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N-Iodosuccinimide-Mediated Oxidative Coupling of Indoles and Phenols: A Synthetic Study toward the Benzofuroindoline Moiety of Bipleiophylline

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Dedicated to Prof. Marco A. Ciufolini

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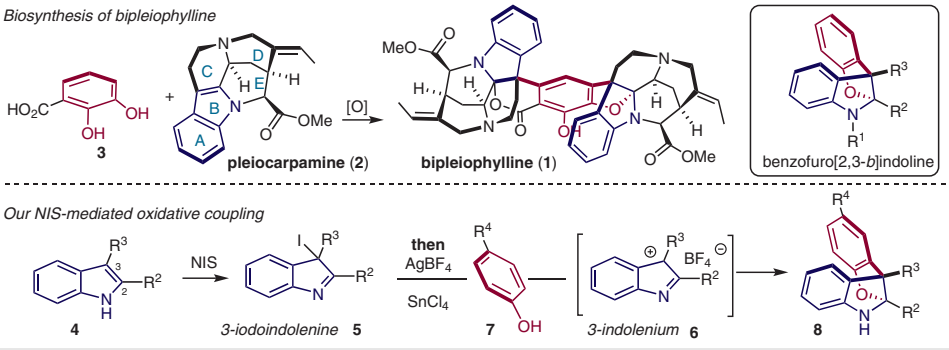
Abstract We report our efforts to apply an *N*-iodosuccinimide-mediated dearomative oxidative coupling of indoles and phenols to benzofuroindoline-containing polycyclic scaffolds related to the natural product bipleiophylline. Suitable conditions from N-substituted indoles are developed and applied to the synthesis of a hexacyclic model starting from a tetracyclic ABCE precursor.

Key words oxidative coupling, indole, dearomatization, phenol, benzofuroindoline, bipleiophylline

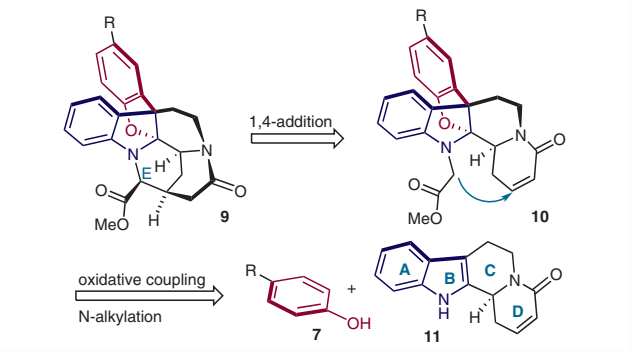
For the last 6 years, our group has been interested in the development of bioinspired synthetic methods to access benzofuroindoline frameworks which are found in several natural products.[1–3] Among them, bipleiophylline (**1**) is of special interest due to its highly complex structure.[4] A double dearomative oxidative coupling between pleiocarpamine (**2**) and 2,3-dihydroxybenzoic acid (**3**) is thought to be the biogenetic pathway toward this natural product (Scheme 1). In 2014, we reported an original method to achieve the bioinspired dearomative assembly of 2,3-disubstituted-NH-indoles **4** and phenols **7** into benzofuro[2,3-*b*]indolines **8** (Scheme 1).[3a,5] The process relied on the oxidation of the NH-indole partner with *N*-iodosuccinimide (NIS) to give the 3-iodoindolenine **5**.[6] The latter can then be converted into a transient 3-indolenium ion **6** with a silver salt and an additive such as tin(IV) chloride or sodium hydroxide to allow the addition of the nucleophilic phenol to this electrophilic intermediate.[7] We now disclose our efforts to implement this method to the synthesis of a benzofuroindoline-containing heptacyclic compound related to bipleiophylline,[8,9] and the outcome that drove us to develop a new oxidative coupling method from indoles toward bipleiophylline.

The biomimetic synthesis of bipleiophylline requires having pleiocarpamine in hand. The synthesis of the pentacyclic framework of this alkaloid is a challenging task.[10] In particular, installation of the E ring from a tetracyclic ABCD precursor is more difficult than expected because of the highly strained nature of pleiocarpamine. Therefore, we en-



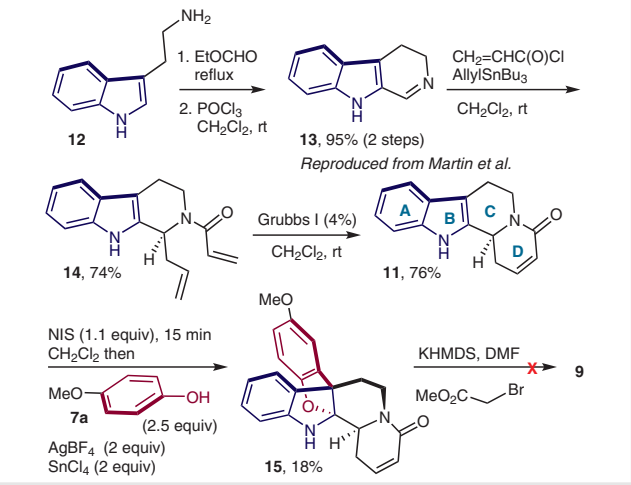
Scheme 1 Bioinspired NIS-mediated oxidative coupling between 2,3-disubstituted-NH-indoles and phenols for the synthesis of benzofuro[2,3-*b*]indolines related to bipleiophylline

visioned closing the E ring after the formation of the benzofuroindoline motif in order to give more flexibility to the precursor **10** of the heptacyclic target **9**, and therefore favor the final cyclization (Scheme 2). To achieve this objective, an intramolecular Michael addition of an ester attached to the indoline nitrogen onto an α,β-unsaturated lactam embedded in the D ring of **10** was planned. Our retrosynthesis required the oxidative coupling between the phenol **7** and the tetracyclic ABCD precursor **11** containing the required unsaturation on lactam D. We previously reported a similar oxidative coupling on an ABCD precursor lacking the double bond on the D ring.[3a]



Scheme 2 Retrosynthesis of the heptacyclic benzofuroindoline part of bipleiophylline yielding a tetracyclic ABCD precursor

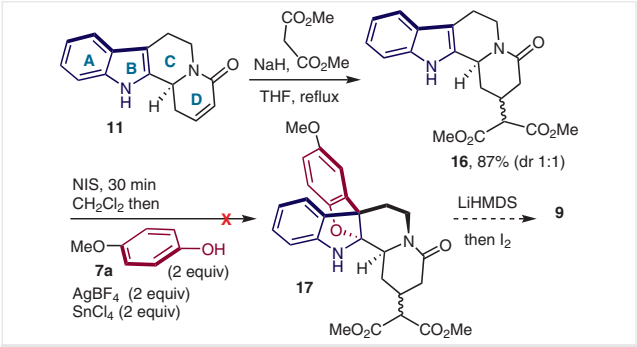
Compound **11** was obtained in only 4 steps from tryptamine (**12**), according to Martin and co-workers (Scheme 3).[11] A Bischler–Napieralski cyclization furnished dihydro-β-carboline **13**. *N*-Acylation and allylation of the latter was followed by ring-closing metathesis with Grubbs I catalyst to deliver **11**.



Scheme 3 NIS-mediated synthesis of a benzofuroindoline-containing hexacyclic framework from an NH-containing ABCD precursor

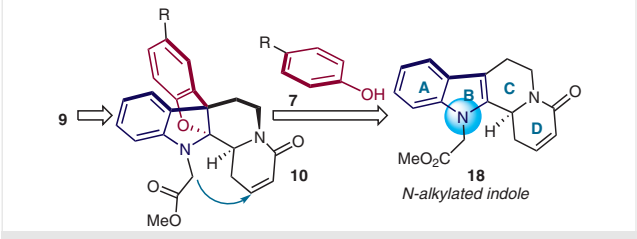
The key oxidative coupling with *p*-methoxyphenol (**7a**) was then deployed to deliver the desired benzofuroindoline **15** in 18% yield, and the formation of the E ring could then be studied. Unfortunately, despite our efforts, we were unable to alkylate the indole nitrogen with methyl bromoacetate, which would have left us with a precursor requiring a final intramolecular Michael addition to form the E ring. Deprotonation of the NH may have resulted in opening of the benzofuroindoline and formation of an indolenine appended by a phenolate.

As an alternative, we envisioned completing the heptacyclic structure **9** via a nitrogen-malonate oxidative coupling as the last step, which was inspired by Ma and Zhu (Scheme 4).[12] Therefore, as described by Martin, the intermolecular 1,4-addition of dimethyl malonate onto α,β-unsaturated lactam **11** led to compound **16** as a mixture of diastereoisomers.[11] Unfortunately, our key NIS-mediated oxidative coupling with *p*-methoxyphenol (**7a**) did not succeed. Evidently, the malonate part of the molecule is interfering with the components of the reaction, presumably due to its nucleophilicity or chelating ability.



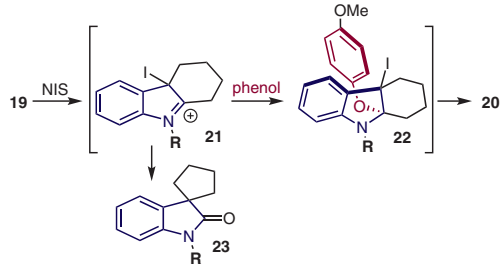
Scheme 4 An attempt to form the benzofuroindoline moiety after the 1,4-addition

To overcome this issue, the third variation of our general strategy was applied to again invert the order of the events (Scheme 5). The NIS-mediated formation of the benzofuroindoline core would be performed on *N*-acetate indole substrate **18**, which would be followed by an intramolecular Michael addition to close the E ring.



Scheme 5 Retrosynthesis with formation of the benzofuroindoline moiety from an *N*-acetate ABCD precursor

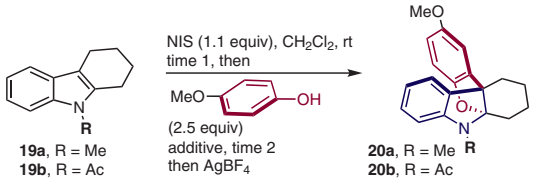
The oxidative coupling of phenol **7** with **18** involves an N-substituted indole, while our method has been developed with NH-indoles. This fact encouraged us to study the NIS-mediated formation of benzofuroindolines with *N*-methyl-tetrahydrocarbazole **19a** as a model substrate (Table 1). Our initial procedure from NH-indoles involves first treating the N-H indole **4** with NIS to form the 3-iodoindolenine intermediate **5**, before adding the other components of the reaction. When we applied this procedure to *N*-methyl-tetrahydrocarbazole **19a**, and added phenol **7a**, $AgBF_4$ and the additive 10 minutes after NIS, poor yields of benzofuroindoline **20a** were obtained with tin(IV) chloride (Table 1, entry 1) or sodium hydroxide (Table 1, entry 2). An improved but still modest yield of 25% was obtained without any additive (Table 1, entry 3). Without $AgBF_4$ nor any additive, **20a** was obtained in 22% yield (Table 1, entry 4). In most cases, we observed the formation of 3,3-spirooxindole **23** (Scheme 6), which results from a 1,2-shift of the substituent at the C2 position to the C3 position of 3-iodoindolenium intermediate **21**. We reasoned that 3-iodoindolenium **21** is more reactive than the corresponding 3-iodoindolenine **5**. Therefore, we decided to add phenol **7a** at the same time as NIS, in order to immediately intercept the iminium function of **21** with the hydroxy group of **7a** and form intermediate **22**.[13] Indeed, a 52% yield of benzofuroindoline **20a** was obtained by adding NIS, **7a** and $AgBF_4$ at the same time (Table 1, entry 5). Reduced yields were obtained without $AgBF_4$ (Table 1, entries 6 and 7). Adding $AgBF_4$ 5 minutes after NIS and **7a** did not impact on the yield since adduct **22** is probably quite stable (Table 1, entries 8 and 9). With the optimum conditions, *N*-acyl-tetrahydrocarbazole **19b** was converted into benzofuroindoline **20b** in 36% yield (Table 1, entry 10). The reduced yield of **20b**, compared to **20a**, can be explained by the fact that **19b** is less nucleophilic than **19a** and therefore less reactive toward NIS.



Scheme 6 Trapping of the 3-iodoindolenium ion **21** with the phenol

The stage was then set to evaluate these conditions with 2-(*N*-indolyl) acetate **18**. Therefore, the indole nitrogen of **11** was first alkylated with methyl bromoacetate in the presence of KHMDS. Unfortunately, the subsequent oxidative coupling with *p*-methoxyphenol (**7a**) failed to provide benzofuroindoline **10** (Scheme 7).

Table 1 Oxidative Coupling with N-Substituted Indoles

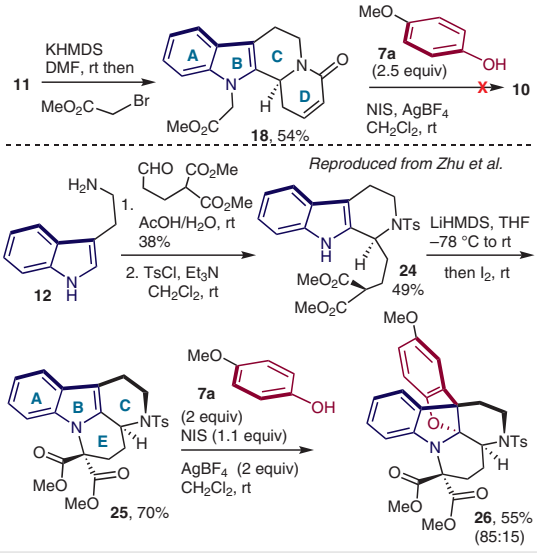


Entry	R	Time 1 (min)	Additive (equiv)	Time 2 (min)	$AgBF_4$ (equiv)	Yield[a]
1	Me	10	$SnCl_4$ (5.0)	0	2.0	15%
2	Me	10	NaOH (5.0)	0	2.0	0%
3	Me	10	none	0	1.1	25%
4	Me	10	none	–	0	22%
5	Me	0	none	0	1.1	52%
6	Me	0	none	–	0	28%
7[b]	Me	0	none	–	0	45%
8	Me	0	none	5	1.1	52%
9[c]	Me	0	none	5	1.6	55%
10	Ac	0	none	5	2.0	36%

[a] Yield of isolated product.
[b] Reaction at reflux temperature.
[c] Reaction with NIS (1.6 equiv).

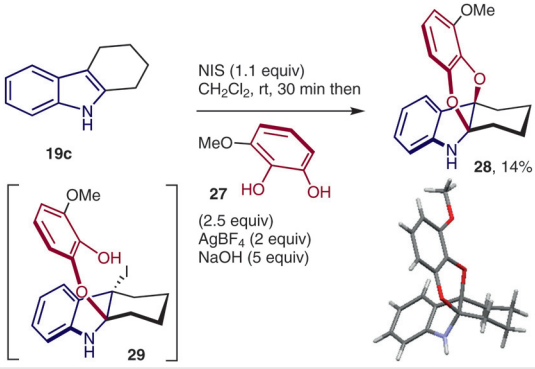
However, we were still eager to obtain a benzofuroindoline from a complex N-substituted indole amenable to construction of the heptacyclic framework **9**. Instead of a functionalized ABCD compound such as **11**, **16** or **18**, we wondered if an ABCE tetracycle would be a suitable precursor to construct the benzofuroindoline core, before forging the D ring (Scheme 7). We selected α-(*N*-indolyl)diester **25**, which was described by Zhu and co-workers through N–C bond formation via an intramolecular oxidative coupling of the diester/*N*-indolyl dianion of β-tetrahydrocarboline **24** with I_2.[12a] In addition, **25** lakes enolizable protons which could be detrimental to the oxidative coupling, such as in **18**. Eventually, treatment of **25** with phenol **7a** and NIS, followed by $AgBF_4$, produced hexacyclic benzofuroindoline **26** in a mixture with a product, which may be a diastereoisomer (85:15 ratio), in a very useful yield of 55%.[14]

Of course, various strategies to build the missing D ring from benzofuroindoline **26** could be designed. However, keeping in mind that the benzofuroindoline part of bipleiophylline is built from a catechol, we needed to evaluate our NIS-mediated oxidative coupling with a 1,2-diphenol. However, treatment of the NH-tetrahydrocarbazole **19c** with NIS followed by 3-methoxycatechol (**27**), $AgBF_4$ and NaOH did not lead to the expected benzofuroindoline (Scheme 8). Instead, we isolated benzodioxinoindoline **28** in a modest yield, the structure of which was ascertained by X-ray crystal structure analysis.[2a,b,15,16] It is thought that the imine function of the 3-iodoindolenine is first intercepted by one



Scheme 7 NIS-mediated synthesis of a benzofuroindoline-containing hexacyclic framework from an N-substituted ABCE precursor

of the hydroxy groups of **27** leading to intermediate **29**, which then cyclized by attack of the second hydroxy onto the iodine.[17] The reaction of *N*-methyl-tetrahydrocarbazole **19a** with catechol **27** only led to traces of the corresponding benzodioxinoindoline.



Scheme 8 NIS-mediated oxidative coupling with a catechol

The fact that the application of this NIS-mediated synthesis of benzofuroindolines is not applicable to catechol derivatives led us to develop, in collaboration with the Evanno and Poupon group, a new biomimetic strategy via the oxidation of catechols into their corresponding *ortho*-quinones, which recently led to the hemisynthesis of bipleiophylline.[2a,b]

In conclusion, different strategies to access a heptacyclic benzofuroindoline model of bipleiophylline have been investigated. The key feature of our retrosynthetic logic was to apply a dearomative NIS-mediated oxidative coupling between indoles and phenols on a tetracyclic substrate before constructing the remaining ring. Our previously reported conditions for the dearomative coupling were successfully applied to a NH indole ABCD precursor. New conditions were developed for N-substituted indoles and implemented in the synthesis of a hexacyclic target from an ABCE compound.

All reactions were carried out under an atmosphere of air or argon. Dichloromethane was distilled under argon over CaH_2. THF was distilled under argon over Na with benzophenone. Unless otherwise noted, all reagent-grade chemicals and other solvents were obtained from commercial suppliers and were used as received. Reactions were monitored by analytical thin-layer chromatography (TLC) with Merck silica gel 60 F254 on aluminum sheets, and samples were visualized under UV (254 nm) and/or by using $KMnO_4$ solution followed by heating. Flash chromatography purifications were performed on silica gel [Chromagel Si60ACC (70–200 μm)]. Preparative thin-layer chromatography purifications were performed using Merck silica gel F254 on glass plates and analyzed by UV light. Infrared spectra were recorded as thin films on NaCl plates using a Perkin Elmer Spectrum one FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC250 (250 MHz, 62.5 MHz), Bruker DRX300 (300 MHz, 75 MHz) and Bruker AM360 (360 MHz, 90 MHz) instruments; chemical shifts (δ) are given in parts per million with respect to the residual protonated solvent (δ = 7.24 and 77.1 ppm, $CDCl_3$), which served as an internal standard. High-resolution mass spectra (HRMS) were recorded with a Bruker Daltonics MicrOTOF-Q instrument using the electrospray ionization (ESI) method. Tetracyclic ABCD indoles **11** and **16** were prepared according to Martin and co-workers,[11] while tetracyclic ABCE indole **25** was synthesized according to Zhu and co-workers.[12a]

Benzofuroindoline 15

To a solution of ABCD tetracyclic indole **11** (29.0 mg, 0.122 mmol) in CH_2Cl_2 (1.2 mL), NIS (30.0 mg, 0.133 mmol) was added at r.t. and the solution was stirred for 15 min at the same temperature. The reaction was then cooled to 0 °C and 4-methoxyphenol (**7a**) (38.0 mg, 0.306 mmol), $AgBF_4$ (47.0 mg, 0.241 mmol), $SnCl_4$ (0.240 mL of a 1 M solution in CH_2Cl_2, 0.240 mmol) were added. The resulting mixture was stirred for 3 h and the temperature was slowly warmed to r.t. prior to quenching with a saturated aqueous NH_4Cl solution (1 mL). The solution was filtered through a pad of Celite and concentrated under reduced pressure. Preparative TLC chromatography (EtOAc) gave benzofuroindoline **15** in 18% yield (8.0 mg, 0.0222 mmol) as a yellow oil.

R_f = 0.65 (EtOAc).

IR (NaCl): 3298, 1709, 1663, 1602, 1489, 1262, 1216, 811, 735 cm^{-1}.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.32 (dd, *J* = 11.4, 3.7 Hz, 1 H), 2.41 (dt, *J* = 14.1, 3.7 Hz, 1 H), 2.64–2.69 (m, 1 H), 2.83 (td, *J* = 17.3, 5.3 Hz, 1 H), 3.13 (dt, *J* = 12.0, 3.9 Hz, 1 H), 3.76 (s, 3 H), 3.81–3.86 (m, 1 H), 4.02 (dd, *J* = 9.8, 6.3 Hz, 1 H), 5.93 (d, *J* = 9.4 Hz, 1 H), 6.53–6.57 (m, 1 H), 6.63 (s, 2 H), 6.67 (d, *J* = 7.5 Hz, 1 H), 6.79 (t, *J* = 7.4 Hz, 1 H), 6.93 (s, 1 H), 7.06 (t, *J* = 7.7 Hz, 1 H), 7.15 (d, *J* = 7.7 Hz, 1 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 23.6, 31.6, 37.5, 53.5, 56.3, 58.0, 107.8, 109.7, 110.2, 110.3, 113.3, 120.9, 123.2, 125.4, 129.0, 131.6, 132.8, 137.1, 145.4, 147.3, 152.2, 155.2.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{20}N_2O_3Na$: 383.1372; found: 383.1362.

N-Methyl-benzofuroindoline 20a

To a solution of *N*-methyl-tetrahydrocarbazole **19a** (53.0 mg, 0.286 mmol) in CH_2Cl_2 (2.8 mL) at 0 °C were added *p*-methoxyphenol (**7a**) (88.0 mg, 0.715 mmol) and NIS (103.0 mg, 0.458 mmol), followed after 5 min by $AgBF_4$ (89.0 mg, 0.458 mmol). The resulting mixture was slowly warmed to r.t. and stirred for 3 h. The reaction was quenched by addition of a saturated aqueous NH_4Cl solution (1 mL), and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. Preparative TLC purification (cyclohexane/EtOAc, 95:5) afforded *N*-methyl-benzofuroindoline **20a** (48.0 mg, 0.156 mmol) in 55% yield as a colorless oil.

R_f = 0.70 (cyclohexane/EtOAc, 95:5).

IR (NaCl): 2935, 2856, 1603, 1487, 1205, 1030, 800, 746 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.26–1.39 (m, 2 H), 1.40–1.47 (m, 1 H), 1.54–1.64 (m, 1 H), 1.69–1.90 (m, 2 H), 2.26–2.37 (m, 2 H), 2.97 (s, 3 H), 3.76 (s, 3 H), 6.53 (d, *J* = 8.0 Hz, 1 H), 6.60–6.62 (m, 2 H), 6.72 (t, *J* = 7.6 Hz, 1 H), 6.90 (d, *J* = 2.4 Hz, 1 H), 7.06 (d, *J* = 6.5 Hz, 1 H), 7.10 (dt, *J* = 7.7, 1.3 Hz, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 20.0, 20.3, 28.3, 28.6, 32.5, 56.3, 56.5, 107.2, 109.8, 109.9, 112.3, 112.5, 119.0, 122.4, 128.2, 133.6, 134.0, 149.4, 153.0, 154.6.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{22}NO_2$: 308.1645; found: 308.1641.

N-Acetyl-benzofuroindoline 20b

To a solution of *N*-acetyl-tetrahydrocarbazole **19b** (61.0 mg, 0.286 mmol) in CH_2Cl_2 (3 mL) at 0 °C were added *p*-methoxyphenol (**7a**) (88.0 mg, 0.715 mmol) and NIS (71.0 mg, 0.315 mmol), followed after 5 min by $AgBF_4$ (111 mg, 0.572 mmol). The resulting mixture was slowly warmed to r.t. and stirred for 3 h. The reaction was quenched by addition of a saturated aqueous NH_4Cl solution (1 mL), and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. Preparative TLC purification (cyclohexane/EtOAc, 90:10) afforded *N*-acetyl-benzofuroindoline **20b** (35.0 mg, 0.104 mmol) in 36% yield as a colorless oil.

R_f = 0.35 (cyclohexane/EtOAc, 90:10).

IR (NaCl): 2939, 1665, 1598, 1487, 1377, 1209, 1168, 1029, 755 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.30–1.38 (m, 1 H), 1.44–1.51 (m, 1 H), 1.54–1.31 (m, 2 H), 1.87–1.64 (m, 1 H), 2.00–2.05 (m, 1 H), 2.30–2.38 (m, 1 H), 2.52 (s, 3 H), 2.66 (dt, *J* = 14.3, 4.8 Hz, 1 H), 3.71 (s, 3 H), 6.65–6.68 (m, 2 H), 6.79 (dd, *J* = 7.4, 1.1 Hz, 1 H), 7.11 (td, *J* = 7.4, 1.1 Hz, 1 H), 7.21 (td, *J* = 7.8, 1.5 Hz, 1 H), 7.35 (dd, *J* = 7.2, 1.5 Hz, 1 H), 8.17 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 18.1, 18.4, 24.7, 30.6, 31.6, 56.2, 57.7, 108.1, 109.6, 110.6, 113.6, 117.4, 122.0, 124.4, 128.5, 132.8, 134.2, 142.5, 150.9, 156.6, 170.5.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{21}NO_3Na$: 358.1414; found: 358.1411.

Methyl-2-(*N*-indolyl) Acetate 18

To a solution of ABCD tetracyclic indole **11** (60.0 mg, 0.252 mmol) in degassed DMF (1.6 mL) under argon was added KHMDS (75.0 mg, 0.376 mmol) at r.t. The reaction was stirred 15 min, then methyl 2-bromoacetate (0.03 mL, 0.353 mmol) was added dropwise and the resulting mixture was stirred for 7 h at r.t. prior to being quenched with a saturated aqueous NH_4Cl solution. The solution was diluted with H_2O, extracted with EtOAc and the combined organic layers washed with H_2O and brine, dried and concentrated under reduced pressure. Flash chromatography on silica gel (cyclohexane/EtOAc, 1:1) afforded the N-substituted indole **18** in 54% yield (42.0 mg, 0.135 mmol) as a yellow oil.

R_f = 0.40 (EtOAc).

IR (NaCl): 3442, 3056, 2951, 1751, 1662, 1609, 1465, 1424, 1351, 1207, 1059, 817, 746, 731 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 2.38 (tt, *J* = 17.4, 2.5 Hz, 1 H), 2.66 (ddd, *J* = 17.4, 4.1, 6.7 Hz, 1 H), 2.80–2.92 (m, 3 H), 3.77 (s, 3 H), 4.73 (d, *J* = 18.0 Hz, 1 H), 4.81 (d, *J* = 18.0 Hz, 1 H), 4.87 (dd, *J* = 13.5, 3.9 Hz, 1 H), 4.99–5.02 (m, 1 H), 6.12 (dd, *J* = 9.8, 2.9 Hz, 1 H), 6.66 (ddd, *J* = 9.4, 6.8, 2.1 Hz, 1 H), 7.15–7.27 (m, 3 H), 7.56 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 21.5, 32.1, 38.8, 45.8, 51.5, 52.9, 109.1, 111.6, 119.0, 120.6, 122.8, 125.9, 126.8, 133.4, 138.2, 138.3, 164.9, 169.0.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}N_2O_3$: 311.1390; found: 311.1379.

Benzofuroindoline 26

To a solution of ABCE tetracyclic indole **25** (115.0 mg, 0.238 mmol) in CH_2Cl_2 (2.4 mL) at 0 °C were added *p*-methoxyphenol (**7a**) (59.0 mg, 0.476 mmol) and NIS (59.0 mg, 0.262 mmol), followed after 3 min by $AgBF_4$ (92.3 mg, 0.476 mmol). The resulting mixture was slowly warmed to r.t. and stirred for 4 h. The reaction was quenched by addition of a saturated aqueous NH_4Cl solution (0.5 mL), then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. Preparative TLC purification (cyclohexane/EtOAc, 50:50) afforded benzofuroindoline **26** (80.0 mg, 0.132 mmol) in 55% yield as a colorless oil.

R_f = 0.54 (cyclohexane/EtOAc, 50:50).

IR (NaCl): 2953, 1739, 1599, 1488, 1266, 1164, 1024, 740 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 1.83 (dd, *J* = 12.8, 3.3 Hz, 1 H), 2.11 (dd, *J* = 14.3, 3.3 Hz, 1 H), 2.33–2.37 (m, 1 H), 2.36 (s, 3 H), 2.43 (d, *J* = 16.4 Hz, 1 H), 2.58 (td, *J* = 12.4, 3.3 Hz, 1 H), 2.68 (dd, *J* = 14.1, 3.3 Hz, 1 H), 3.31 (d, *J* = 12.2 Hz, 1 H), 3.50–3.54 (m, 1 H), 3.59 (t, *J* = 2.5 Hz, 1 H), 3.68 (s, 3 H), 3.71 (s, 3 H), 3.78 (s, 3 H), 6.43 (d, *J* = 6.9 Hz, 1 H), 6.48–6.55 (m, 2 H), 6.71 (d, *J* = 2.8 Hz, 1 H), 6.74–6.78 (m, 1 H), 7.01 (d, *J* = 7.5 Hz, 2 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 7.60 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 21.6, 23.0, 26.7, 32.4, 41.8, 51.6, 52.8, 53.5, 54.7, 56.1, 66.6, 106.1, 109.5, 109.9, 111.3, 112.6, 120.7, 122.8, 127.3 (2 C), 127.8, 129.9 (2 C), 131.8, 132.5, 136.1, 143.9, 145.8, 152.1, 154.9, 170.0, 170.4.

HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{33}N_2O_8S$: 605.1952; found: 605.1956.

Benzodioxinoindoline 28

To a solution of tetrahydrocarbazole **19c** (51.0 mg, 0.298 mmol) in CH_2Cl_2 (2 mL) under argon was added NIS (74.0 mg, 0.328 mmol). The solution was stirred for 30 min, then cooled to 0 °C and 3-methoxycathecol (**27**) (104.0 mg, 0.742 mmol), $AgBF_4$ (116.0 mg, 0.596 mmol) and NaOH (60 mg, 1.49 mmol) were added. The resulting mixture was stirred for 3 h prior to being quenched with a saturated aqueous NH_4Cl solution (0.5 mL) and filtered through a pad of Celite. Preparative TLC (cyclohexane/EtOAc, 9:1) afforded benzodioxinoindoline (13.0 mg, 0.042 mmol) in 14% yield as a white solid.

R_f = 0.30 (cyclohexane/EtOAc, 9:1).

IR (NaCl): 3341, 2936, 1604, 1498, 1474, 1098, 1019, 746 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.60 (m, 2 H), 1.62–1.70 (m, 2 H), 1.73–1.80 (m, 2 H), 2.03–2.10 (m, 1 H), 2.33–2.40 (m, 1 H), 3.88 (s, 3 H), 4.34 (s, 1 H), 6.35 (dd, *J* = 8.1, 1.4 Hz, 1 H), 6.43 (dd, *J* = 8.1, 1.4 Hz, 1 H), 6.64 (d, *J* = 7.5 Hz, 1 H), 6.70 (d, *J* = 8.0 Hz, 1 H), 6.77 (t, *J* = 7.5 Hz, 1 H), 7.08 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.21 (d, *J* = 7.4 Hz, 1 H).

^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 20.7, 23.3, 31.5, 37.1, 56.6, 81.6, 94.2, 104.6, 109.7, 111.7, 120.2, 120.6, 122.6, 129.2, 131.6, 132.9, 143.9, 146.7, 149.3.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{19}NO_3Na$: 332.1257; found: 332.1247.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1592002.

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