), 130.1 (CH), 132.3 (C), 134.6 (C), 135.2 (C), 167.2 (C), 168.1 (C), 174.0 (C); HRFABMS  $m/z$  calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_3$  ( $\text{M}^+$ ): 358.1317, found: 358.1313.

**2-Methyl-1H-indole-3-acetic acid tert-butyl ester (4a).**

To a stirred solution of **3**<sup>6</sup> (229 mg, 1.0 mmol) in THF (4 mL) at -78 °C was added dropwise  $\text{MeMgBr}$  (1.4 mL, 1.3 mmol; 0.95 M in THF). The mixture was gradually warmed to 0 °C during 3.5 h, and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 mL). The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and evaporated. The residue was purified by flash chromatography (AcOEt-Hexane; 1:3) to give **4a** (175 mg, 71%) as a yellow oil. MS  $m/z$ : 245 ( $\text{M}^+$ ); IR (ATR)  $\nu$ ,  $\text{cm}^{-1}$ : 3394 (NH), 1718 (CO);  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.42 (9H, s, *tert*-Bu), 2.37 (3H, s, Ar-Me), 3.58 (2H, s,  $\text{CH}_2$ ), 7.06–7.12 [2H, m, C(5)-H, C(6)-H], 7.23 and 7.53 [1H each, br d,  $J = 7.2$  Hz, C(4)-H, C(7)-H], 7.84 (1H, s, NH);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 11.6 ( $\text{CH}_3$ ), 28.2 ( $\text{CH}_3$ ), 31.9 ( $\text{CH}_2$ ), 80.7 (C), 104.9 (C), 110.5 (CH), 118.2 (CH), 119.3 (CH), 121.0 (CH), 128.6 (C), 132.8 (C), 135.3 (C), 171.8 (C); HRMS  $m/z$  calcd for  $\text{C}_{15}\text{H}_{19}\text{NO}_2$ : 245.1416, found: 245.1415.

**2-Phenyl-1H-indole-3-acetic acid tert-butyl ester (4b).**

Prepared from **3** (115 mg, 0.5 mmol) and  $\text{PhMgCl}$  (0.33 mL, 0.65 mmol; 2.0 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:6)

gave **4b** (123 mg, 80%) as a pale yellow solid. mp 111.5–112 °C; MS  $m/z$ : 307 ( $M^+$ ); IR (ATR)  $\nu$ ,  $\text{cm}^{-1}$ : 3359 (NH), 1708 (CO);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.45 (9H, s, *tert*-Bu), 3.75 (2H, s,  $\text{CH}_2$ ), 7.16 and 7.22 [1H each, dd,  $J = 7.5, 7.5$  Hz, C(5)-H, C(6)-H], 7.36–7.72 [7H, m, C(4)-H, C(7)-H, Ph], 8.12 (1H, s, NH);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 28.1 ( $\text{CH}_3$ ), 32.5 ( $\text{CH}_2$ ), 80.9 (C), 106.4 (C), 110.8 (CH), 119.5 (CH), 119.9 (CH), 122.5 (CH), 128.0 (CH), 128.3 (CH), 128.9 (CH), 129.2 (C), 132.6 (C), 135.8 (C), 136.0 (C), 171.6 (C); HRMS  $m/z$  calcd for  $\text{C}_{20}\text{H}_{21}\text{NO}_2$ : 307.1572, found: 307.1571.

#### 2-Isopropyl-1*H*-indole-3-acetic acid *tert*-butyl ester (**4c**).

Prepared from **3** (115 mg, 0.5 mmol) and *i*-PrMgCl (0.33 mL, 0.65 mmol; 2.0 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:6) gave **4c** (106 mg, 77%) as a pale yellow solid. mp 56–56.5 °C; MS  $m/z$ : 273 ( $M^+$ ); IR (ATR)  $\nu$ ,  $\text{cm}^{-1}$ : 3384 (NH), 1718, 1701 (CO);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.32 (6H, d,  $J = 7.0$  Hz,  $\text{CHMe}_2$ ), 1.40 (9H, s, *tert*-Bu), 3.30 (1H, m,  $\text{CHMe}_2$ ), 3.61 (2H, s,  $\text{CH}_2$ ), 7.06–7.13 [2H, m, C(5)-H, C(6)-H], 7.27 and 7.57 [1H each, br d,  $J = 7.5$  Hz, C(4)-H, C(7)-H], 7.89 (1H, s, NH);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 22.6 ( $\text{CH}_3$ ), 25.6 (CH), 28.1 ( $\text{CH}_3$ ), 31.8 ( $\text{CH}_2$ ), 80.4 (C), 103.5 (C), 110.4 (CH), 118.6 (CH), 119.4 (CH), 121.1 (CH), 128.6 (C), 135.0 (C), 141.9 (C), 171.4 (C); HRMS  $m/z$  calcd for  $\text{C}_{17}\text{H}_{23}\text{NO}_2$ : 273.1729, found: 273.1727.

#### 2-Cyclohexyl-1*H*-indole-3-acetic acid *tert*-butyl ester (**4d**).

Prepared from **3** (115 mg, 0.5 mmol) and  $\text{C}_6\text{H}_{11}\text{MgBr}$  (0.65 mL, 0.65 mmol; 1.0 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:7) gave **4d** (95 mg, 71%) as a pale yellow solid. mp 130–131 °C; MS  $m/z$ : 313 ( $M^+$ ); IR (ATR)  $\nu$ ,  $\text{cm}^{-1}$ : 3415 (NH), 1711 (CO);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.24–1.49 (5H, m), 1.77–1.98 (5H, m), and 2.88–2.94 (1H, m) ( $\text{C}_6\text{H}_{11}$ ), 1.41 (9H, s, *tert*-Bu), 3.61 (2H, s,  $\text{CH}_2$ ), 7.06–7.13 [2H, m, C(5)-H, C(6)-H], 7.28 and 7.57 [1H each, d,  $J = 7.2$  Hz, C(4)-H, C(7)-H], 7.86 (1H, s, NH);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 26.1 ( $\text{CH}_2$ ), 26.7 ( $\text{CH}_2$ ), 28.1 ( $\text{CH}_3$ ), 31.9 ( $\text{CH}_2$ ), 33.2 ( $\text{CH}_2$ ), 35.8 (CH), 80.5 (C), 103.7 (C), 110.4 (CH), 118.6 (CH), 119.4 (CH), 121.1 (CH), 128.6 (C), 135.0 (C), 141.5 (C), 171.5 (C); HRMS  $m/z$  calcd for  $\text{C}_{20}\text{H}_{27}\text{NO}_2$ : 313.2042, found: 313.2035.

#### 2-(4-Chlorophenyl)-1*H*-indole-3-acetic acid *tert*-butyl ester (**4e**).

Prepared from **3** (458 mg, 2.0 mmol) and 4-ClPhMgBr (2.8 mL, 2.8 mmol; 1.0 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:7) gave **4e** (365 mg, 53%) as a pale yellow solid. mp 133–133.5 °C; MS  $m/z$ : 341, 343 ( $M^+$ ); IR (ATR)  $\nu$ ,  $\text{cm}^{-1}$ : 3354 (NH), 1709 (CO);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.45 (9H, s, *tert*-Bu), 3.71 (2H, s,  $\text{CH}_2$ ), 7.16 and 7.23 [1H each, dd,  $J = 8.0, 7.0$  Hz, C(5)-H, C(6)-H], 7.38 and 7.70 [1H each, d,  $J = 8.0$  Hz, C(4)-H, C(7)-H], 7.46 and 7.65 (2H each, d,  $J = 8.3$  Hz,  $\text{C}_6\text{H}_4\text{Cl}$ ), 8.11 (1H, s, NH);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 28.1 ( $\text{CH}_3$ ), 32.4 ( $\text{CH}_2$ ), 81.1 (C), 106.8 (C), 110.9 (CH), 119.5 (CH), 120.1 (CH), 122.8 (CH), 129.07 (C),

129.12 (CH), 129.4 (CH), 131.0 (C), 134.0 (C), 134.8 (C), 135.9 (C), 171.5 (C); HRMS  $m/z$  calcd for  $C_{20}H_{20}ClNO_2$ : 341.1183, found: 341.1179.

**2-(4-Methoxyphenyl)-1*H*-indole-3-acetic acid *tert*-butyl ester (4f).**

Prepared from **3** (115 mg, 0.5 mmol) and 4-MeOPhMgBr (1.3 mL, 0.65 mmol; 0.5 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:4) gave **4f** (99 mg, 59%) as a pale yellow solid. mp 134–134.5 °C; MS  $m/z$ : 337 ( $M^+$ ); IR (ATR)  $\nu$ ,  $cm^{-1}$ : 3362 (NH), 1712 (CO);  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.45 (9H, s, *tert*-Bu), 3.71 (2H, s,  $CH_2$ ), 3.87 (3H, s, OMe), 7.02 and 7.63 (2H each, d,  $J = 8.7$  Hz,  $C_6H_4OMe$ ), 7.14 and 7.19 [1H each, dd,  $J = 8.0, 7.0$  Hz, C(5)-H, C(6)-H], 7.36 and 7.68 [1H each, d,  $J = 8.0$  Hz, C(4)-H, C(7)-H], 8.06 (1H, s, NH);  $^{13}C$ -NMR ( $CDCl_3$ )  $\delta$ : 28.2 ( $CH_3$ ), 32.6 ( $CH_2$ ), 55.5 ( $CH_3$ ), 80.9 (C), 105.7 (C), 110.8 (CH), 114.4 (CH), 119.4 (CH), 119.9 (CH), 122.2 (CH), 125.1 (C), 129.3 (C), 129.6 (CH), 135.7 (C), 136.1 (C), 159.6 (C), 171.8 (C); HRMS  $m/z$  calcd for  $C_{21}H_{23}NO_3$ : 337.1678, found: 337.1671.

**$\alpha$ -Methyl-2-phenyl-1*H*-indole-3-acetic acid methyl ester (6a).**

Prepared from **5a**<sup>3b,e</sup> (101 mg, 0.5 mmol) and PhMgCl (0.33 mL, 0.65 mmol; 2.0 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:15) gave **6a** (54 mg, 38%) as a pale yellow oil. MS  $m/z$ : 279 ( $M^+$ ); IR (ATR)  $\nu$ ,  $cm^{-1}$ : 3358 (NH), 1713 (CO);  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.61 (3H, d,  $J = 7.2$  Hz,  $CH_3Me$ ), 3.65 (3H, s, OMe), 4.15 (1H, q,  $J = 7.2$  Hz,  $CH_3Me$ ), 7.13 and 7.21 [1H each, dd,  $J = 8.0, 7.1$  Hz, C(5)-H, C(6)-H], 7.38 and 7.77 [1H each, d,  $J = 8.0$  Hz, C(4)-H, C(7)-H], 7.40–7.64 (5H, m, Ph), 8.08 (1H, s, NH);  $^{13}C$ -NMR ( $CDCl_3$ )  $\delta$ : 17.6 ( $CH_3$ ), 36.7 (CH), 52.0 ( $CH_3$ ), 110.0 (CH), 112.0 (C), 120.0 (CH), 120.5 (CH), 122.4 (CH), 127.2 (C), 128.3 (CH), 128.8 (CH), 129.0 (CH), 132.8 (C), 135.4 (C), 136.0 (C), 175.5 (C); HRMS  $m/z$  calcd for  $C_{18}H_{17}NO_2$ : 279.1259, found: 279.1263.

**$\alpha$ -Methyl-2-phenyl-1*H*-indole-3-acetic acid *tert*-butyl ester (6b).**

Prepared from **5b**<sup>3e</sup> (78.5 mg, 0.34 mmol) and PhMgCl (0.22 mL, 0.44 mmol; 2.0 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:15) gave **6b** (37 mg, 35%) as a pale yellow oil.  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.39 (9H, s, *tert*-Bu), 1.55 (3H, d,  $J = 7.2$  Hz,  $CH_3Me$ ), 4.04 (1H, q,  $J = 7.2$  Hz,  $CH_3Me$ ), 7.11 and 7.19 [1H each, dd,  $J = 8.0, 6.8$  Hz, C(5)-H, C(6)-H], 7.36 and 7.82 [1H each, d,  $J = 8.0$  Hz, C(4)-H, C(7)-H], 7.38–7.67 (5H, m, Ph), 8.04 (1H, s, NH);  $^{13}C$ -NMR ( $CDCl_3$ )  $\delta$ : 17.4 ( $CH_3$ ), 28.0 ( $CH_3$ ), 38.0 (CH), 80.5 (C), 110.8 (CH), 112.6 (C), 119.6 (CH), 120.9 (CH), 122.1 (CH), 127.3 (C), 128.0 (CH), 128.77 (CH), 128.83 (CH), 132.9 (C), 135.2 (C), 136.0 (C), 174.2 (C).

**(2*E*)-3-[2-(Formylamino)-5-methylphenyl]-2-propenoic acid *tert*-butyl ester (8a).**

*N*-(2-Iodo-4-methylphenyl)formamide (**7a**)<sup>7a,b</sup> (5.30 g, 20.3 mmol), Pd(OAc)<sub>2</sub> (300 mg, 1.3 mmol),

tri-*o*-tolylphosphine (816 mg, 2.7 mmol) were placed in a dry three necked flask under Ar. Then, MeCN (116 mL), Et<sub>3</sub>N (4.0 mL, 29 mmol), *tert*-butyl acrylate (4.7 mL, 32 mmol) were added and the mixture was refluxed for 20 h under Ar. The mixture was evaporated, diluted with EtOAc and washed water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The residue was purified by flash chromatography (AcOEt-Hexane; 1:2) to give **8a** (4.90 g, 92%) as a colorless solid. mp 140–141 °C; MS *m/z*: 261 (M<sup>+</sup>); IR (ATR)  $\nu$ , cm<sup>-1</sup>: 3227 (NH), 1703 (ester CO), 1662, 1633 (amide CO); <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.51 and 1.52 (9H, s each, *tert*-Bu), 2.33 and 2.36 [3H, s each, C(5)-Me], 6.34 and 6.35 [1H, d each, *J* = 15.8 Hz, C( $\alpha$ )-H], 7.09 and 7.78 [1H, d each, *J* = 8.0 Hz, C(3)-H], 7.19 [1H, br d, *J* = 8.0 Hz, C(4)-H], 7.36 and 7.40 [1H, s each, C(6)-H], 7.73 and 7.76 [1H, d each, *J* = 15.8 Hz, C( $\beta$ )-H], 7.69 (br s) and 8.06 (br d, *J* = 11.1 Hz) (1H, NH), 8.43 (d, *J* = 11.1 Hz) and 8.44 (d, *J* = 1.8 Hz) (1H, CHO); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 20.90 (CH<sub>3</sub>), 20.93 (CH<sub>3</sub>), 28.1 (CH<sub>3</sub>), 28.2 (CH<sub>3</sub>), 80.9 (C), 81.0 (C), 122.4 (CH), 123.0 (CH), 123.2 (CH), 124.5 (CH), 126.9 (C), 127.4 (CH), 128.22 (C), 128.23 (CH), 131.4 (CH), 131.6 (CH), 132.4 (C), 132.7 (C), 135.5 (C), 136.5 (C), 137.7 (CH), 138.2 (CH), 159.9 (CH), 163.8 (CH), 165.8 (C), 166.4 (C); HRMS *m/z* calcd for C<sub>15</sub>H<sub>19</sub>NO<sub>3</sub>: 261.1365, found: 261.1360.

**(2E)-3-[5-Chloro-2-(formylamino)phenyl]-2-propenoic acid *tert*-butyl ester (8b).**

Prepared from **7b**<sup>6.7</sup> (5.73 g, 20.4 mmol) according to the procedure described for the preparation of **8a**. Purification by flash chromatography (AcOEt-Hexane; 1:2) gave **8b** (4.58 g, 80%) as a pale yellow solid. mp 154–156 °C; MS *m/z*: 281, 283 (M<sup>+</sup>); IR (ATR)  $\nu$ , cm<sup>-1</sup>: 3230 (NH), 1705 (ester CO), 1664, 1632 (amide CO); <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.526 and 1.530 (9H, s each, *tert*-Bu), 6.35 and 6.36 [1H, d each, *J* = 15.8 Hz, C( $\alpha$ )-H], 7.15 and 7.96 [1H, d each, *J* = 8.6 Hz, C(3)-H], 7.35 and 7.36 [1H, dd each, *J* = 8.6, 2.4 Hz, C(4)-H], 7.45 (br s) and 7.75 (br d, *J* = 11.1 Hz) (1H, NH), 7.51 and 7.57 [1H, d each, *J* = 2.4 Hz, C(6)-H], 7.65 and 7.67 [1H, d each, *J* = 15.8 Hz, C( $\beta$ )-H], 8.46 (s) and 8.47 (d, *J* = 11.1 Hz) (1H, CHO); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 28.09 (CH<sub>3</sub>), 28.11 (CH<sub>3</sub>), 81.3 (C), 81.4 (C), 123.8 (CH), 124.3 (CH), 124.4 (CH), 125.5 (CH), 126.7 (CH), 127.5 (CH), 128.2 (C), 129.9 (C), 130.4 (CH), 130.7 (CH), 130.9 (C), 132.3 (C), 133.5 (C), 133.9 (C), 136.4 (CH), 136.8 (CH), 160.0 (CH), 163.8 (CH), 165.4 (C), 166.0 (C); HRMS *m/z* calcd for C<sub>14</sub>H<sub>16</sub>ClNO<sub>3</sub>: 281.0819, found: 281.0826.

**(2E)-3-[5-Cyano-2-(formylamino)phenyl]-2-propenoic acid *tert*-butyl ester (8c).**

Prepared from **7c**<sup>7c.8</sup> (1.03 g, 3.77 mmol) according to the procedure described for the preparation of **8a**. Purification by flash chromatography (AcOEt-Hexane; 1:2) gave **8c** (845 mg, 82%) as a pale yellow solid. mp 142–143 °C; MS *m/z*: 272 (M<sup>+</sup>); IR (ATR)  $\nu$ , cm<sup>-1</sup>: 3318 (NH), 2226 (CN), 1708 (ester CO), 1685, 1635 (amide CO); <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.51 and 1.52 (9H, s each, *tert*-Bu), 6.40 and 6.43 [1H, d each, *J* = 15.7 Hz, C( $\alpha$ )-H], 7.38 and 8.40 [1H, d each, *J* = 8.4 Hz, C(3)-H], 7.65 and 7.68 [1H, d each, *J* = 8.4 Hz, C(4)-H], 7.75 and 7.78 [1H, d each, *J* = 15.7 Hz, C( $\beta$ )-H], 7.80 and 7.89 [1H, s each, C(6)-H], 8.43

(br s) and 9.02 (br d,  $J = 10.6$  Hz) (1H, NH), 8.54 (s) and 8.68 (d,  $J = 10.6$  Hz) (1H, CHO);  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 28.2 ( $\text{CH}_3$ ), 81.7 (C), 81.8 (C), 108.3 (C), 109.9 (C), 117.9 (C), 118.3 (C), 121.9 (CH), 123.2 (CH), 125.6 (CH), 125.7 (CH), 126.3 (C), 128.3 (C), 131.4 (CH), 132.1 (CH), 133.9 (CH), 134.1 (CH), 135.7 (CH), 136.0 (CH), 139.1 (C), 139.4 (s), 160.3 (CH), 163.5 (CH), 165.2 (C), 165.7 (C); HRMS  $m/z$  calcd for  $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3$ : 272.1161, found: 272.1166.

**(2E)-3-(2-Isocyano-5-methylphenyl)-2-propenoic acid tert-butyl ester (9a).**

To a cooled mixture of **8a** (2.78 g, 10.6 mmol),  $\text{Et}_3\text{N}$  (5.3 mL, 38 mmol) and THF (98 mL) was added dropwise  $\text{POCl}_3$  (1.22 mL, 13.3 mmol) and the mixture was stirred at rt for 2 h. The reaction mixture was quenched with saturated aqueous  $\text{NaHCO}_3$  (18 mL) and the resultant mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and evaporated. The residue was purified by flash chromatography (AcOEt-Hexane; 1:4) to give **9a** (2.50 g, 97%) as a pale yellow solid. mp 64–65 °C; IR (ATR)  $\nu$ ,  $\text{cm}^{-1}$ : 2118 (NC), 1703 (CO);  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.55 (9H, s, *tert*-Bu), 2.39 [3H, s, C(5)-Me], 6.45 [1H, d,  $J = 16.0$  Hz, C( $\alpha$ )-H], 7.19 [1H, d,  $J = 8.1$  Hz, C(4)-H], 7.31 [1H, d,  $J = 8.1$  Hz, C(3)-H], 7.45 [1H, s, C(6)-H], 7.85 [1H, d,  $J = 16.0$  Hz, C( $\beta$ )-H];  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 21.3 ( $\text{CH}_3$ ), 28.1 ( $\text{CH}_3$ ), 81.0 (C), 123.9 (CH), 127.2 (CH), 127.4 (CH), 130.6 (C), 131.2 (CH), 136.8 (CH), 139.9 (C), 165.3 (C), 167.9 (C); HRFABMS  $m/z$  calcd for  $\text{C}_{15}\text{H}_{18}\text{NO}_2$  ( $\text{MH}^+$ ): 244.1338, found: 244.1337.

**(2E)-3-(5-Chloro-2-isocyanophenyl)-2-propenoic acid tert-butyl ester (9b).**

Prepared from **8b**<sup>9</sup> (3.00 g, 10.6 mmol) according to the procedure described for the preparation of **9a**. Purification by flash chromatography (AcOEt-Hexane; 1:10) gave **9b** (2.58 g, 92%) as a pale yellow solid. mp 114–116 °C; IR (ATR)  $\nu$ ,  $\text{cm}^{-1}$ : 2126 (NC), 1703 (CO);  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.55 (9H, s, *tert*-Bu), 6.47 [1H, d,  $J = 16.0$  Hz, C( $\alpha$ )-H], 7.34–7.39 [2H, m, C(3)-H, C(4)-H], 7.63 [1H, br s, C(6)-H], 7.80 [1H, d,  $J = 16.0$  Hz, C( $\beta$ )-H];  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 28.1 ( $\text{CH}_3$ ), 81.5 (C), 124.3 (C), 125.6 (CH), 126.9 (CH), 128.8 (CH), 130.4 (CH), 132.7 (C), 135.4 (CH), 135.7 (C), 164.8 (C), 170.0 (C); HRFABMS  $m/z$  calcd for  $\text{C}_{14}\text{H}_{15}\text{ClNO}_2$  ( $\text{MH}^+$ ): 264.0791, found: 264.0781.

**(2E)-3-(5-Cyano-2-isocyanophenyl)-2-propenoic acid tert-butyl ester (9c).**

Prepared from **8c** (610 mg, 2.23 mmol) according to the procedure described for the preparation of **9a**. Purification by flash chromatography (AcOEt-Hexane; 1:10) gave **9c** (419 mg, 74%) as a pale yellow solid. mp 134–136 °C; IR (ATR)  $\nu$ ,  $\text{cm}^{-1}$ : 2242 (CN), 2112 (NC), 1699 (CO);  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.55 (9H, s, *tert*-Bu), 6.54 [1H, d,  $J = 16.0$  Hz, C( $\alpha$ )-H], 7.56 [1H, d,  $J = 8.2$  Hz, C(3)-H], 7.69 [1H, dd,  $J = 8.2$ , 1.7 Hz, C(4)-H], 7.82 [1H, d,  $J = 16.0$  Hz, C( $\beta$ )-H], 7.96 [1H, d,  $J = 1.7$  Hz, C(6)-H];  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 28.1 ( $\text{CH}_3$ ), 81.8 (C), 113.9 (C), 116.9 (C), 126.9 (CH), 128.6 (CH), 130.9 (CH), 132.6 (C), 133.3 (CH),



134.4 (CH), 164.5 (C), 173.2 (C); HRFABMS  $m/z$  calcd for  $C_{15}H_{15}N_2O_2$  ( $MH^+$ ): 255.1134, found: 255.1137.

#### 5-Methyl-2-phenyl-1*H*-indole-3-acetic acid *tert*-butyl ester (**10a**).

Prepared from **9a** (122 mg, 0.5 mmol) and PhMgBr (0.63 mL, 0.70 mmol; 1.1 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:7) gave **10a** (55 mg, 34%) as a pale yellow solid. mp 132–133 °C; MS  $m/z$ : 321 ( $M^+$ ); IR (ATR)  $\nu$ ,  $cm^{-1}$ : 3362 (NH), 1718 (CO);  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.45 (9H, s, *tert*-Bu), 2.47 [3H, s, C(5)-Me], 3.72 (2H, s,  $CH_2$ ), 7.04 [1H, d,  $J = 8.2$  Hz, C(6)-H], 7.26 [1H, d,  $J = 8.2$  Hz, C(7)-H], 7.36–7.70 [6H, m, C(4)-H, Ph], 8.02 (1H, s, NH);  $^{13}C$ -NMR ( $CDCl_3$ )  $\delta$ : 21.6 ( $CH_3$ ), 28.1 ( $CH_3$ ), 32.5 ( $CH_2$ ), 80.8 (C), 105.9 (C), 110.4 (CH), 119.2 (CH), 124.0 (CH), 127.8 (CH), 128.2 (CH), 128.9 (CH), 129.1 (C), 129.4 (C), 132.7 (C), 134.1 (C), 136.1 (C), 171.6 (C); HRMS  $m/z$  calcd for  $C_{21}H_{23}NO_2$ : 321.1729, found: 321.1724.

#### 5-Chloro-2-phenyl-1*H*-indole-3-acetic acid *tert*-butyl ester (**10b**).

Prepared from **9b** (132 mg, 0.5 mmol) and PhMgBr (0.63 mL, 0.70 mmol; 1.1 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:7) gave **10b** (169 mg, 98%) as a pale yellow solid. mp 157–158 °C; MS  $m/z$ : 341, 343 ( $M^+$ ); IR (ATR)  $\nu$ ,  $cm^{-1}$ : 3343 (NH), 1710 (CO);  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.46 (9H, s, *tert*-Bu), 3.69 (2H, s,  $CH_2$ ), 7.14 [1H, dd,  $J = 8.6, 2.0$  Hz, C(6)-H], 7.26 [1H, d,  $J = 8.6$  Hz, C(7)-H], 7.38–7.67 (5H, m, Ph), 7.68 [1H, d,  $J = 2.0$  Hz, C(4)-H], 8.19 (1H, s, NH);  $^{13}C$ -NMR ( $CDCl_3$ )  $\delta$ : 28.1 ( $CH_3$ ), 32.4 ( $CH_2$ ), 81.1 (C), 106.1 (C), 111.8 (CH), 119.1 (CH), 122.7 (CH), 125.6 (C), 128.2 (CH), 128.3 (CH), 129.0 (CH), 130.3 (C), 132.0 (C), 134.1 (C), 137.4 (C), 171.3 (C); HRMS  $m/z$  calcd for  $C_{20}H_{20}ClNO_2$ : 341.1183, found: 341.1186.

#### 5-Cyano-2-phenyl-1*H*-indole-3-acetic acid *tert*-butyl ester (**10c**).

Prepared from **9c** (127 mg, 0.5 mmol) and PhMgBr (0.63 mL, 0.70 mmol; 1.1 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:7) gave **10c** (140 mg, 84%) as a pale yellow solid. mp 137–139 °C; MS  $m/z$ : 332 ( $M^+$ ); IR (ATR)  $\nu$ ,  $cm^{-1}$ : 3307 (NH), 2219 (CN), 1710 (CO);  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.47 (9H, s, *tert*-Bu), 3.73 (2H, s,  $CH_2$ ), 7.38 and 7.42 [1H each, d,  $J = 8.3$  Hz, C(6)-H, C(7)-H], 7.41–7.66 (5H, m, Ph), 8.04 [1H, s, C(4)-H], 8.57 (1H, s, NH);  $^{13}C$ -NMR ( $CDCl_3$ )  $\delta$ : 28.1 ( $CH_3$ ), 32.2 ( $CH_2$ ), 81.5 (C), 103.0 (C), 106.9 (C), 111.7 (CH), 120.8 (C), 125.1 (CH), 125.4 (CH), 128.3 (CH), 128.7 (CH), 128.9 (C), 129.1 (CH), 131.3 (C), 137.4 (C), 138.3 (C), 171.0 (C); HRMS  $m/z$  calcd for  $C_{21}H_{20}N_2O_2$ : 332.1525, found: 332.1519.

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