Synthesis of Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles by Oxidative Cyclization of Bisindolylmaleimides with a Rhodium(III)–Copper(II) Catalytic System

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Abstract: A novel catalytic protocol for the synthesis of a series of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles based on the bimetallic system $RhCl_3 \cdot 3H_2O$ and $Cu(OAc)_2 \cdot H_2O$ in the presence of molecular oxygen was investigated. The method was applied to the synthesis of the glycosidated fluoroindolocarbazole **3** that was recently isolated as a metabolite from feeding experiments of *Saccharothrix aerocolonigenes* ATCC 39243 with fluorotryptophanes.

Key words: glycosides, rebeccamycin, catalysis, rhodium, copper

Considerable interest is devoted to the synthesis of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole derived natural products and synthetic analogues thereof because of their diverse spectrum of biological activities.[1] For example, the alkaloid staurosporine (**1**) was isolated from *Streptomyces staurosporeus* (AM 2282).[2,3] Its biological properties include antifungal,[2a] hypotensive,[4] and platelet aggregation activities,[5] whilst its cytotoxic activity against protein kinase C and other cycline-dependent kinases is one of the most important aspects of its biological profile (Figure 1).[6] Rebeccamycin (**2**) is another important member of this class of indolocarbazoles displaying a broad spectrum of in vivo activity in tumor-bearing murine models. Most importantly, rebeccamycin (**2**) is, like camptothecin, a topoisomerase I poison.[7,8] Recently, the fluoroindolocarbazole **3** was identified as one of several metabolites obtained from feeding experiments of *Saccharothrix aerocolonigenes* ATCC 39243 cultures with 5-fluorotryptophane and glucose.[9] The fluoroindolocarbazole **3** is a quite selective topoisomerase I active agent and was reported of being more potent than rebeccamycin (**2**) in in vivo antitumor assays.[9,10]

Despite numerous synthetic efforts towards the synthesis of this class of compounds, a flexible and efficient access to the aglycon indolocarbazole core is still an important challenge. Several routes to the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole ring system have been reported.[1,11–15] Amongst them, the most attractive approach is the oxidative cyclization of readily available bisindolylmaleimides to the corresponding indolocarbazoles and numerous synthetic variants to perform this reaction have been explored. For example, the oxidative cyclization of bisindolylmaleimides was carried out with iodine (with or without light),[8a,b,16] 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[17] or with hypervalent iodine species such as phenyliodine(III)bis(trifluoroacetate) (PIFA) and phenyliodine(III)diacetate (PIDA).[18] Furthermore, it was performed with stoichiometric amounts of $Pd(OAc)_2$,[8c,19] $PdCl_2$,[20] $Pd(O_2CCF_3)_2$,[21] or $CuCl_2$.[22] However, these methods are not general with respect to the substitution pattern of the bisindolylmaleimide and present a number of other limitations: reactions with iodine necessitate high dilution and long reaction times and cyclizations carried out with DDQ maintain problems with the removal of the DDQ by-products. Pd^{2+}- or Cu^{2+}-mediated oxidative cyclizations require one to five equivalents of the palladium or copper salt and cause severe difficulties when the formed Pd(0)- or Cu(0)-slurry has to be separated from the often insoluble indolocarbazoles.

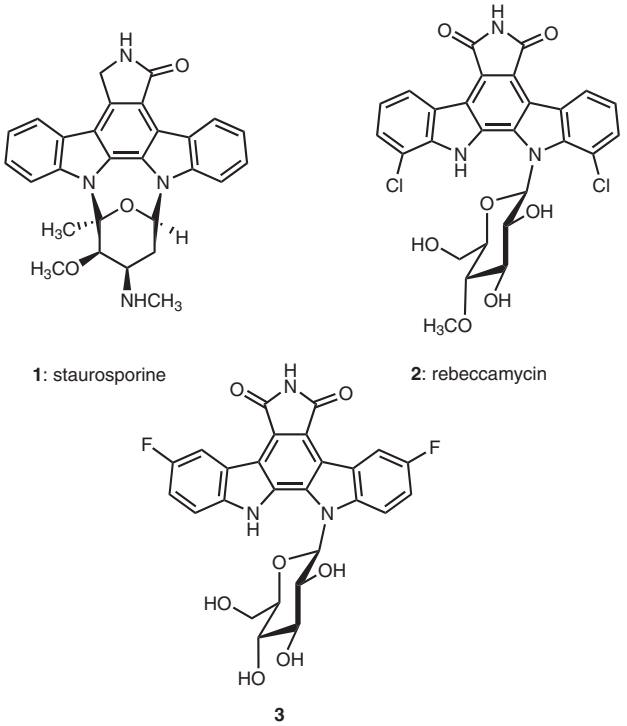

Figure 1

Recently, Wang et al. reported the oxidative cyclization of bisindolylmaleimides with a Pd^{2+}/Cu^{2+} Wacker-type reaction system, where aglycons of rebeccamycin derivatives were obtained in 58–88% yield.[23] The catalytic system described took advantage of the reoxidation of Pd(0) and

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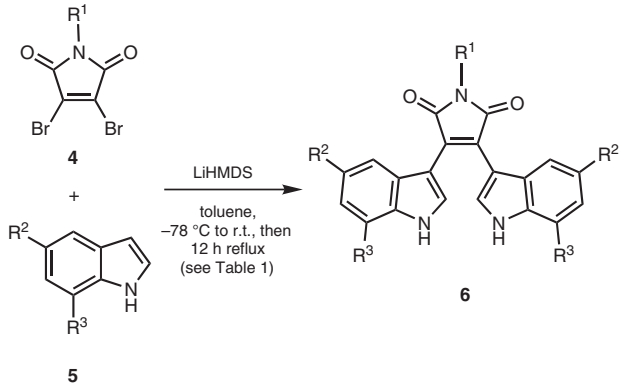
Cu(0) by molecular oxygen making the process itself operationally simple and amenable to a scale-up. However, the bimetallic system used was only catalytic with respect to the palladium source, whilst a stoichiometric amount of Cu^{2+} salt was still necessary to accomplish the desired reaction.

We report herein our results on the use of a rhodium(III)–copper(II) catalytic system to perform the oxidative cyclization of bisindolylmaleimides to appropriately substituted indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles and its application in the synthesis of the potent topoisomerase I active agent **3**.[29]

The synthesis of the bisindolylmaleimides **6** was accomplished by the coupling of two equivalents of the indolyl-based lithium salts of **5** with the 2,3-dibromomaleimides **4** in close analogy to the protocol of Ohkubo et al. (Scheme 1 and Table 1).[20]



Scheme 1

Table 1 Synthesis of the Bisindolylmaleimides **6a–g**

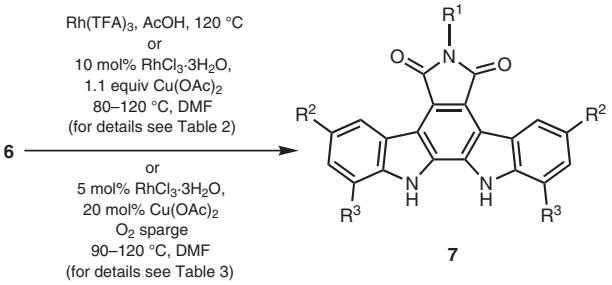
4	R^1	5	R^2	R^3	6	Yield (%)[a]
4a	CH_3	**5a**	H	H	**6a**	75
4a	CH_3	**5b**	F	H	**6b**	63
4a	CH_3	**5c**	OCH_3	H	**6c**	43
4b	CH_2Ph	**5b**	F	H	**6d**	47
4b	CH_2Ph	**5c**	OCH_3	H	**6e**	40
4b	CH_2Ph	**5a**	H	H	**6f**	50
4b	CH_2Ph	**5d**	H	Cl	**6g**	54

[a] Yield refers to isolated product after column chromatography.

Adding the indoles **5** to a freshly prepared solution of LiHMDS in toluene, followed by the addition of the N-protected dibromomaleimides **4**, gave the bisindolylmaleimides **6** in moderate to good yields (40–75%). Although the coupling of **5** to **4** needed elevated temperatures for its completion, this protocol was more valuable than the use of the corresponding indolylmagnesium bromides as described by Steglich et al. in the synthesis of arcyriarubin A and B.[24] In this case more than four equivalents of the indolylmagnesium salt were necessary to effect the desired reaction.

With the bisindolylmaleimides **6** in hand, rhodium(III)-mediated cyclizations to the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles **7** were studied (Scheme 2). Electrophilic Rh(III)-species, such as $Rh(tfa)_3$ in the presence of $K_2S_2O_8$ or the redox-couple $RhCl(PPh_3)_3/Cu^{2+}$, have previously been used in oxidative carbonylations of arenes via an S_EAr type C–H activation as the initiating step of the catalytic cycle.[25,26] We therefore assumed that the strong electrophilic nature of rhodium(III)-based catalysts might also be of value to induce the cyclization to the rebeccamycin-type indolocarbazole core starting from the bisindolylmaleimides **6**. In a first attempt, reactions of **6a** with stoichiometric quantities of $Rh(tfa)_3$ in either trifluoroacetic acid or acetic acid at elevated temperatures were studied to give the indolocarbazole **7a**, albeit in a low yield of 15% (Table 2). All further efforts to perform these reactions with catalytic amounts of $Rh(tfa)_3$ and $K_2S_2O_8$ as an additional oxidant led to the decomposition of the starting bisindolylmaleimide **6a**. Therefore, the less electrophilic chlororhodium species $RhCl_3{\cdot}3H_2O$ and a stoichiometric amount of a copper(II) salt as a possible co-oxidant were investigated next.

Gratifyingly, the formation of the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles **7a–f** could be accomplished when the bisindolylmaleimides **6a–g** were heated to 120 °C in the presence of 10 mol% of $RhCl_3{\cdot}3H_2O$ and 1.1 equivalents of $Cu(OAc)_2{\cdot}H_2O$ in DMF. Under these conditions, a full conversion of the starting bisindolylmaleimides **6** was observed and the cyclized products **7a–g** were obtained in reasonable to good yields after column chromatography on silica gel (Table 2).



Scheme 2

Although oxidative cyclizations towards indolocarbazoles have been described with copper(II) salts alone, the use of a catalytic amount of $RhCl_3{\cdot}3H_2O$ was crucial to accomplish an efficient reaction. For example, the oxidative cyclization of **6a** to **7a** was achieved in 73% yield in the presence of 10 mol% $RhCl_3{\cdot}3H_2O$ and 1.1 equivalents of $Cu(OAc)_2{\cdot}H_2O$, whereas omitting the rhodium salt under otherwise identical reaction conditions resulted in the significant lower yield of 47%. Furthermore, the cyclization of **6a** was also induced by a stoichiometric amount of $RhCl_3{\cdot}3H_2O$. However, the lower yield of 25% of the indolocarbazole **7a** thus obtained makes clear that the bime-

Table 2 Oxidative Cyclization of **6a–g** to Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles **7a–g** in the Presence of $RhCl_3·3H_2O$ (10 mol%) and $Cu(OAc)_2·H_2O$ (1.1 equiv)

7	R^1	R^2	R^3	Temp (°C)	t (h)	Yield (%)[a]
7a	CH_3	H	H	120	24	15[b]
7a	CH_3	H	H	120	1.5	73
7a	CH_3	H	H	120	0.5	47[c]
7a	CH_3	H	H	120	24	25[d]
7b	CH_3	F	H	120	3.0	58
7c	CH_3	OCH_3	H	90	3.0	54
7d	CH_2Ph	F	H	120	9.5	73
7e	CH_2Ph	OCH_3	H	80	3.0	74
7f	CH_2Ph	H	H	120	0.5	78
7g	CH_2Ph	H	Cl	120	6.0	44

[a] Yield refers to isolated product after column chromatography.
[b] The reaction was carried out in the presence of $Rh(TFA)_3$ (1.1 equiv) in HOAc.
[c] The reaction was carried out with $Cu(OAc)_2·H_2O$ (1.1 equiv) and without $RhCl_3·3H_2O$.
[d] The reaction was carried out with $RhCl_3·3H_2O$ (1.1 equiv) and without $Cu(OAc)_2·H_2O$.

tallic system of Rh(III) and Cu(II) effects the underlying reaction.

Notably, the reaction protocol still gave satisfactory results with the bisindolylmaleimides **6b**, **d**, or **g** bearing electron withdrawing substituents. Indeed, the electron deficient indolocarbazoles **7b**,**d**, as well as the aglycon of rebeccamycin **7g** were obtained in 58%, 73% and 44% yield, respectively. Milder reaction conditions could be applied with the electron rich bisindolylmaleimides **6c** or **e**. For these compounds temperatures of 80–90 °C were ample for the completion of the reaction and the ring-closure products **7c** and **e** were obtained in yields of 54% and 74%.

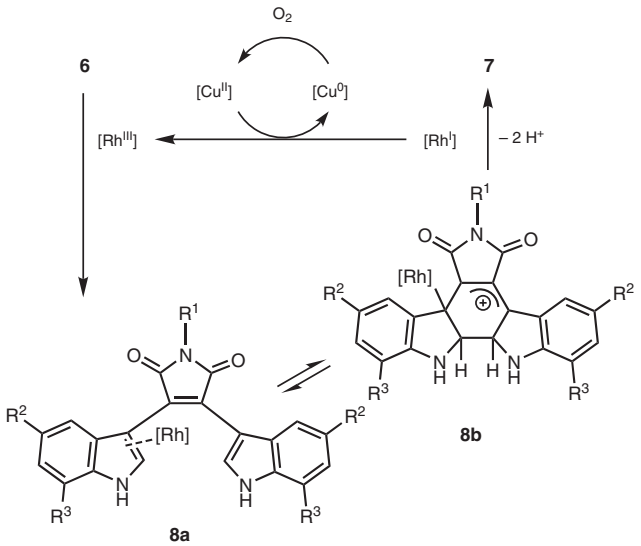
Next, our attention was drawn to promote the oxidative cyclization to the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles **7** by using catalytic amounts of Rh(III) and catalytic amounts of Cu(II) salts in the presence of molecular oxygen as a reliable reoxidant for the formed copper(0) byproducts (Table 3). For this purpose the bisindolylmaleimides **6** were treated with 5 mol% $RhCl_3·3H_2O$ and with 20 mol% $Cu(OAc)_2·H_2O$ in DMF at 90–120 °C while oxygen was introduced into the reaction mixture for the whole reaction period (4–5 hours). The starting bisindolylmaleimides **6a**,**d**,**f** were completely consumed in this truly catalytic protocol as indicated by TLC, and the products **7a**,**d**,**f** were obtained in 53%, 47%, and 75% yield, respectively. However, although the overall yields were slightly lower in the catalytic version, the protocol gained its advantage from the work-up procedure: at the end of the reaction the rhodium and copper salts retained their initial oxidation state and could be easily separated from the organic products by simple extraction.

Table 3 Oxidative Cyclization of **6a**,**d**,**f** to the Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles **7a**,**d**,**f** in the Presence of $RhCl_3·3H_2O$ (5 mol%), $Cu(OAc)_2·H_2O$ (20 mol%), and O_2

7	R^1	R^2	R^3	Temp (°C)	t (h)	Yield (%)[a]
7a	CH_3	H	H	110	4.0	53
7d	CH_2Ph	F	H	120	3.0	47
7f	CH_2Ph	H	H	90	5.0	75

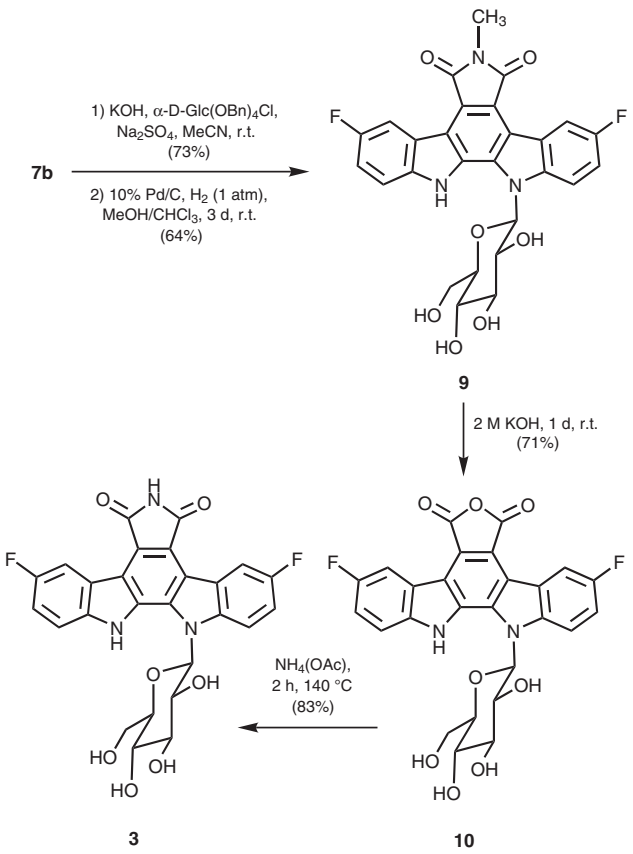
[a] Yield refers to isolated product after column chromatography.

A mechanistic rationale for the underlying oxidative cyclization of **6** to **7** is outlined in Scheme 3. Most likely the cyclization is initiated by an electrophilic Rh(III) species that is capable of inducing a cationic driven ring closure (**8a** to **8b**), and the overall process is based on three coupled redox processes: the Rh(III)–Rh(I) couple and the Cu(II)–Cu(0) redox pair, whilst in the catalytic version the formed copper(0) is reoxidized to copper(II) by molecular oxygen.



Scheme 3

With the aim to complete the synthesis of the potent topoisomerase I active fluoroindolocarbazole **3** the obtained cyclisation product **7b** was *N*-glycosidated with 1-chloro-2,3,4,6-tetra-*O*-benzyl-α-D-glucose in the presence of powdered KOH in anhyd acetonitrile (73% yield), followed by the removal of the benzyl protective groups via hydrogenolysis with catalytic quantities of palladium on charcoal (10% Pd/C, 1 atm H_2, 64% yield) to give the fluoroindolocarbazole glycoside **9** with high stereoselectivity (Scheme 4).



Scheme 4

Hydrolysis of **9** with aqueous potassium hydroxide gave the anhydride **10** in 71% yield. Finally, treatment of the anhydride **9** with neat ammonium acetate in a sealed tube at 140 °C without additional solvents gave the fluoroindolocarbazole **3** in 83% yield and completed the targeted reaction sequence.

In summary, the oxidative cyclization of bisindolylmaleimides **6** to a set of indolocarbazoles **7** was accomplished by the bimetallic catalytic system comprising catalytic quantities of $RhCl_3 \cdot 3H_2O$ and either stoichiometric or catalytic quantities of $Cu(OAc)_2 \cdot H_2O$ and molecular oxygen. Furthermore, this novel catalytic protocol was applied in a six-step synthesis of the potent topoisomerase I active fluoroindolocarbazole **3**.

All reagents used were analytical grades and all solvents were purified by standard methods and distilled prior to use. Reaction mixtures were stirred magnetically and were monitored by TLC using Polygram Sil G/UV254 silica plates from Macherey-Nagel & Co. (Düren, Germany). Flash column chromatography was performed with Merck silica gel 60 (40–60 μm). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC200 and Bruker AMX400 using TMS (δ = 0.00, ^{1}H) and $CDCl_3$ (δ = 77.0, ^{13}C), or DMSO-d_6 (δ = 39.7, ^{13}C) as internal standards. ^{13}C NMR assignments were made on the basis of DEPT experiments. Mass spectra were obtained on a Finnigan MAT 90 spectrometer (EI, 70 eV) and on a Quattro-LCZ from Waters-Micromass (ESI). IR-spectra were recorded as solids in KBr pellets on a Perkin–Elmer FT-IR spectrometer. Mps were recorded on a Büchi apparatus, and are uncorrected. The dibromomaleimides **4a** and **b** were synthesized according to literature procedures.[27] Petroleum ether refers to the fraction with bp 40–60 °C.

Bisindolylmaleimides 6a–g; General Procedure

To a solution of HMDS (4.8 g, 29.7 mmol) in anhyd toluene (20 mL) was added BuLi (29.6 mmol; 18.5 mL of a 1.6 M solution in hexanes) at –78 °C. The reaction mixture was brought to 0 °C and thereafter again cooled to –78 °C. A solution of indole **5a–d** (13.6 mmol) in anhyd toluene (40 mL) was added to the reaction mixture, followed by stirring for 45 min at –78 °C. Thereafter, a solution of **4a** or **b** (6.3 mmol) in anhyd toluene (20 mL) was added and the resulting blue reaction mixture was kept for 20 min at r.t., followed by heating to reflux for 12 h. The reaction mixture was poured into an aq HCl (0.2 M; 150 mL), extracted with EtOAc (3 × 100 mL), and the organic layer was washed with aq $NaHCO_3$ (150 mL), H_2O (150 mL) and brine (150 mL), dried ($MgSO_4$), filtered through a plug of Celite and concentrated. The residue was purified by column chromatography (silica gel; petroleum ether–EtOAc) with the exception of **6c**, where the crude product after aqueous work-up was washed with cold MeOH, and **6f** where the crude product was washed with EtOAc.

2,3-Bis(1*H*-indol-3-yl)-*N*-methylmaleimide (6a)

These data are in agreement with those published.[24b]

Red solid; yield: 75%; mp > 260 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 11.65 (br s, 2 H), 7.74 (d, *J* = 2.8 Hz, 2 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 6.96 (t, *J* = 7.6 Hz, 2 H), 6.80 (d, *J* = 8.0 Hz, 2 H), 6.62 (t, *J* = 7.6 Hz, 2 H), 3.03 (s, 3 H).

2,3-Bis(5-fluoro-1*H*-indol-3-yl)-*N*-methylmaleimide (6b)

Red solid; yield: 63%; mp > 260 °C.

IR (KBr): 3420, 3341, 3136, 1694, 1526, 1444, 1429, 1391, 1150, 1097, 934, 802, 616 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.80 (d, *J* = 2.2 Hz, 2 H), 7.85 (d, *J* = 2.8 Hz, 2 H), 7.38 (dd, *J* = 8.8, 4.7 Hz, 2 H), 6.82 (dt, *J* = 9.1, 2.5 Hz, 2 H), 6.39 (dd, *J* = 10.6, 2.6 Hz, 2 H), 3.03 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.0 (s), 157.1 (d, $^1J_{CF}$ = 231.8 Hz, CF), 133.0 (s), 131.4 (d), 127.2 (s), 126.2 (d, $^3J_{CF}$ = 11.0 Hz, C_q), 113.3 (d, $^3J_{CF}$ = 10.3 Hz, CH), 110.3 (d, $^2J_{CF}$ = 26.4 Hz, CH), 106.1 (s), 105.9 (d, $^2J_{CF}$ = 29.3 Hz, CH), 24.4 (q).

MS (EI, 70 eV): *m*/*z* (%) = 377 (1) [M$^+$], 292 (1), 215 (15), 213 (13), 177 (1), 135 (100), 134 (22), 107 (32), 81 (6), 57 (8), 43 (17), 32 (8).

HRMS (ESI): calcd for $C_{21}H_{13}F_2N_3NO_2$ [M + Na]$^+$: 400.0868; found: 400.0864.

2,3-Bis(5-methoxy-1*H*-indol-3-yl)-*N*-methylmaleimide (6c)

Red solid; yield: 43%; mp > 260 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.55 (br s, 2 H), 7.79 (s, 2 H), 7.25 (d, *J* = 8.8 Hz, 2 H), 6.57 (dd, *J* = 8.9, 2.6 Hz, 2 H), 6.23 (d, *J* = 2.5 Hz, 2 H), 3.10 (s, 6 H), 3.05 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.8 (s), 154.0 (s), 131.6 (s), 130.1 (d), 127.6 (s), 127.1 (s), 113.1 (d), 113.0 (d), 106.8 (s), 103.4 (d), 55.1 (q), 24.8 (q).

IR (KBr): 3448, 1771, 1685, 1636, 1437, 1275, 1261, 764, 750 cm^{-1}.

MS (EI, 70 eV): *m*/*z* (%) = 401 (3) [M$^+$], 356 (15), 341 (4), 255 (35), 213 (6), 183 (1), 149 (4), 145 (34), 130 (2), 116 (6), 91 (6), 89 (8), 77 (3), 73 (4).

HRMS (ESI): calcd for $C_{23}H_{19}N_3O_4$ [M + Na]$^+$: 424.1268; found: 424.1255.

3,4-Bis(5-fluoro-1*H*-indol-3-yl)-*N*-benzylmaleimide (6d)
Red solid; yield: 47%; mp 256–258 °C.

IR (KBr): 3392, 1756, 1690, 1627, 1582, 1527, 1483, 1462, 1432, 1400, 1346, 1298, 1186 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.88 (d, *J* = 2.7 Hz, 2 H), 7.91 (d, *J* = 2.7 Hz, 2 H), 7.36–7.41 (m, 6 H), 7.27–7.32 (m, 1 H), 6.84 (m, 2 H), 6.39 (dd, *J* = 10.5, 2.6 Hz, 2 H), 4.77 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.7 (s), 157.1 (d, $^1J_{CF}$ = 232.9 Hz, CF), 137.6 (s), 133.0 (s), 131.6 (d), 129.0 (d), 127.9 (d), 127.8 (d), 127.0 (s), 126.2 (d, $^3J_{CF}$ = 10.8 Hz, C_q), 113.3 (d, $^3J_{CF}$ = 10.1 Hz, CH), 110.4 (d, $^2J_{CF}$ = 25.7 Hz, CH), 106.0 (d, $^4J_{CF}$ = 4.1 Hz, C_q), 105.9 (d, $^2J_{CF}$ = 24.3 Hz, CH), 41.5 (t).

MS (EI, 70 eV): *m*/*z* (%) = 453 (100) [M^+], 293 (14), 292 (46), 291 (19), 108 (10), 91 (16).

HRMS (EI, 70 eV): calcd for $C_{27}H_{17}F_2N_3O_2$: 453.1289; found: 453.1287.

2,3-Bis(5-methoxy-1*H*-indol-3-yl)-*N*-benzylmaleimide (6e)
Red solid; yield: 40%; mp 184–186 °C.

IR (KBr): 3374, 2935, 1757, 1694, 1624, 1583, 1526, 1400, 1352, 1282, 1248, 1213, 1164, 1117, 1071, 1034 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.62 (d, *J* = 2.3 Hz, 2 H), 7.84 (d, *J* = 2.7 Hz, 2 H), 7.34–7.39 (m, 4 H), 7.28–7.31 (m, 1 H), 7.24 (d, *J* = 8.8 Hz, 2 H), 6.56 (dd, *J* = 8.8, 2.5 Hz, 2 H), 6.21 (d, *J* = 2.5 Hz, 2 H), 4.77 (s, 2 H), 3.08 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.0 (s), 153.6 (s), 137.8 (s), 131.2 (s), 129.9 (d), 129.1 (d), 128.1 (d), 128.0 (d), 127.8 (d), 126.9 (s), 126.8 (s), 112.7 (d), 106.3 (s), 103.0 (d), 54.7 (q), 41.6 (t).

MS (EI, 70 eV): *m*/*z* (%) = 477 (100) [M^+], 343 (5), 330 (9), 317 (6), 316 (26), 315 (6), 301 (7), 300 (6).

HRMS (EI, 70 eV): calcd for $C_{29}H_{23}N_3O_4$: 477.1689; found: 477.1695.

2,3-Bis(1*H*-indol-3-yl)-*N*-benzylmaleimide (6f)
These data are in agreement with those published.[17a,28]

Red solid; yield: 50%; mp > 260 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.68 (br s, 2 H), 7.77 (d, *J* = 2.2 Hz, 2 H), 7.31–7.38 (m, 6 H), 7.24–7.29 (m, 1 H), 6.95 (t, *J* = 7.5 Hz, 2 H), 6.78 (d, *J* = 8.3 Hz, 2 H), 6.61 (t, *J* = 7.6 Hz, 2 H), 4.75 (s, 2 H).

2,3-Bis(7-chloro-1*H*-indol-3-yl)-*N*-benzylmaleimide (6g)
Red solid; yield: 54%; mp > 260 °C.

IR (KBr): 3330, 1759, 1696, 1619, 1564, 1532, 1432, 1398, 1340, 1296, 1205, 1179, 1144 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.13 (d, *J* = 2.2 Hz, 2 H), 7.83 (d, *J* = 2.9 Hz, 2 H), 7.26–7.35 (m, 5 H), 7.06 (d, *J* = 7.3 Hz, 2 H), 6.72 (d, *J* = 8.1 Hz, 2 H), 6.64 (t, *J* = 7.9 Hz, 2 H), 4.76 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.5 (s), 137.6 (s), 133.3 (s), 130.8 (d), 129.1 (d), 128.0 (d), 127.9 (d), 127.6 (s), 127.6 (s), 121.9 (d), 121.0 (d), 120.2 (d), 116.6 (s), 106.9 (s), 41.7 (t).

MS (EI, 70 eV): *m*/*z* (%) = 487 (92) [M^+], 418 (4), 398 (4), 390 (6), 336 (4), 326 (6).

HRMS (ESI): calcd for $C_{27}H_{17}Cl_2N_3O_2$ [M + Na]$^+$: 508.0590: found: 508.0592.

Indolocarbazoles 7a–f; General Procedure Using Rh(III) as Catalyst and Cu(II) as Re-oxidant
A solution of the bisindolylmaleimide **6a–f** (0.12 mmol), $Cu(OAc)_2{\cdot}H_2O$ (34 mg, 0.13 mmol), $RhCl_3{\cdot}3H_2O$ (4 mg, 0.005 mmol, 10 mol%) in DMF (10 mL) was heated to 120 °C (to 80–90 °C in the case of **7c** and **e**) in a Schlenk tube with a screw cap until TLC showed complete consumption of the bisindolylmaleimide. Thereafter, the reaction mixture was poured into aq HCl (0.2 M; 20 mL), and was extracted with EtOAc (3 × 25 mL). The organic phase was washed with aq $NaHCO_3$ (25 mL), H_2O (25 mL) and brine (25 mL), dried ($MgSO_4$), filtered through Celite and concentrated. The residue was purified by column chromatography (silica gel; petroleum ether–EtOAc).

12,13-Dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6-methyl-5,7(6*H*)-dione (7a)
These data are in agreement with those published.[14d]

Yellow solid; yield: 73%; mp > 260 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.70 (s, 2 H), 9.00 (d, *J* = 7.9 Hz, 2 H), 7.81 (d, *J* = 8.1 Hz, 2 H), 7.56 (t, *J* = 7.1 Hz, 2 H), 7.36 (t, *J* = 7.1 Hz, 2 H), 3.18 (s, 3 H).

3,9-Difluoro-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6-methyl-5,7(6*H*)-dione (7b)
Yellow solid; yield: 58%; mp > 260 °C.

IR (KBr): 3462, 1700, 1653, 1540, 1476, 1380, 1275, 1262, 763 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.73 (br s, 2 H), 8.56 (dd, *J* = 9.7, 2.7 Hz, 2 H), 7.78 (dd, *J* = 8.9, 4.6 Hz, 2 H), 7.39 (m, 2 H), 3.06 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.1 (s), 157.3 (d, $^1J_{CF}$ = 234.0 Hz, CF), 137.2 (s), 130.3 (s), 122.1 (d, $^3J_{CF}$ = 10.9 Hz, C_q), 119.3 (s), 115.6 (d, $^3J_{CF}$ = 3.8 Hz, C_q), 115.1 (d, $^2J_{CF}$ = 25.3 Hz, CH), 113.7 (d, $^4J_{CF}$ = 9.0 Hz, C_q), 109.5 (d, $^2J_{CF}$ = 25.4 Hz, CH), 23.8 (q).

MS (EI, 70 eV): *m*/*z* (%) = 375 (6) [M^+], 261 (1), 228 (5), 187 (3), 172 (5), 149 (8), 139 (13), 116 (5), 106 (41), 91 (26), 84 (100), 79 (61), 77 (28).

HRMS (ESI): calcd for $C_{21}H_{11}F_2N_3NO_2$ [M + Na]$^+$: 398.0712; found: 398.0712.

3,9-Dimethoxy-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6-methyl-5,7(6*H*)-dione (7c)
Yellow solid; yield: 54%; mp > 260 °C.

IR (KBr): 3463, 1844, 1684, 1653, 1559, 1481, 1274, 1261, 746 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.50 (br s, 2 H), 8.54 (d, *J* = 2.6 Hz, 2 H), 7.69 (d, *J* = 8.8 Hz, 2 H), 7.18 (dd, *J* = 8.8, 2.6 Hz, 2 H), 3.91 (s, 6 H), 3.16 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.7 (s), 154.4 (s), 137.7 (s), 129.1 (s), 121.6 (s), 118.2 (s), 115.8 (d), 115.0 (s), 112.4 (d), 105.7 (d), 55.0 (q), 23.1 (q).

MS (ESI): *m*/*z* (%) = 422 [M + Na]$^+$.

HRMS (ESI): calcd for $C_{23}H_{17}N_3O_4$ [M + Na]$^+$: 422.1111; found: 422.1118.

3,9-Difluoro-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6-benzyl-5,7(6*H*)-dione (7d)
Yellow solid; yield: 73%; mp > 260 °C.

IR (KBr): 3408, 2924, 2854, 1748, 1698, 1628, 1584, 1483, 1383 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.77 (br s, 2 H), 8.55 (dd, *J* = 9.7, 2.6 Hz, 2 H), 7.78 (dd, *J* = 8.9, 4.5 Hz, 2 H), 7.32–7.45 (m, 6 H), 7.25–7.31 (m, 1 H), 4.80 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.8 (s), 157.4 (d, $^1J_{CF}$ = 234.3 Hz, CF), 137.8 (s), 137.2 (s), 130.4 (s), 129.1 (d), 127.9 (d), 127.8 (d), 122.1 (d, $^3J_{CF}$ = 11.5 Hz, C_q), 119.0 (s), 115.8 (d,

$^4J_{CF}$ = 4.1 Hz, C_q), 115.3 (d, $^2J_{CF}$ = 25.7 Hz, CH), 113.8 (d, $^3J_{CF}$ = 8.8 Hz, CH), 109.3 (d, $^2J_{CF}$ = 25.0 Hz, CH), 41.1 (t).

MS (ESI): *m*/*z* (%) = 474 $[M + Na]^+$.

HRMS (ESI): calcd for $C_{27}H_{15}F_2N_3O_2$ $[M + Na]^+$: 474.0125; found: 474.0128.

3,9-Dimethoxy-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6-benzyl-5,7(6*H*)-dione (7e)

Orange solid; yield: 74%; mp > 260 °C.

IR (KBr): 3416, 3260, 2931, 1747, 1693, 1658, 1624, 1581, 1484, 1403, 1382 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.60 (br s, 2 H), 8.55 (d, *J* = 2.6 Hz, 2 H), 7.74 (d, *J* = 8.7 Hz, 2 H), 7.25–7.46 (m, 5 H), 7.21 (dd, *J* = 8.8, 2.6 Hz, 2 H), 4.93 (s, 2 H), 3.92 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.2 (s), 154.4 (s), 138.1 (s), 135.6 (s), 130.1 (s), 129.1 (d), 127.7 (d), 127.7 (d), 122.4 (s), 118.7 (s), 116.9 (d), 116.0 (s), 113.3 (d), 106.5 (d), 56.0 (q), 41.1 (t).

MS (EI, 70 eV): *m*/*z* (%) = 475 (100) $[M^+]$, 460 (6), 453 (11), 432 (3), 415 (4), 292 (6), 237 (12), 92 (3), 73 (6).

HRMS (EI, 70 eV): calcd for $C_{29}H_{21}N_3O_4$: 475.1532; found: 475.1539.

12,13-Dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6-benzyl-5,7(6*H*)-dione (7f)

These data are in agreement with those published.[17a,28]

Yellow solid; yield: 78%; mp > 260 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.62 (br s, 2 H), 8.93 (d, *J* = 8.0 Hz, 2 H), 7.74 (d, *J* = 8.1 Hz, 2 H), 7.52 (dt, *J* = 7.1, 1.3 Hz, 2 H), 7.38–7.41 (m, 2 H), 7.29–7.36 (m, 4 H), 7.23–7.27 (m, 1 H), 4.78 (s, 2 H).

1,11-Dichloro-12,13-dihydro-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6-benzyl-5,7(6*H*)-dione (7g)

Yellow solid; yield: 44%; mp > 260 °C.

IR (KBr): 3422, 2926, 2761, 1694, 1598, 1492, 1455, 1405, 1388, 1357 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.19 (br s, 2 H), 8.92 (d, *J* = 7.8 Hz, 2 H), 7.53–7.51 (m, 2 H), 7.41 (m, 2 H), 7.32–7.24 (m, 3 H), 7.21 (t, *J* = 7.8 Hz, 2 H), 4.91 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7 (s), 137.5 (s), 137.4 (s), 129.2 (s), 128.6 (d), 128.5 (d), 127.5 (s), 125.9 (d), 123.9 (d), 123.7 (d), 121.1 (d), 119.9 (s), 116.7 (s), 116.0 (s), 41.4 (t).

HRMS (ESI): calcd for $C_{27}H_{15}O_2N_3Cl_2$ $[M + Na^+]$: 506.0434; found: 506.0429.

Indolocarbazoles 7a,d,f; General Procedure Using Rh(III) as Catalyst, Cu(II) as Co-catalyst and Oxygen as Re-oxidant

A 100 mL 3-necked flask was equipped with a condenser and was charged with bisindolylmaleimide **6a**, **d** or **f** (0.15 mmol), $RhCl_3 \cdot 3H_2O$ (2 mg, 0.008 mmol, 5 mol%) $Cu(OAc)_2 \cdot H_2O$ (16 mg, 20 mol%) and DMF (40 mL). The resulting suspension was heated to 90–110 °C while oxygen was sparged into the reaction mixture. The reaction was performed until TLC indicated the complete consumption of the bisindolylmaleimide **6** (4 h). Thereafter, the reaction mixture was poured into aq HCl (0.2 M; 40 mL) and extracted with EtOAc (3 × 30 mL). The organic phase was washed with aq $NaHCO_3$ (30 mL), H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$), filtrated through a plug of Celite and concentrated in vacuo. The residue was purified by column chromatography (silica gel; petroleum ether–EtOAc) to give the indolocarbazoles **7a**, **7d**, and **7f** in 53%, 47%, and 75% yield, respectively.

3,9-Difluoro-12,13-dihydro-13-(β-D-glucopyranosyl)-5*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6-methyl-5,7(6*H*)-dione (9)

Indolocarbazole **7b** (451 mg, 1.20 mmol) was added to a suspension of powdered KOH (228 mg, 4.07 mmol) and Na_2SO_4 (1.29 g, 9.06 mmol) in anhyd MeCN (10 mL) under a nitrogen atmosphere. The reaction mixture was allowed to stir for 1 h at r.t. Then a solution of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (1.37 g, 2.40 mmol) in anhyd MeCN (20 mL) was added. The reaction mixture was stirred at r.t. for 18 h, poured into aq (50 mL), and then extracted with EtOAc (3 × 40 mL). The organic layer was washed with H_2O (40 mL), aq $NaHCO_3$ (40 mL), H_2O (40 mL) and brine (40 mL), dried (Na_2SO_4), filtered through a plug of Celite and concentrated. Purification by column chromatography (silica gel; petroleum ether–EtOAc, 3:1) afforded the benzyl protected **9**.

Yield: 784 mg (73%); yellow solid.

Then palladium on charcoal (200 mg; 10% Pd/C) was added to a solution of the benzyl protected **9** (600 mg, 0.67 mmol) in $CHCl_3$–MeOH (1:1; 20 mL). The mixture was stirred for 3 d in a hydrogen atmosphere. Then the catalyst was filtered off, washed with MeOH (60 mL) and the solvent was removed in vacuo. Purification by column chromatography (silica gel; EtOAc–MeOH, 50:1) afforded the glycoside **9**.

Yellow solid; yield: 233 mg (64%); mp 234–236 °C.

IR (KBr): 3329, 2925, 1745, 1690, 1624, 1586, 1482, 1380, 1326, 1288, 1249, 1188 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.76 (s, 1 H), 8.84 (dd, *J* = 9.5, 2.5 Hz, 1 H), 8.77 (dd, *J* = 9.5, *J* = 2.6, 1 H), 8.03 (dd, *J* = 9.5, 3.8 Hz, 1 H), 7.69 (dd, *J* = 8.9, 4.5 Hz, 1 H), 7.49 (m, 2 H), 6.30 (d, *J* = 8.8 Hz, 1 H), 6.10 (t, *J* = 3.9 Hz, 1 H), 5.42 (d, *J* = 4.6 Hz, 1 H), 5.16 (d, *J* = 5.5 Hz, 1 H), 4.95 (d, *J* = 5.5 Hz, 1 H), 3.95–4.11 (m, 3 H), 3.82–3.86 (m, 1 H), 3.56–3.62 (m, 1 H), 3.46–3.52 (m, 1 H), 3.19 (s, 3 H).

^{13}C (100 MHz, DMSO-d_6): δ = 170.1 (s), 170.0 (s), 157.5 (d, $^2J_{CF}$ = 234.3 Hz), 157.5 (d, $^2J_{CF}$ = 234.3 Hz, CH), 139.2 (s), 137.8 (s), 131.0 (s), 129.5 (s), 122.1 (d, $^3J_{CF}$ = 11.5 Hz), 121.7 (d, $^3J_{CF}$ = 10.8 Hz), 120.8 (s), 119.1 (s), 118.5 (d, $^4J_{CF}$ = 4.1 Hz), 117.1 (d, $^4J_{CF}$ = 4.7 Hz), 115.7 (d, $^2J_{CF}$ = 25.0 Hz), 115.3 (d, $^2J_{CF}$ = 25.7 Hz), 113.8 (d, $^3J_{CF}$ = 8.8 Hz), 113.8 (d, $^3J_{CF}$ = 8.8 Hz), 109.6 (d, $^2J_{CF}$ = 25.0 Hz), 109.6 (d, $^2J_{CF}$ = 25.7 Hz), 85.2 (d), 79.1 (d), 77.0 (d), 73.7 (d), 68.0 (d), 58.8 (t), 24.2 (q).

MS (ESI): *m*/*z* (%) = 560 $[M + Na]^+$.

HRMS (ESI): calcd for $C_{27}H_{21}F_2N_3O_7$ $[M + Na]^+$: 560.1240; found: 560.1248.

3,9-Difluoro-11,12-dihydro-12-(β-D-glucopyranosyl)indolo[2,3-*a*]carbazole-5,6-dicarboxylic Anhydride (10)

The glycoside **9** (193 mg, 0.36 mmol) was dissolved in aq KOH (2 M; 20 mL) at r.t. and the resulting solution was stirred overnight. The solution was acidified with aq HCl (2 M) and extracted with EtOAc–MEK (30 mL; 1:1) and the organic layer was washed with brine (30 mL), dried ($MgSO_4$) and concentrated. The residual solid was washed with $CHCl_3$ (40 mL) to obtain the anhydride **10** (130 mg).

Orange solid; yield: 71%; mp > 260 °C.

IR (KBr): 3443, 3312, 2916, 1820, 1749, 1620, 1587, 1486, 1389, 1347, 1321, 1288 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.00 (br s, 1 H), 8.61 (dd, *J* = 9.5, 2.6 Hz, 1 H), 8.55 (dd, *J* = 9.5, 2.6 Hz, 1 H), 8.09 (dd, *J* = 9.2, 4.4 Hz, 1 H), 7.75 (dd, *J* = 8.8 Hz, *J* = 4.6 Hz, 1 H), 7.52–7.58 (m, 2 H), 6.37 (d, *J* = 8.8 Hz, 1 H), 6.18 (br s, 1 H), 5.45 (br s, 1 H), 5.18 (d, *J* = 4.8 Hz, 1 H), 4.99 (d, *J* = 5.3 Hz, 1 H), 4.11 (d, *J* = 11.0 Hz, 1 H), 3.96–4.02 (m, 2 H), 3.87 (d, *J* = 10.2 Hz, 1 H), 3.56–3.64 (m, 1 H), 3.40–3.48 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.0 (s), 164.9 (s), 157.7 (d, $^1J_{CF}$ = 234.8 Hz), 139.1 (s), 139.1 (s), 137.7 (s), 131.8 (s), 130.4 (s), 121.7 (d, $^3J_{CF}$ = 11.5 Hz), 121.2 (d, $^3J_{CF}$ = 10.7 Hz), 119.8 (s), 118.4 (d, $^4J_{CF}$ = 3.8 Hz), 118.1 (s), 117.0 (d, $^4J_{CF}$ = 4.6 Hz), 116.3 (d, $^2J_{CF}$ = 25.2 Hz), 115.9 (d, $^2J_{CF}$ = 26.0 Hz), 114.4 (d, $^3J_{CF}$ = 9.2 Hz), 114.4 (d, $^3J_{CF}$ = 9.2 Hz), 108.8 (d, $^2J_{CF}$ = 25.2 Hz), 108.7 (d, $^2J_{CF}$ = 25.2 Hz), 85.2 (d), 79.2 (d), 76.9 (d), 73.9 (d), 68.0 (d), 58.7 (t).

MS (ESI): *m*/*z* (%) = 547 [M + Na]$^+$.

HRMS (ESI): calcd for $C_{26}H_{18}F_2N_2NaO_8$ [M + Na]$^+$: 547.0929; found: 547.0937.

3,9-Difluoro-6,12,13-trihydro-13-(β-D-glucopyranosyl)-5*H*-indolo[2,3-*a*]pyrrolo-[3,4-*c*]carbazole-5,7(6*H*)-dione (3)

In a Schlenk tube with screw cap, the anhydride compound **10** (65 mg, 0.12 mmol) was heated with ammonium acetate (1 g, 13.0 mmol) for 2 h at 140 °C. The mixture was cooled and extracted with EtOAc–MEK (40 mL; 1:1) after the addition of H_2O (20 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and concentrated. Purification by column chromatography (silica gel; EtOAc–MeOH, 50:1) afforded the fluoroindolocarbazole **3**.

These data are in agreement with those published.[9]

Yellow solid; yield: 51 mg (83%); mp 257–259 °C.

IR (KBr): 3330, 2924, 2854, 1746, 1712, 1621, 1586, 1482, 1621, 1586, 1482, 1390, 1325, 1287 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.74 (s, 1 H), 11.21 (s, 1 H), 8.84 (dd, *J* = 9.6, 2.5 Hz, 1 H), 8.76 (dd, *J* = 9.6, 2.5 Hz, 1 H), 8.00 (dd, *J* = 9.4, 4.3 Hz, 1 H), 7.67 (dd, *J* = 8.8, 4.5 Hz, 1 H), 7.43–7.48 (m, 2 H), 6.28 (d, *J* = 9.0 Hz, 1 H), 6.07 (t, *J* = 3.7 Hz, 1 H), 5.39 (d, *J* = 4.3 Hz, 1 H), 5.14 (d, *J* = 5.5 Hz, 1 H), 4.93 (d, *J* = 5.5 Hz, 1 H), 4.06–4.10 (m, 1 H), 3.94–4.01 (m, 2 H), 3.81–3.83 (m, 1 H), 3.55–3.60 (m, 1 H), 3.45–3.51 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.5 (s), 171.4 (s), 157.5 (d, $^1J_{CF}$ = 234.0 Hz), 157.5 (d, $^1J_{CF}$ = 234.0 Hz), 139.1 (s), 137.7 (s), 131.1 (s), 129.6 (s), 122.2 (d, $^3J_{CF}$ = 10.7 Hz), 121.8 (d, $^3J_{CF}$ = 11.5 Hz), 121.8 (s), 120.1 (s), 118.4 (d, $^4J_{CF}$ = 3.8 Hz), 117.1 (d, $^4J_{CF}$ = 4.6 Hz), 115.6 (d, $^2J_{CF}$ = 25.2 Hz), 115.2 (d, $^2J_{CF}$ = 25.2 Hz) 113.8 (d, $^3J_{CF}$ = 8.4 Hz), 113.8 (d, $^3J_{CF}$ = 8.4 Hz), 109.7 (d, $^2J_{CF}$ = 25.2 Hz), 109.7 (d, $^2J_{CF}$ = 25.2 Hz), 85.2 (d), 79.1 (d), 77.0 (d), 73.7 (d), 68.0 (d), 58.8 (t).

HRMS (ESI): calcd for $C_{26}H_{19}F_2N_3O_7$ [M + Na$^+$]: 546.1083; found: 546.1084.

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