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Multicomponent Reactions of Indole, Ethyl Glyoxylate and Anilines: From Friedel–Crafts to Aza-Diels–Alder Reactions Catalysed by Scandium Triflate

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The multicomponent reaction (MCR) of indole (**1**), ethyl glyoxylate (**2**) and 3,4-dimethoxy- or 3,4-methylenedioxyanilines (**3a**,**b**) give, in analogy to Friedel–Crafts alkylation of indole, expected acetates **4a**,**b**. When the reactions are catalysed by scandium triflate, however, a completely different reaction pathway is followed and two pairs of diastereomeric aza-Diels–Alder adducts (**7a**,**b** and **8a**,**b**) are isolated, which result from the reactions in which the ethyl 2-(arylimino)acetates (azomethynes of **2** with **3a**,**b**) behave as heterodienes and indole is the dienophile. These products, whose structures were confirmed by X-ray crystal structure analysis of **7a**, are not derived from the scandium-catalysed rearrangement of **4a**,**b**, because when these latter are treated with $Sc(OTf)_3$, the rearrangement produces acetates **5a**,**b** only. The limits of the aza-Diels–Alder reaction were investigated by performing the MCR on substituted anilines **3f–k**.
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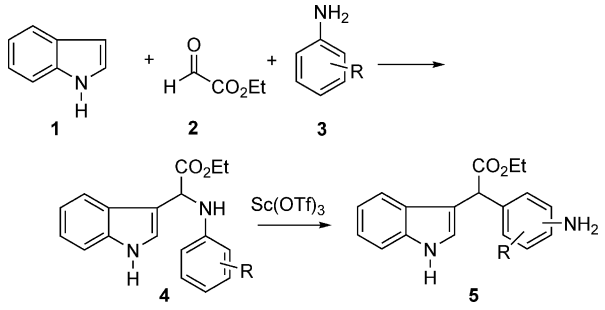
Introduction

The multicomponent reaction (MCR)[1] between indole (**1**), ethyl glyoxylate (**2**) and anilines (**3**),[2–6] in analogy to the Friedel–Crafts alkylation reaction first described by Passerini more than 80 years ago,[7] gives the expected acetates **4**. Copper[8] and lanthanide cations[9a–9c] have been found to be efficient catalysts for the electrophilic alkylation of indoles, but whereas dysprosium and ytterbium triflate simply increase the reaction rate,[10a,10b] the use of scandium triflate [$Sc(OTf)_3$] gives new product **5** derived from a rearrangement involving the migration of the arylamino fragment of **4**. Even if this rearrangement is observed in the case of unsubstituted aniline, the use of methoxy-substituted anilines favours the rearrangement and determines the selective formation of one specific regioisomer. When the *para* position to the amino group of **4** is unsubstituted, the rearrangement involves this position to give ethyl 2-(4-aminoaryl)-2-(1*H*-indol-3-yl)acetates, whereas methoxy substituents in the *ortho* and *para* positions to the amino group force the rearrangement to the *meta* position to produce ethyl 2-(5-amino-2,4-dimethoxyphenyl)-2-(1*H*-indol-3-yl)acetate (Scheme 1).



Scheme 1. MCR between indole, glyoxylate and anilines and rearrangement of the reaction product.

To define the limits induced by the position of these substituents on the aryl group, the reaction with 3,4-dimethoxy- and 3,4-methylenedioxyanilines (**3a**,**b**) were tested, in which both the *para* and *meta* positions to the amino group are unavailable to the rearrangement.

Results and Discussion

Preliminarily, the reactions between **1**, **2** and **3a**,**b** were run at ambient temperature in CH_2Cl_2 with 5 Å molecular sieves (MS). The reaction of **1**, **2** and aniline **3a** gives expected product acetate **4a** as the sole product in 55% yield (Scheme 2; Table 1, Entry 1). The analogous reaction with **3b**, together with a 55% yield of **4b** (R,R^1 = OCH_2O), gives a further product (**6b**) that does not include the indole fragment, with a structure similar to that of a dimer of ethyl 2-(benzo[*d*][1,3]dioxol-5-ylimino)acetate, the Schiff base of **2**

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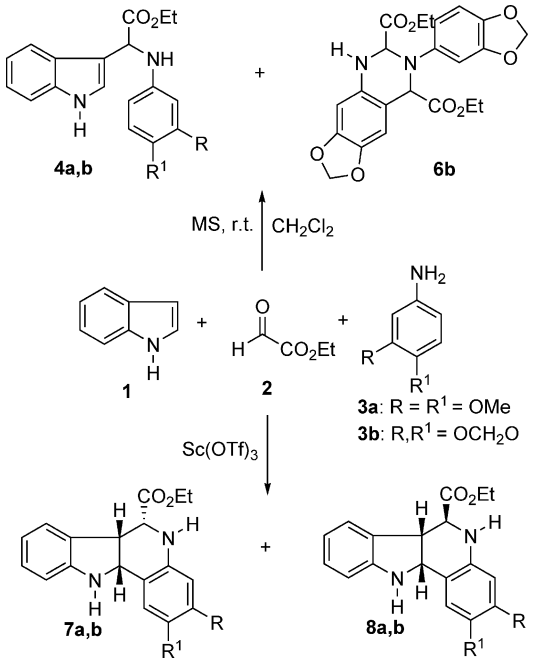
Table 1. Reactions of indole (**1**), ethyl glyoxylate (**2**) and anilines (**3a**,**b**) in CH_2Cl_2 with or without scandium triflate (5 mol-%) in CH_2Cl_2.

Entry	Reagents[a]	$Sc(OTf)_3$	*T* [°C]	Time [h]	**4**%[b]	**6**%[b]	**7** and **8**%[c]
1	**1**+**2**+**3a**	–	r.t.	24	55	–	–
2	**1**+**2**+**3b**	–	r.t.	3	55	15	–
3	**1**+**2**+**3a**	5 mol-%	–50	4	25	–	55[d]
4	**1**+**2**+**3a**	5 mol-%	r.t.	0.5	–	–	83[e]
5	**1**+**2**+**3b**	5 mol-%	–50	1	–	–	75[f]

[a] Ratio **1/2/3**, 1:1:1; in the presence of MS. [b] Isolated yields. [c] Ratio determined by ^1H NMR spectroscopy. [d] Ratio **7a/8a**, 68:32. [e] Ratio **7a/8a**, 70:30. [f] Ratio **7b/8b**, 85:15.

and **3b** (Table 1, Entry 2). Even if three-component aza-Diels-Alder (DA) cycloadditions have been reported in the literature,[11] this seems to be an example of a four-component aza-DA reaction.



Scheme 2. MCR between indole, glyoxylate and 3,4-dialkoxyanilines with and without $Sc(OTf)_3$.

The catalytic effect of $Sc(OTf)_3$ on the MCR of **1** and **2** with **3a** was first studied at –50 °C and, after 4 h, unreacted **4a** (29% yield) was again isolated, together with two new products (**7a** and **8a**) in up to 60% yield in a 68:32 ratio (Table 1, Entry 3). Compounds **7a** and **8a** could be purified by fractional crystallisation, and the structure of **7a** was determined by X-ray analysis (Figure 1; Scheme 2). From the comparison of the ^1H NMR spectra of **7a** and **8a**, the relative configuration (6*S**,6a*S**,11a*R**) can be attributed to diastereoisomer **8a**. The same reaction, run at ambient temperature, gave only the DA products, and a mixture of diastereoisomers **7a** and **8a** was obtained in up to 73% yield in a 70:30 ratio (Table 1, Entry 4).

The scandium-catalysed reaction of **1**, **2** and **3b** at –50 °C is complete after 20 min. The aza-DA was the only reaction pathway, and the diastereoisomeric mixture **7b/8b** (85:15) was obtained in up to 75% yield (Table 1, Entry 5). Their

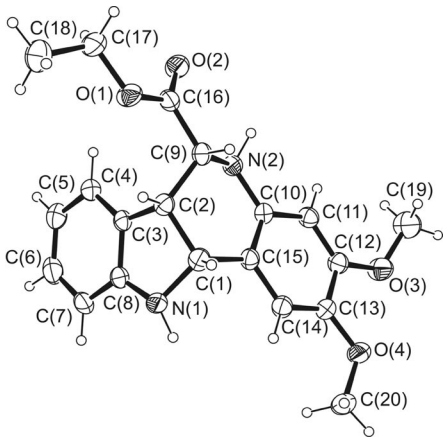


Figure 1. An ORTEP view of the crystal structure of **7a** (ellipsoids are drawn at the 30% probability level) labelled with crystallographic atom names.

isolation as pure products can be achieved by column chromatography and fractional crystallisation (see Experimental Section).

Therefore, the $Sc(OTf)_3$-catalysed MCR of **1**, **2** and **3a**,**b** gives two pairs of diastereomeric aza-DA adducts (i.e., **7a**,**b** and **8a**,**b**).

To infer the mechanism by which the aza-DA adducts are formed, specifically if they arise from a Sc^{III}-catalysed rearrangement of **4a**,**b**, these latter were allowed to react in the presence of $Sc(OTf)_3$. A CH_2Cl_2 solution of **4a** was cooled to –50 °C in the presence of $Sc(OTf)_3$ (5 mol-%) and the reaction was monitored by TLC. After a few minutes two new products began to form at the expense of **4a**. Intermediate product **9a**, after reaching a maximum concentration after about 1 h, was then transformed into product **5a**, which is the final product of the transformation. Both products were isolated by chromatography, and the final product was **5a**, whereas the intermediate product, which can be converted into **5a** by treatment with $Sc(OTf)_3$ at ambient temperature, was **9a** (Scheme 3; Table 2, Entries 1 and 2). The isolation of **9a** and its conversion into **5a** was already observed in the same MCR involving different anilines.[2]

The reaction of **4b** was run at 0 °C and, after 1 h, the starting product disappeared to give **5b** (Scheme 3; Table 2, Entry 3).

All attempts to obtain **7** and **8** from **4a**,**b** failed, which allowed the latter products to be excluded as the intermediates of the aza-DA products. To rationalise the formation

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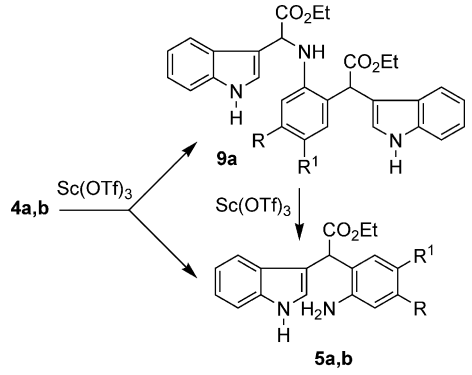
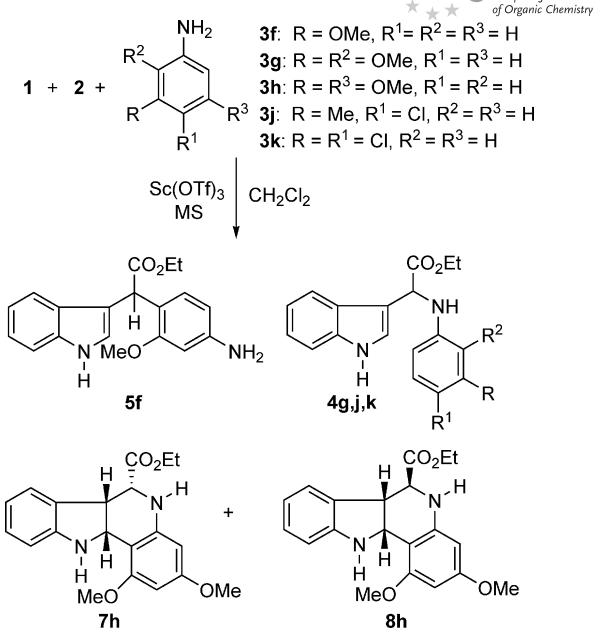


Scheme 3. The $Sc(OTf)_3$-catalysed rearrangement of adducts **4a**,**b**.

Table 2. Reactions of adducts **4a**,**b** with scandium triflate (5 mol-%) in CH_2Cl_2.

Entry	Reagents	*T* [°C]	Time [h]	% Yield[a]	**4**%[b]	**5**%[b]	**9**%[b]
1	**4a**	–50	1	65	22[c]	56	9
2	**4a**	r.t.	1	81	–	81	–
3	**4b**	0	2	76	–	76	–

[a] Overall reaction yield. [b] Isolated yields. [c] Percent of recovered starting product.



Scheme 4. $Sc(OTf)_3$-catalysed MCR between indole, glyoxylate and anilines.

of the aza-DA adducts, the effect of the substituents on the aromatic ring of the starting aniline was further investigated.

In the previous report, no aza-DA products were evidenced in the reactions with 2-methoxy, 4-methoxy- and 2,4-dimethoxy-substituted anilines **3c**–**e** (Table 3, Entries 1–3).[2] Now the reactions of **1** and **2** with 3-methoxyaniline (**3f**), 2,3-dimethoxyaniline (**3g**) and 3,5-dimethoxyaniline (**3h**) were tested (Scheme 4; Table 3, Entries 4–6).

The reactivity of **3f** (R = OMe) is poor and, at ambient temperature, a low yield (22%) of **5f** was obtained, evidently derived from the primary reaction product **4f** that underwent the Sc^{III}-catalysed rearrangement in the position *para* to the amino group (Table 3, Entry 4). On the contrary, **3g** (R and R^2 = OMe) is very reactive at –50 °C, but no aza-DA products were isolated and only a good yield of product **4g** was obtained (Table 3, Entry 5).

Even if the reaction of **1**, **2** and **3h** (R and R^3 = OMe) was influenced by a serious decomposition of the starting amine, only aza-DA products **7h** and **8h** were isolated in poor yields, which is not comparable with those of **3a**,**b** (Table 1), in a **7h/8h** ratio of 78:22 (Table 3, Entry 6).

To explore the type of 3,4-disubstituted aniline required to induce the aza-DA reaction, 4-chloro-3-methyl and 3,4-dichloroanilines (**3j**,**k**) were tested. Both reactions run at –50 °C within one night, and only products **4j**,**k** were obtained in excellent yields (Scheme 4; Table 3, Entries 7 and 8).

Conclusions

The research started with the aim to define the effect induced by the position of a methoxy group on the regioselectivity of the scandium-catalysed rearrangement of products **4** obtained from the MCR between indole, ethyl glyoxylate and anilines.[2] The rearrangement occurs on products of **3a**,**b** (Table 2 and Scheme 3) and involves different positions, which always correspond to the most nucleophilic and also the less hindered site of **4**.

A further interesting result was observed: when the MCR between **1**, **2**, and **3a**,**b**,**h** was catalysed by $Sc(OTf)_3$, the re-

Table 3. Reactions of indole (**1**), ethyl glyoxylate (**2**) and anilines (**3c**–**k**)[a] with scandium triflate (5 mol-%) in CH_2Cl_2.

n		Reagents				*T* [°C]	Time [h]	**4**%[b]	**5**%[b]	**7** and **8**%[c]
		R	R^1	R^2	R^3					
1[d]	**3c**	H	H	OMe	H	–50	0.5	92	–	–
2[d]	**3d**	H	OMe	H	H	–50	0.2	88	–	–
3[d]	**3e**	H	OMe	OMe	H	–50	0.5	98	–	–
4	**3f**	OMe	H	H	H	r.t.	72	–	22	–
5	**3g**	OMe	H	OMe	H	–50	12	73	–	–
6	**3h**	OMe	H	H	OMe	–50	12	–	–	14[e]
7	**3j**	Me	Cl	H	H	–50	12	83	–	–
8	**3k**	Cl	Cl	H	H	–50	12	93	–	–

[a] Ratio **1/2/3**, 1:1:1; in the presence of MS. [b] Isolated yields. [c] Ratio determined by ^1H NMR spectroscopy. [d] Data taken from ref.[2] [e] Ratio **7h/8h**, 78:22.

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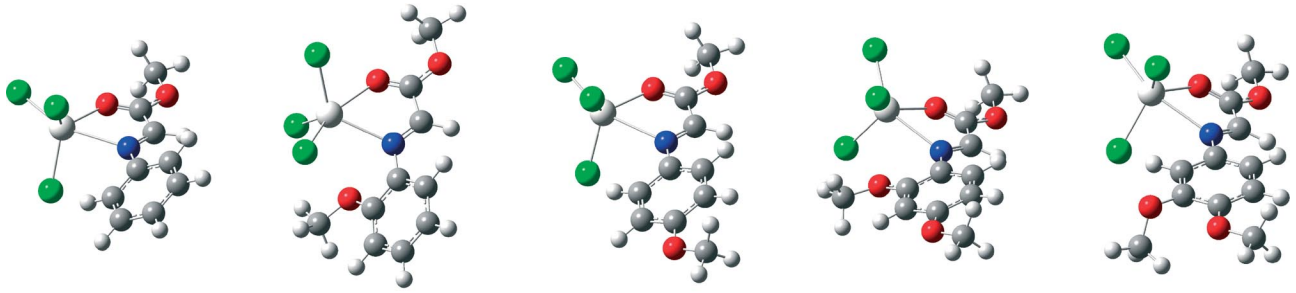

Figure 2. The molecular structures of $ScCl_3$ complexes with five methyl 2-(arylimino) acetates (**10**) optimised at the B3LYP/6-31G* level and the respective values of the dihedral angle between the aryl group and the C=N bond.

action followed a different pathway, and two pairs of diastereomeric aza-DA adducts (i.e., **7a**,**b**,**h** and **8a**,**b**,**h**) were isolated.

The reasons of this behaviour cannot be easily rationalised, but some experimental evidence have to be taken into account: (i) The aza-DA reaction is an independent pathway that does not involve **4** as an intermediate (Table 2, Entries 1–3), and therefore, it occurs in competition with the Friedel–Crafts reaction (Table 1, Entry 3 vs. 4). (ii) No aza-DA products are obtained from the scandium-catalysed process involving anilines with only one methoxy group, regardless of its placement in the aromatic ring; hence, at least two methoxy groups are required. (iii) Aza-DA products are not obtained with 2,4- and 2,5-dimethoxyaniline[2] or with the 2,3-disubstituted isomer (**3g**); hence, a 2-methoxy group inhibits this pathway. (iv) The aza-DA cycloaddition is regioselective, as products **7a**,**b** and **8a**,**b** are derived from the indole approach to the less-hindered *ortho* position of the coordinated Schiff base.

Substrates giving the highest yields of the aza-DA products are those with two substituents on the aromatic ring in the 3,4-positions (i.e., **3a**,**b**), and these substituents cannot be anything else than methoxy groups, because **3j**,**k** induce a different behaviour. Methoxy groups in the 3,5-positions (**3h**) give an analogous result, but the reaction yield is lower. If a comparison between these results does not allow electronic effects to be excluded, the steric effect induced by an *ortho*-methoxy substituent is the key factor that inhibits the aza-DA pathway.

To react in accordance to a DA reaction, a reasonable coplanarity between the aryl group and the C=N bond of the azadiene is required; this is not conceivable with an *ortho*-substituted phenyl group, but only with disubstituted 3,4- (or 3,5-) anilines. Mechanistic investigations support this scenario. Models of Sc^{III} complex of **3a**,**c**–**e**, (**10a**, **10c**, **10d** and **10e**) versus that with the unsubstituted phenyl ring (**A**) were optimised with DFT calculations[12] performed by using the GAUSSIAN98 program package[13] at the B3LYP/6-31G* level (the methyl ester and $ScCl_3$ were used for sake of simplicity, scandium was assumed with a pentavalent coordination, Figure 2).

Taking **A** as the reference (the dihedral angle between the phenyl group and the C=N bond is 28.6°), the effect of a methoxy group on the distortion can be evaluated. A comparison between **10c** and **10d** shows that an *ortho* methoxy group increases the distortion between the C=N bond and the aryl group as a result of the steric interactions of the *ortho* methoxy group with the scandium ligands, whereas the same group in the *para* position lowers the distortion (36.3 vs. 21.3°). The negative and positive effects in the above systems are balanced in **10e**, as its dihedral angle is similar to that in **A** (26.3 vs. 28.6°).

In conclusion, the best compromise requires an aromatic ring with two methoxy groups, one of them being in the *para* position, and unsubstituted *ortho* positions. The result is that **10a** has the smallest dihedral angle between the aryl group and the C=N bond (α = 18.9°), which results in a "planar" structure suitable for a DA reaction.

Experimental Section

General: Melting points were determined by the capillary method and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. IR spectra were registered with a Perkin–Elmer RX I spectrophotometer. Separation and purification of the products was carried out by column chromatography by using Merck silica gel 60 (230–400 mesh).

Materials: Dichloromethane was hydrocarbon-stabilised Aldrich ACS grade, distilled from calcium hydride and used immediately. Other solvents were purified according to standard procedures. Scandium triflate, indole, ethyl glyoxylate and anilines **3a**,**b** were commercially available Aldrich reagents; powdered 5 Å molecular sieves were Aldrich reagents heated under vacuum at 300 °C for 5 h and kept in sealed vials in a dryer.

General Procedure for the Reaction Between Indole (1), Methyl Glyoxylate (2) and Anilines (3a,b): To a solution of indole (**1**; 2 or 10 mmol), ethyl glyoxylate (**2**; 50% solution in toluene, 0.41 mL, 2 mmol) and arylamine **3a**,**b** (2 mmol) in CH_2Cl_2 (5.0 mL) was added MS (0.10–0.15 g) and stirring at ambient temperature was continued for the time reported in Table 1. Column chromatography with the eluent reported in each specific description gave **4a**,**b** (together with possible side products) with the yields reported in Table 1.

Compound 4a: Eluent: cyclohexane/ethyl acetate (70:30). Light cream-coloured needles, m.p. 137–138 °C (ethyl acetate/hexane). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.28 (br. s, 1 H, NH), 7.86 [d, ^3J(H,H) = 7.7 Hz, 1 H, indole H4], 7.38 [d, ^3J(H,H) =

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7.8 Hz, 1 H, indole H7], 7.28–7.17 (m, 2 H, indole H5 and H6), 7.25 (s, 1 H, indole H2), 6.73 [d, ^3J(H,H) = 8.6 Hz, 1 H, aromatic H5], 6.34 [d, ^4J(H,H) = 2.4 Hz, 1 H, aromatic H2], 6.19 [dd, ^3J(H,H) = 8.6 Hz, ^4J(H,H) = 2.4 Hz, 1 H, aromatic H6], 5.37 (s, 1 H, CH acetate), 4.53 (bb, 1 H, NH), 4.29 (m, 1 H, CH*H* ethyl), 4.16 (m, 1 H, C*H*H ethyl), 3.80 (s, 3 H, methoxy), 3.79 (s, 3 H, methoxy), 1.24 [t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3 ethyl] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.3, 149.4, 141.5, 141.0, 135.9, 125.4, 122.5, 122.0, 119.5, 119.0, 112.5, 112.2, 110.9, 103.6, 99.2, 61.0, 56.1, 55.2, 54.5, 13.7 ppm. IR (nujol): $\tilde{\nu}$ = 3376 (NH), 3337 (NH), 1727 (C=O) cm^{-1}. $C_{20}H_{22}N_2O_4$ (354.4): calcd. C 67.78, H 6.26, N 7.90; found C 67.59, H 6.31, N 7.98.

Compound 4b: Eluent: cyclohexane/ethyl acetate (85:15). Light cream-coloured needles, m.p.92 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.31 (br. s, 1 H, NH), 7.85 [d, ^3J(H,H) = 7.7 Hz, 1 H, indole H4], 7.36 [d, ^3J(H,H) = 7.6 Hz, 1 H, indole H7], 7.22–7.16 (m, 2 H, indole H5 and H6), 7.17 (s, 1 H, indole H2), 6.66 [d, ^3J(H,H) = 8.3 Hz, 1 H, aromatic H5], 6.32 [d, ^4J(H,H) = 2.3 Hz, 1 H, aromatic H2], 6.12 [dd, ^3J(H,H) = 8.3 Hz, ^4J(H,H) = 2.3 Hz, 1 H, aromatic H6], 5.86 (s, 2 H, OCH_2O), 5.34 (s, 1 H, CH acetate), 4.6 (bb, 1 H, NH), 4.24 (m, 1 H, CH*H* ethyl), 4.17 (m, 1 H, C*H*H ethyl), 1.24 [t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3 ethyl] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.2, 147.8, 141.8, 139.6, 136.0, 125.3, 122.6, 122.0, 119.5, 119.0, 112.0, 110.9, 108.1, 104.7, 100.1, 96.2, 61.1, 54.7, 13.6 ppm. IR (nujol): $\tilde{\nu}$ = 3397 (NH), 1727 (C=O) cm^{-1}. $C_{19}H_{18}N_2O_4$ (338.4): calcd. C 67.44, H 5.36, N 8.28; found C 67.58, H 5.31, N 8.17.

Compound 6b: Elution with cyclohexane/ethyl acetate (85:15) gave as a second fraction, partly overlapped to **4b**, product **6b** as soft white needles, m.p. 138 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.78 (s, 1 H, H4), 6.66 [d, ^3J(H,H) = 8.3 Hz, 1 H, aromatic H7′], 6.62 [d, ^4J(H,H) = 2.3 Hz, 1 H, aromatic H4′], 6.54 [dd, ^3J(H,H) = 8.3 Hz, ^4J(H,H) = 2.3 Hz, 1 H, aromatic H6′], 6.35 (s, 1 H, H9), 5.91 (s, 4 H, 2OCH_2O), 5.58 (s, 1 H, H6), 4.88 (s, 1 H, H8), 4.63 (bb, 1 H, NH), 4.28–4.16 (m, 4 H, 2CH_2 ethyl), 1.29 [t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3 ethyl], 1.20 [t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3 ethyl] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.3, 169.0, 147.4, 143.5, 141.4, 141.2, 136.0, 114.8, 109.5, 107.7, 107.5, 106.5, 103.9, 100.6, 100.4, 98.1, 67.7, 63.3, 61.3, 61.0, 13.7, 13.6 ppm. IR (nujol): $\tilde{\nu}$ = 3395 (NH), 1726 (C=O) cm^{-1}. $C_{22}H_{22}N_2O_8$ (442.4): calcd. C 59.73, H 5.01, N 6.33; found C 59.58, H 5.12, N 6.39.

General Procedure for the Reaction Between Indole (1), Methyl Glyoxylate (2) and Anilines (3a,b,f–k) Catalysed by Sc(OTf)$_3$: To a solution of indole (**1**; 0.117 g, 1 mmol), ethyl glyoxylate (**2**; 50% solution in toluene, 0.204 mL, 1 mmol) and arylamine **3a**,**b**,**f**–**k** (1 mmol) in CH_2Cl_2 (1.5 mL) was added MS (0.07–0.10 g). To the mixture, in a rubber-sealed vial, cooled to the temperature reported in Tables 1 and 3 was added $Sc(OTf)_3$ (0.025 g, 0.05 mmol) and stirring was continued for the time reported in Tables 1 and 3. The reaction was quenched with water, the mixture was extracted with CH_2Cl_2, the organic layer was dried and the residue was column chromatographed. Eluent and products separation are reported below.

Reaction between 1, 2 and 3a (Table 1, **Entries 3 and 4):** Chromatographic separation on a column 60 cm length × 1.5 cm diameter with cyclohexane/ethyl acetate (80:20), after the eventual elution of **4a** (Entry 3), a mixture of **6a** and **7a** was eluted with the first fraction enriched with the latter product and the last fraction with **6a** nearly pure. These pure products were obtained by careful fractional crystallisation.

Compound 7a: Light cream-coloured needles, m.p. 140–141 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.23 [d, ^3J(H,H) = 7.5 Hz, 1 H, H10], 7.10 [dt, ^3J(H,H) = 7.8 Hz, ^4J(H,H) = 0.9 Hz, 1 H, H8], 6.80 [dt, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 1.2 Hz, 1 H, H9], 6.71 (s, 1 H, H1), 6.70 [d, ^3J(H,H) = 7.8 Hz, 1 H, H7], 6.28 (s, 1 H, H4), 4.82 [d, ^3J(H,H) = 8.1 Hz, 1 H, H11a], 4.26 [q, ^3J(H,H) = 7.2 Hz, 2 H, CH_2], 4.0 (bb, 2 H, 2NH), 3.97 [d, ^3J(H,H) = 8.1 Hz, 1 H, H6], 3.86 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 3.74 [t, ^3J(H,H) = 8.1 Hz, 1 H, H6a], 1.30 [t, ^3J(H,H) = 7.2 Hz, 3 H, CH_3] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.2, 149.9, 149.4, 142.9, 137.1, 129.0, 128.3, 125.2, 119.1, 113.6, 112.1, 110.2, 100.4, 61.4, 57.8, 56.5, 55.7 (2OMe), 42.4, 14.1 ppm. IR (nujol): $\tilde{\nu}$ = 3360 (NH), 1723 (C=O) cm^{-1}. $C_{20}H_{22}N_2O_4$ (354.4): calcd. C 67.78, H 6.26, N 7.90; found C 67.69, H 6.31, N 7.79.

Compound 8a: Whitish crystals, m.p. 170–172 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.02 [t, ^3J(H,H) = 7.6 Hz, 1 H, H8], 6.90 [d, ^3J(H,H) = 7.5 Hz, 1 H, H10], 6.72 [t, ^3J(H,H) = 7.5 Hz, 1 H, H9], 6.68 (s, 1 H, H1), 6.60 [d, ^3J(H,H) = 7.7 Hz, 1 H, H7], 6.19 (s, 1 H, H4), 5.00 [d, ^3J(H,H) = 9.0 Hz, 1 H, H11a], 4.37 [q, ^3J(H,H) = 7.1 Hz, 2 H, CH_2], 4.33 [dd, ^3J(H,H) = 9.0, 3.3 Hz, 1 H, H6a], 4.2 (bb, 2 H, 2NH), 4.12 [d, ^3J(H,H) = 3.3 Hz, 1 H, H6], 3.85 (s, 3 H, OMe), 3.78 (s, 3 H, OMe), 1.36 [t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.0, 150.6, 148.7, 142.8, 138.1, 127.6, 126.0, 123.4, 118.8, 115.9, 111.0, 110.2, 100.0, 61.1, 58.4, 56.2, 55.4, 55.2, 44.4, 13.6 ppm. IR (nujol): $\tilde{\nu}$ = 3360 (NH), 1728 (C=O) cm^{-1}. $C_{20}H_{22}N_2O_4$ (354.4): calcd. C 67.78, H 6.26, N 7.90; found C 68.02, H 6.41, N 7.75.

Reaction between 1, 2 and 3b (Table 1, **Entry 5):** Chromatographic separation on a column 60 cm length × 1.5 cm diameter with cyclohexane/ethyl acetate (85:15) gave a mixture of **7b** and **8b** with the first fraction enriched with the latter product and the last fraction with **7b** nearly pure. These pure products were obtained by careful fractional crystallisation.

Compound 7b: Soft white needles, m.p. 120–121 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.21 [d, ^3J(H,H) = 7.4 Hz, 1 H, H10], 7.10 [dt, ^3J(H,H) = 7.7 Hz, ^4J(H,H) = 0.9 Hz, 1 H, H8], 6.79 [dt, ^3J(H,H) = 7.4 Hz, ^4J(H,H) = 0.9 Hz, 1 H, H9], 6.69 [d, ^3J(H,H) = 7.8 Hz, 1 H, H7], 6.65 (s, 1 H, H1), 6.27 (s, 1 H, H4), 5.88 (AB system, 2 H, OCH_2O), 4.79 [d, ^3J(H,H) = 8.0 Hz, 1 H, H11a], 4.26 [q, ^3J(H,H) = 7.1 Hz, 2 H, CH_2], 4.10 (bb, 2 H, 2NH), 3.96 [d, ^3J(H,H) = 7.6 Hz, 1 H, H6], 3.74 [t, ^3J(H,H) = 7.8 Hz, 1 H, H6a], 1.30 [t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.8, 149.5, 147.2, 140.8, 137.7, 128.5, 127.9, 124.8, 118.6, 114.0, 109.7, 107.6, 100.3, 97.4, 61.0, 57.8, 55.4, 42.2, 13.7 ppm. IR (nujol): $\tilde{\nu}$ = 3323 (NH), 1737 (C=O) cm^{-1}. $C_{19}H_{18}N_2O_4$ (338.4): calcd. C 67.44, H 5.36, N 8.28; found C 67.62, H 5.41, N 8.33.

Compound 8b: White needles, m.p. 183 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.02 [t, ^3J(H,H) = 7.7 Hz, 1 H, H8], 6.89 [d, ^3J(H,H) = 7.5 Hz, 1 H, H10], 6.72 [dt, ^3J(H,H) = 7.5 Hz, ^4J(H,H) = 0.9 Hz, 1 H, H9], 6.63 (s, 1 H, H1), 6.59 [d, ^3J(H,H) = 7.7 Hz, 1 H, H7], 6.18 (s, 1 H, H4), 5.85 (AB system, 2 H, OCH_2O), 4.97 [d, ^3J(H,H) = 9.1 Hz, 1 H, H11a], 4.38 [q, ^3J(H,H) = 7.1 Hz, 2 H, CH_2], 4.32 [dd, ^3J(H,H) = 9.1, 3.1 Hz, 1 H, H6a], 4.21 [d, ^3J(H,H) = 3.1 Hz, 1 H, H6], 4.15 (bb, 1 H, NH), 3.92 (bb, 1 H, NH), 1.37 [t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 170.9, 150.6, 146.9, 141.0, 139.0, 127.7, 125.9, 123.4, 118.8, 116.8, 110.1, 106.8, 100.3, 97.4, 61.1, 58.7, 55.6, 44.3, 13.6 ppm. IR (nujol): $\tilde{\nu}$ = 3383

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(NH), 3341 (NH),1712 (C=O) cm^{-1}. $C_{19}H_{18}N_2O_4$ (338.4): C 67.44, H 5.36, N 8.28; found C 67.32, H 5.53, N 8.30.

Reaction between 1, 2 and 3f (Table 3, Entry 4): Chromatographic separation of the reaction mixture with several impurities and small amounts of side products was performed on a column 30 cm length × 1.5 cm diameter with cyclohexane/ethyl acetate (70:30), and **5f** was the only significant product separated in about 22% yield.

Compound 5f: Eluent: cyclohexane/ethyl acetate (70:30). Light cream-coloured crystals, m.p. 114–115 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.26 (br. s, 1 H, NH), 7.56 [d, ^3J(H,H) = 7.9 Hz, 1 H, indole H4], 7.33 [d, ^3J(H,H) = 8.0 Hz, 1 H, indole H7], 7.19 [t, ^3J(H,H) = 7.9 Hz, 1 H, indole proton], 7.09 [t, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 0.9, 1 H, indole proton], 7.08 (s, 1 H, indole H2), 6.93 [d, ^3J(H,H) = 8.1 Hz, 1 H, aromatic proton], 6.27 [d, ^4J(H,H) = 2.1 Hz, 1 H, aromatic proton], 6.16 [dd, ^3J(H,H) = 8.1 Hz, ^4J(H,H) = 2.1 Hz, 1 H, aromatic proton], 5.48 (s, 1 H, CH acetate), 4.21 (m, 2 H, OCH_2), 3.83 (s, 3 H, methoxy), 3.6 (bb, 1 H, NH), 1.7 (bb, 1 H, NH), 1.27 [t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3 ethyl] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 173.6, 157.2, 146.3, 135.9, 129.5, 126.5, 122.9, 121.5, 119.0, 117.3, 112.7 110.7, 106.5, 97.9, 60.3, 54.9, 41.4, 26.4, 13.8 ppm. IR (nujol): $\tilde{\nu}$ = 3395 and 3300 (NH and NH_2), 1732 (C=O) cm^{-1}. $C_{19}H_{20}N_2O_3$ (324.4): calcd. C 70.35, H 6.21, N 8.64; found C 70.19, H 6.28, N 8.68.

Reaction between 1, 2 and 3g (Table 3, Entry 5): Chromatographic separation was performed on a column 30 cm length × 1.5 cm diameter with cyclohexane/ethyl acetate (80:20).

Compound 4g: Colourless prisms, m.p. 94 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.54 (br. s, 1 H, NH), 7.92 [d, ^3J(H,H) = 7.3 Hz, 1 H, indole H4], 7.35 [dd, ^3J(H,H) = 6.8 Hz, ^4J(H,H) = 1.1 Hz, 1 H, indole H7], 7.28–7.18 (m, 3 H, indole protons), 6.93 [t, ^3J(H,H) = 8.3 Hz, 1 H, aromatic proton], 6.40 [t, ^3J(H,H) = 8.3 Hz, 2 H, aromatic protons], 5.48 (s, 1 H, CH acetate), 5.4 (bb, 1 H, NH), 4.30 (m, 1 H, CH*H* ethyl), 4.18 (m, 1 H, C*H*H ethyl), 3.90 (s, 3 H, methoxy), 3.89 (s, 3 H, methoxy), 1.26 [t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3 ethyl] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.2, 152.2, 141.5, 140.5, 136.1, 135.3, 125.3, 124.0, 122.9, 121.9, 119.4, 119.0, 111.7, 111.1, 104.6, 101.7, 61.0, 59.6, 55.3, 54.0, 13.7 ppm. IR (nujol): $\tilde{\nu}$ = 3395 (NH), 1731 (C=O) cm^{-1}. $C_{20}H_{22}N_2O_4$ (354.4): calcd. C 67.78, H 6.26, N 7.90; found C 67.59, H 6.35, N 8.01.

Reaction between 1, 2 and 3h (Table 3, Entry 6): Chromatographic separation on a column 30 cm length × 1.5 cm diameter with cyclohexane/ethyl acetate (78:22), after unreacted indole, gave a mixture of **7h** and **8h**. Fractional crystallisation with ethyl acetate/hexane allowed the separation of pure **7h**, addition of hexane to the mother liquors gave pure **8h**.

Compound 7h: White needles, m.p. 110–111 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.20 [d, ^3J(H,H) = 7.4 Hz, 1 H, H10], 7.10 [t, ^3J(H,H) = 7.6 Hz, 1 H, H8], 6.75 [t, ^3J(H,H) = 7.4 Hz, 1 H, H9], 6.70 [d, ^3J(H,H) = 7.7 Hz, 1 H, H7], 5.98 [d, 1 H, ^4J(H,H) = 2.0 Hz, aromatic proton], 5.90 [d, ^4J(H,H) = 2.0 Hz, 1 H, aromatic proton], 4.91 [d, ^3J(H,H) = 7.8 Hz, 1 H, H11a], 4.3 (bb, 1 H, NH), 4.28 [q, ^3J(H,H) = 7.1 Hz, 2 H, OCH_2], 3.93 [d, ^3J(H,H) = 8.7 Hz, 1 H, H6], 3.86 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 3.58 [t, ^3J(H,H) = 8.3 Hz, 1 H, H6a], 1.32 [t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.1, 160.5, 159.8, 150.4, 144.6, 128.3, 125.7, 118.3, 109.7, 103.2, 92.2, 89.7, 61.3, 55.3, 55.1, 54.8, 54.7, 42.2, 14.1 ppm. IR (nujol): $\tilde{\nu}$ = 3384 and 3325 (NH), 1734 (C=O) cm^{-1}. $C_{20}H_{22}N_2O_4$ (354.4): calcd. C 67.78, H 6.26, N 7.90; found C 67.75, H 6.32, N 7.83.

Compound 8h: White crystals, m.p. 182 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.02 [t, ^3J(H,H) = 7.5 Hz, 1 H, H8], 6.90 [d, ^3J(H,H) = 7.6 Hz, 1 H, H10], 6.71 [t, ^3J(H,H) = 7.4 Hz, 1 H, H9], 6.64 [d, ^3J(H,H) = 7.4 Hz, 1 H, H7], 5.94 [d, ^4J(H,H) = 2.2 Hz, 1 H, aromatic proton], 5.79 [d, ^4J(H,H) = 2.2 Hz, 1 H, aromatic proton], 5.12 [d, ^3J(H,H) = 8.5 Hz, 1 H, H11a], 4.34 [q, ^3J(H,H) = 7.1 Hz, 2 H, OCH_2], 4.29 [dd, ^3J(H,H) = 8.5, 3.3 Hz, 1 H, H6a], 4.26 [d, ^3J(H,H) = 3.3 Hz, 1 H, H6], 3.86 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 3.6 (bb, 2 H, 2NH), 1.32 [t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.4, 160.3, 159.4, 150.4, 145.9, 127.9, 123.7, 119.0, 110.7, 92.3, 89.8, 61.6, 56.2, 55.3, 55.1, 54.6, 43.7, 14.0 ppm. IR (nujol): $\tilde{\nu}$ = 3380 (NH), 1734 (C=O) cm^{-1}. $C_{20}H_{22}N_2O_4$ (354.4): calcd. C 67.78, H 6.26, N 7.90; found C 68.04, H 6.11, N 8.09.

Reaction between 1, 2 and 3j (Table 3, Entry 7): Chromatographic separation was performed on a column 30 cm length × 1.5 cm diameter with cyclohexane/ethyl acetate (80:20).

Compound 4j: Soft-white needles, m.p. 88–89 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.2 (br. s, 1 H, NH), 7.85 [d, ^3J(H,H) = 7.9 Hz, 1 H, indole H4], 7.38 [d, ^3J(H,H) = 8.1 Hz, 1 H, indole H7], 7.29–7.18 (m, 3 H, indole protons), 7.11 [d, ^3J(H,H) = 8.5 Hz, 1 H, aromatic proton], 6.55 [d, ^4J(H,H) = 2.6 Hz, 1 H, aromatic proton], 6.43 [dd, ^3J(H,H) = 8.5 Hz, ^4J(H,H) = 2.6 Hz, 1 H, aromatic proton], 5.38 (s, 1 H, CH acetate), 4.7 (bb, 1 H, NH), 4.31 (m, 1 H, CH*H* ethyl), 4.17 (m, 1 H, C*H*H ethyl), 2.29 (s, 3 H, methyl), 3.89, 1.25 [t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3 ethyl] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.0, 144.7, 136.1, 136.0, 129.0, 125.2, 122.7, 122.6, 122.1, 119.6, 119.0, 115.4, 111.8, 111.5, 111.0, 61.2, 53.8, 19.8, 13.7 ppm. IR (nujol): $\tilde{\nu}$ = 3344 (NH), 1707 (C=O) cm^{-1}. $C_{19}H_{19}ClN_2O_2$ (342.8): calcd. C 66.57, H 5.59, N 8.17; found C 66.39, H 5.68, N 8.09.

Reaction Between 1, 2 and 3k (Table 3, Entry 8): Chromatographic separation was performed on a column 30 cm length × 1.5 cm diameter with cyclohexane/ethyl acetate (80:20).

Compound 4k: White crystals, m.p. 80 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.54 (br. s, 1 H, NH), 7.92 [d, ^3J(H,H) = 7.3 Hz, 1 H, indole H4], 7.35 [dd, ^3J(H,H) = 6.8 Hz, ^4J(H,H) = 1.1 Hz, 1 H, indole H7], 7.28–7.18 (m, 3 H, indole protons), 6.93 [t, ^3J(H,H) = 8.3 Hz, 1 H, aromatic proton], 6.40 [t, ^3J(H,H) = 8.3 Hz, 2 H, aromatic protons], 5.48 (s, 1 H, CH acetate), 5.4 (br. s, 1 H, NH), 4.30 (m, 1 H, CH*H* ethyl), 4.18 (m, 1 H, C*H*H ethyl), 3.90 (s, 3 H, methoxy), 3.89 (s, 3 H, methoxy), 1.26 [t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3 ethyl] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.2, 152.2, 141.5, 140.5, 136.1, 135.3, 125.3, 124.0, 122.9, 121.9, 119.4, 119.0, 111.7, 111.1, 104.6, 101.7, 61.0, 59.6, 55.3, 54.0, 13.7 ppm. IR (nujol): $\tilde{\nu}$ = 3356 (NH), 1703 (C=O) cm^{-1}. $C_{18}H_{16}Cl_2N_2O_2$ (363.2): C 59.52, H 4.44, N 7.71; found C 59.37, H 4.39, N 7.85.

General Procedure for the Reaction of Products 4a,b Catalysed by $Sc(OTf)_3$: To a CH_2Cl_2 (1.0 mL) solution of **4** (0.2 mmol) in a rubber sealed vial cooled to the temperature reported in Table 2 was added $Sc(OTf)_3$ (0.005 g, 0.01 mmol) and stirring was continued for the time reported hereto. The reaction was quenched with water, the mixture was extracted with CH_2Cl_2, the organic layer was dried and the residue was column chromatographed to separate the different products with the eluent reported below in the specific description of each product.

Compound 5a: From the reaction described in Table 2, Entry 1, unreacted **4a**, **5a** and **9a** were eluted in the order on a column 40 cm

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length × 1.5 cm diameter and the eluent was cyclohexane/ethyl acetate (70:30). For the reaction described in Table 2, Entry 2, only **5a** was easily separated. Glassy solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.27 (br. s, 1 H, NH), 7.44 [d, ^3J(H,H) = 7.9 Hz, 1 H, indole H4], 7.35 [d, ^3J(H,H) = 8.1 Hz, 1 H, indole H7], 7.19 [d, ^3J(H,H) = 2.4 Hz, 1 H, indole H2] 7.18 [dt, ^3J(H,H) = 8.1 Hz, ^4J(H,H) = 1.0 Hz, 1 H, indole proton], 7.08 [dt, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 0.9, 1 H, indole proton], 6.83 (s, 1 H, aromatic proton), 6.33 (s, 1 H, aromatic proton), 5.24 (s, 1 H, CH acetate), 4.28 (m, 2 H, OCH_2), 3.84 (s, 3 H, methoxy), 3.72 (s, 3 H, methoxy), 3.7 (bb, 1 H, NH), 1.7 (br. s, 1 H, NH), 1.31 [t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3 ethyl] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.4, 148.6, 141.6, 138.1, 135.9, 128.3, 126.2, 123.1, 121.8, 119.2, 118.6, 114.2, 113.2, 111.7, 110.7, 101.3, 60.7, 56.1, 55.3, 44.1, 13.8 ppm. IR (nujol): $\tilde{\nu}$ = 3363 (bb, NH_2), 1719 (C=O) cm^{-1}. $C_{20}H_{22}N_2O_4$ (354.4): C 67.78, H 6.26, N 7.90; found C 67.99, H 6.39, N 8.08.

Compound 9a: From the reaction described in Table 2, Entry 1, **9a** was obtained as a pale-yellow oil. ^{1}H NMR [pair of diastereoisomers (the signal of the second stereoisomer, when detectable, is reported in parenthesis)] (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.15 (br. s, 1 H, NH), 8.09 (8.06) (br. s + br. s, 1 H, NH), 7.73 (7.70) [d + d, ^3J(H,H) = 8.5 Hz, 1 H, indole H4], 7.56 [d, ^3J(H,H) = 7.9 Hz, 1 H, indole H4], 7.37–6.84 (m, 8 H, indole protons), 6.88 (6.87) (s + s, 1 H, H3 aromatic proton), 6.33 (6.29) (s + s, 1 H, H6 aromatic proton), 5.39 (5.38) (s + s, 1 H, CH acetate), 5.36 (5.34) (s + s, 1 H, CH acetate), 5.17 (br. s, 1 H, NH), 5.11 (bb, 1 H, NH), 4.25–4.05 (m, 4 H, 2 OCH_2), 3.70, 3.695, 3.69 (s + s + s, 6 H, 2 methoxy), 1.28, 1.27 (1.20, 1.18) [t + t + t + t, ^3J(H,H) = 7.1 Hz, 6 H, 2 CH_3 ethyl] ppm. ^{13}C NMR [pair of diastereoisomers (the signal of the second stereoisomer, when detectable, is reported in parenthesis)] (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.81 (172.76), 172.56 (172.52), 148.84 (148.78), 141.33 (141.25), 138.9 (138.8), 136.30 (136.25), 136.18 (136.15), 126.7 (126.6), 125.77 (125.75), 123.8, 122.8 (122.7), 122.26 (122.23), 122.1 (122.0), 119.8, 119.54 (119.50), 119.4 (119.2), 119.17 (119.12), 115.5 (115.3), 114.3 (114.2), 112.6 (112.4), 112.1.(111.9), 111.18 (111.14), 111.06 (111.0), 98.68 (98.58), 61.29 (61.24), 61.15 (61.09), 56.59 (56.53), 55.54, 54.86 (54.83), 44.8 (44.5), 14.09 (14.05), 14.05 (13.95) ppm. IR (nujol): $\tilde{\nu}$ = 3404 (NH), 1718 (C=O) cm^{-1}.

Compound 5b: For the reaction described in Table 2, Entry 3, **5b** was separated by column chromatography with cyclohexane/ethyl acetate (7525) as eluent. Cream-coloured crystals, m.p. 151–152 °C (ethyl acetate/hexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.13 (br. s, 1 H, NH), 7.42 [d, ^3J(H,H) = 7.9 Hz, 1 H, indole H4], 7.39 [d, ^3J(H,H) = 8.1 Hz, 1 H, indole H7], 7.40 [d, ^3J(H,H) = 2.0 Hz, 1 H, indole H2], 7.21 [dt, ^3J(H,H) = 7.0 Hz, ^4J(H,H) = 1.0 Hz, 1 H, indole], 7.08 [dt, ^3J(H,H) = 7.0 Hz, ^4J(H,H) = 1.0 Hz, 1 H, indole], 6.70 (s, 1 H, aromatic proton), 6.33 (s, 1 H, aromatic proton), 5.84 (AB system, 2 H, OCH_2O), 5.25 (s, 1 H, CH acetate), 4.26 [q, ^3J(H,H) = 7.1 Hz, 2 H, OCH_2], 3.74 (bb, 1 H, NH), 1.31 [t, ^3J(H,H) = 7.1 Hz, 3 H, CH_3 ethyl] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.5, 147.1, 140.7, 139.1, 136.2, 126.6, 123.4, 122.3, 119.7, 118.9, 115.7, 112.2, 111.0, 109.0, 100.6, 98.6, 61.1, 44.2, 14.1 ppm. IR (nujol): $\tilde{\nu}$ = 3396, 3332 (NH_2 and NH), 1717 (C=O) cm^{-1}. $C_{19}H_{18}N_2O_4$ (338.4): calcd. C 67.44, H 5.36, N 8.28; found C 67.32, H 5.29, N 8.20.

X-ray Crystallographic Study: Diffraction data for a single crystal of **7a** were collected with an Enraf–Nonius CAD4 diffractometer, working with graphite-monochromated Mo-K_α X-radiation (λ = 0.71073 Å). Crystal data for **7a**: $C_{20}H_{22}N_2O_4$; M_r = 354.40; T = 293 K; crystal dimensions 0.51 × 0.30 × 0.14 mm; triclinic; $P\bar{1}$ (No. 2); a = 7.399(1) Å, b = 10.363(2) Å, c = 12.234(4) Å; α = 84.21(3)°, β = 77.69(2)°, γ = 77.49(2)°; V = 893.30(45) Å^3; Z = 2; $\rho_{calcd.}$ = 1.318; $F(000)$ = 376; μ = 0.092 mm^{-1}; $2\theta_{max}$ = 50°; 4059 measured reflections; 3168 independent reflections (R_{int} = 0.017); 1840 strong reflections [$I_0 > 2\sigma(I_0)$]; 244 refined parameters; R_1 = 0.0517 (strong data) and 0.1065 (all data); wR_2 = 0.1133 (strong data) and 0.1369 (all data); GOF = 1.009; 0.13 and –0.18 max. and min. residual electron density. Data reduction (including intensity integration, background, Lorentz and polarisation corrections) was performed with the WinGX package.[14] Absorption effects were evaluated by the psi-scan method[15] and absorption correction was applied to the data (min./max. transmission factors were 0.873/0.987). Crystal structure was solved by direct methods (SIR 97)[16] and refined by full-matrix least-square procedures on F^2 by using all reflections (SHELXL 97).[17] Anisotropic displacement parameters were refined for all non-hydrogen atoms. Hydrogen atoms bonded to carbon atoms were placed at calculated positions with the appropriate AFIX instructions and refined by using a riding model; hydrogen bonded to N atoms were located in the ΔF map and refined restraining the N–H distance to be 0.96 ± 0.01 Å.

CCDC-705354 (for **7a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for compounds **4a**,**b**,**g**,**j**,**k**; **5b**,**f**; **6a**,**b**; **7a**,**b**,**e**; **8a**,**b**,**e**; **9a**.

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