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Synthesis-driven mapping of the dictyodendrin alkaloids

Philipp Buchgraber, Mathias M. Domostoj, Bodo Scheiper, Conny Wirtz, Richard Mynott, Jörg Rust, Alois Fürstner *

Max-Planck-Institut für Kohlenforschung, D-45470 Mülheim/Ruhr, Germany

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Dedicated to Professor Larry E. Overmann, the 2008 recipient of the Tetrahedron Prize, with admiration and respect

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ABSTRACT

The dictyodendrin alkaloids have been described as the first telomerase inhibitors of marine origin. As such they represent interesting lead compounds in the quest for small molecule inhibitors of this tumor-marker enzyme. Described herein is the preparation of a collection of dictyodendrin-like compounds that hinges on the formation of their indole subunit by reductive cyclization of appropriate keto-amide precursors mediated by low valent titanium. It is shown that the underlying concept can be extended from the synthesis of heterocycles to the preparation of phenol and aniline derivatives using oxo-acid, oxo-nitrile or oxo-lactam derivatives as the substrates; such arene formations can even be carried out in cascade. Exploratory studies into the closure of the B-ring of the dictyodendrins with the aid of electrophilic reagents such as $Ph_3PAuCl/AgSbF_6$ or I^+ revealed the bias of these polycyclic heteroarenes to undergo unusual skeletal rearrangements. It is demonstrated that the individual dictyodendrins and analogues are capable of cleaving double stranded DNA under oxidative conditions, provided that they exhibit at least one unprotected phenol group in their periphery.

1. Introduction

Telomeric DNA that protects chromosomes at both ends is shortened in each round of cell division through replication-dependent sequence loss.[1] This process constitutes an internal clock of aging which is counteracted in cancer cells by the action of telomerase, an enzyme with inverse transcriptase properties. The fact that telomerase is over-expressed in >85% of all malignant tumors but largely silent in healthy tissue suggests that this enzyme constitutes a selective tumor marker and may hence serve as molecular target for a new generation of cancer drugs with improved therapeutic windows.[1,2]

Chemotherapy based on telomerase inhibition, however, is confronted with the problem that it may take many rounds of cell division before the growing tumor becomes affected. Therefore it is particularly important that any drug candidate not only shows high potency and selectivity, but also exhibits minimal toxicity even in combination with other drugs and is not subject to export from the cells by multidrug resistance (MDR) mechanisms.[2]

Small molecule telomerase inhibitors that meet these stringent criteria and that may hence qualify as lead compounds are rare. Therefore, the dictyodendrin alkaloids **1**–**5** isolated from the sponge *Dictyodendrilla verongiformis* deserve attention as they were claimed to be the first marine natural products with telomerase inhibitory activity (100% inhibition at a concentration of 50 μg mL^{-1}) (Scheme 1).[3,4] Unfortunately however, no further information on the bioassays used nor on other relevant pharmaceutical properties of these compounds were disclosed.

Even though the dictyodendrins are rather unusual from the structural viewpoint, many distantly related pyrrole alkaloids are known that exhibit promising biological activity profiles (for selected examples, see Scheme 2).[5] In the case of storniamide **11**, for example, it was shown that the inherent cytotoxicity of the compound can be largely switched off by methylation of the peripheral hydroxy groups. Moreover, compound **12** representing the permethylated storniamide core was reported to reverse multidrug resistance and was even found capable of hypersensitizing the human colon cancer cell line HTC116/VM46 towards vincristine and doxorubicin.[6] If a similar profile could be grafted onto dictyodendrin descendants while maintaining or even increasing the reported telomerase inhibitory capacity, such derivatives might become candidates for preclinical development.

Any such endeavor requires a secured supply of material. To this end, we reported the first and so far only total synthesis of three members of this family of natural products.[7,8] As part of

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* Corresponding author. Tel.: +49 208 306 2342; fax: +49 208 306 2994.
E-mail address: fuerstner@kofo.mpg.de (A. Fürstner).

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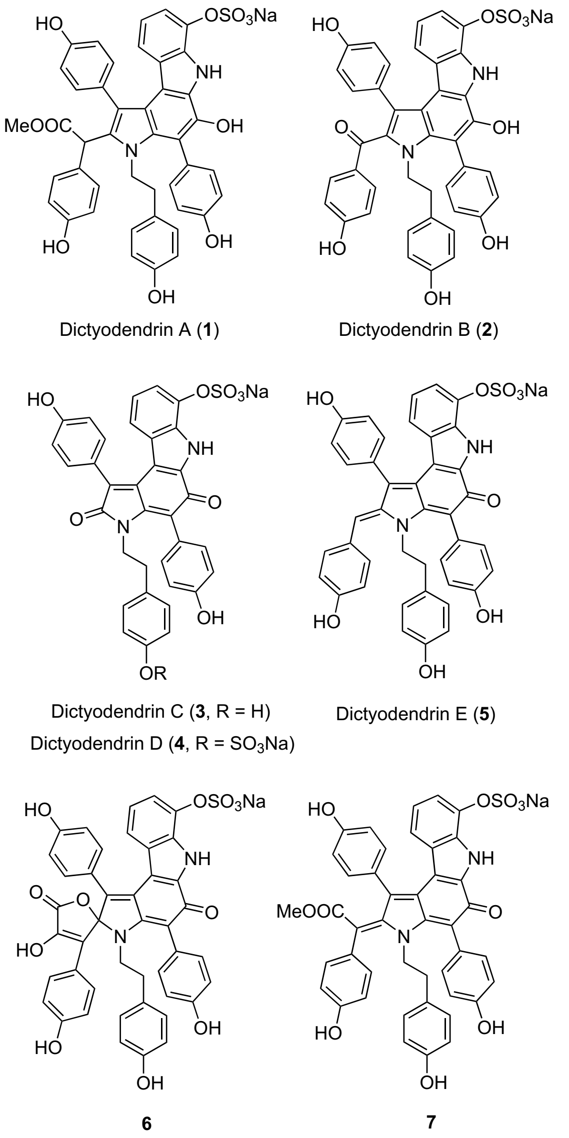
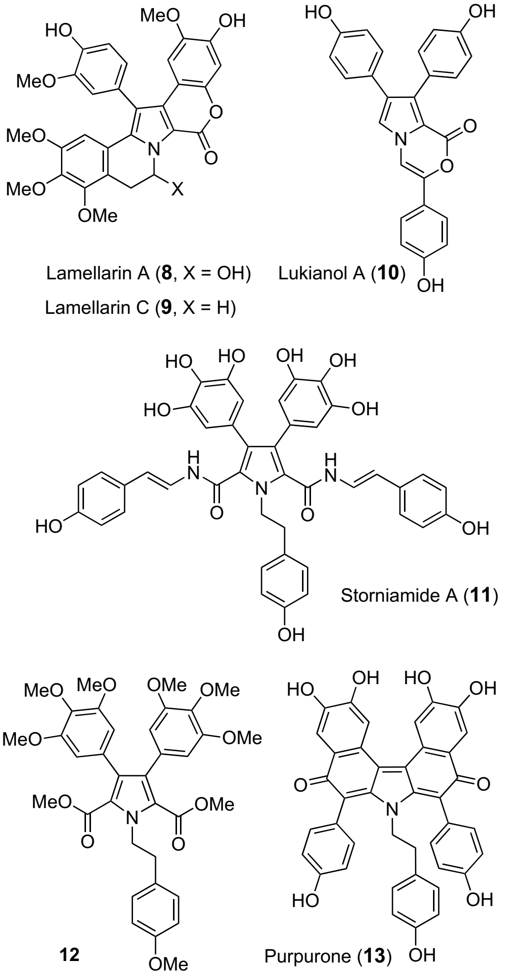


Scheme 1. Structures of the dictyodendrins and related compounds.



Scheme 2. Selected examples of related pyrrole alkaloids of marine origin.

a longstanding program dealing with bioactive pyrrole alkaloids,[7,9–12] we set out to map these interesting pyrrolocarbazole derivatives more systematically. Outlined below are some of the synthetic aspects of this venture in 'diverted total synthesis',[13,14] which led to a collection of over 30 dictyodendrin-inspired 'natural product like' compounds; at the same time, our study provides insights into the unusual reactivity of these highly condensed, electron rich heteroarenes. While a detailed biochemical profiling of the individual products is pending, we describe here their previously unknown ability to cleave double stranded DNA under oxidative conditions.

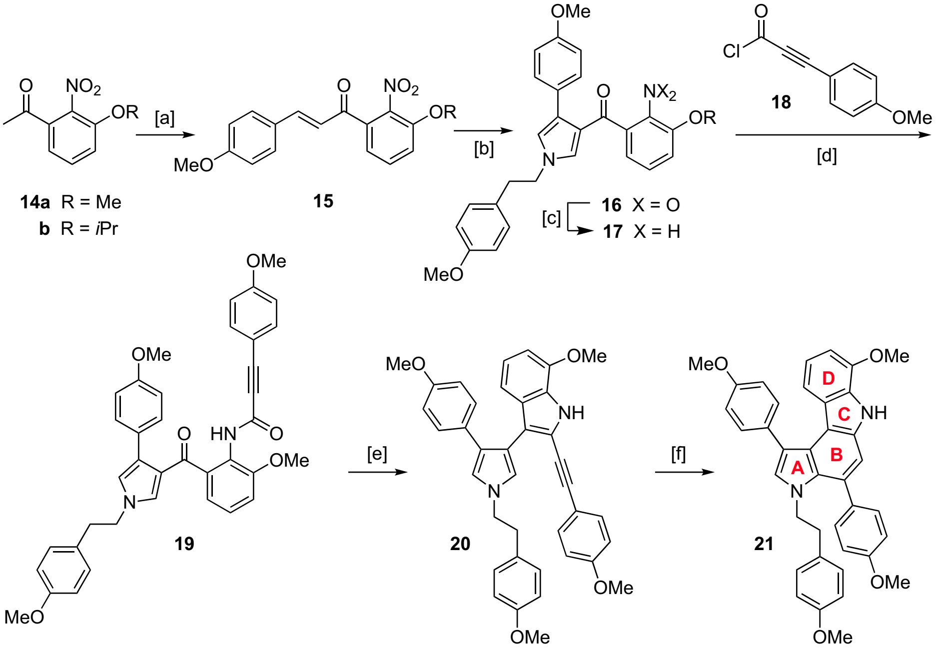
2. Results and discussion

2.1. Electrophilic closure of the B-ring

Our total synthesis of **2**, **3** and **5** used a common building block, which was formed by a titanium-induced reductive keto-amide coupling reaction[15–17] followed by a photochemical 6π-electrocyclization/aromatization cascade.[7] Even though the latter transformation was high yielding and could be performed on a reasonable scale, it seemed worthwhile to explore alternative strategies to close the B-ring.

To probe various electrophile-induced cyclization modes, pyrrole **17a** (R=Me) was prepared by adaptation of the established route and then converted into amide **19** on treatment with the very sensitive acid chloride **18** (Scheme 3).[18] Exposure of **19** to low-valent titanium[19,20] prepared by reduction of $TiCl_3$ with KC_8 in DME [15] afforded indole **20**, which turned out to be rather unstable and could therefore be isolated in only 59% yield. Gratifyingly, however, reaction of this product with catalytic amounts of $(Ph_3P)AuCl$ and $AgSbF_6$ in CH_2Cl_2 at 0 °C resulted in the almost instantaneous closure of the missing B-ring.[21,22] The constitution of the resulting permethylated dictyodendrin analogue **21** was confirmed by extensive NMR investigations, amongst which the $^{15}N,^{1}H$-HMBC experiments turned out to be particularly informative (see Experimental section). The structure assignment was later confirmed by single crystal structure analysis (Fig. 1).

21 shows a peculiar behavior upon exposure to Lewis acids. Specifically, attempts at Friedel–Crafts acylation with 4-methoxybenzoyl chloride in the presence of $SnCl_4$ failed to afford any of the desired ketone, but instead led to clean isomerization of the starting material with formation of compound **24** (Scheme 4). $TiCl_4$ and $BF_3{\cdot}Et_2O$ trigger this unusual migration of the aryl substituent with similar efficiency.[23] It is believed that this rearrangement commences with attack of the Lewis acid to the C-3 position of **21**. The resulting iminium cation **22** then reacts with the adjacent arene ring to form the Wheland-type complex **23**, which, upon



Scheme 3. (a) 4-Methoxybenzaldehyde, NaOMe, MeOH, reflux, 77% (R=Me), 74% (R=*i*-Pr); (b) (i) NaH, TosMIC, THF, −30 °C; (ii) *p*-$MeOC_6H_4CH_2CH_2Br$, reflux, 90% (R=Me), 83% (R=*i*-Pr); (c) Pd/C, H_2 (1 atm), EtOAc, 84% (R=Me), *or*: Fe powder, aq HCl, EtOH, 96% (R=*i*-Pr); (d) **18**, CH_2Cl_2, −30 °C, 70%; (e) $TiCl_3/2KC_8$, DME, reflux, 59%; (f) $(Ph_3P)AuCl$ (5 mol %), $AgSbF_6$ (5 mol %), CH_2Cl_2, 0 °C, 67%.

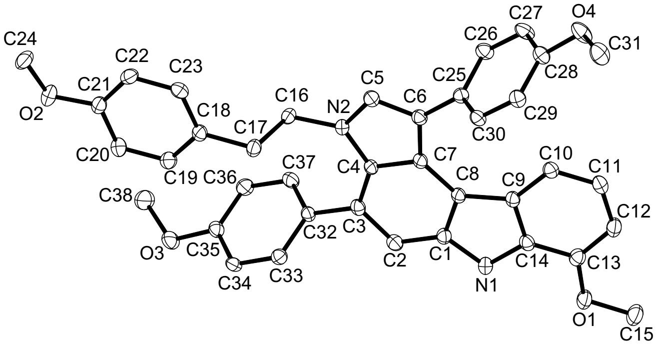
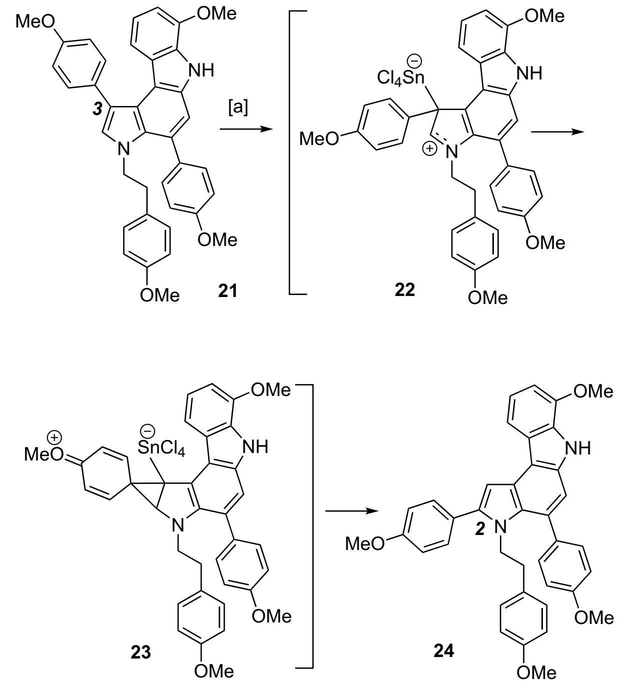


Figure 1. Molecular structure of compound **21** in the solid state. Anisotropic displacement parameters are shown at the 50% probability level.

collapse, engenders the observed 3→2 shift of the aryl group driven by the relief of the strain resulting from the *peri*-interaction of the migrating aryl group in the starting material **21**.

The sensitivity of polycyclic arenes of the dictyodendrin series also surfaced in attempted cyclizations of **20** with various X^+ sources. Whereas treatment with either I_2/K_2CO_3 or ICl led to instantaneous decomposition, the use of $[I(pyridine)_2]BF_4$[24] afforded two isomeric iodides (Scheme 5). The major product was shown by X-ray crystallography to be the expected 12-iodo derivative **25** (Fig. 2), but the constitution of the byproduct was established only after extensive NMR investigations.

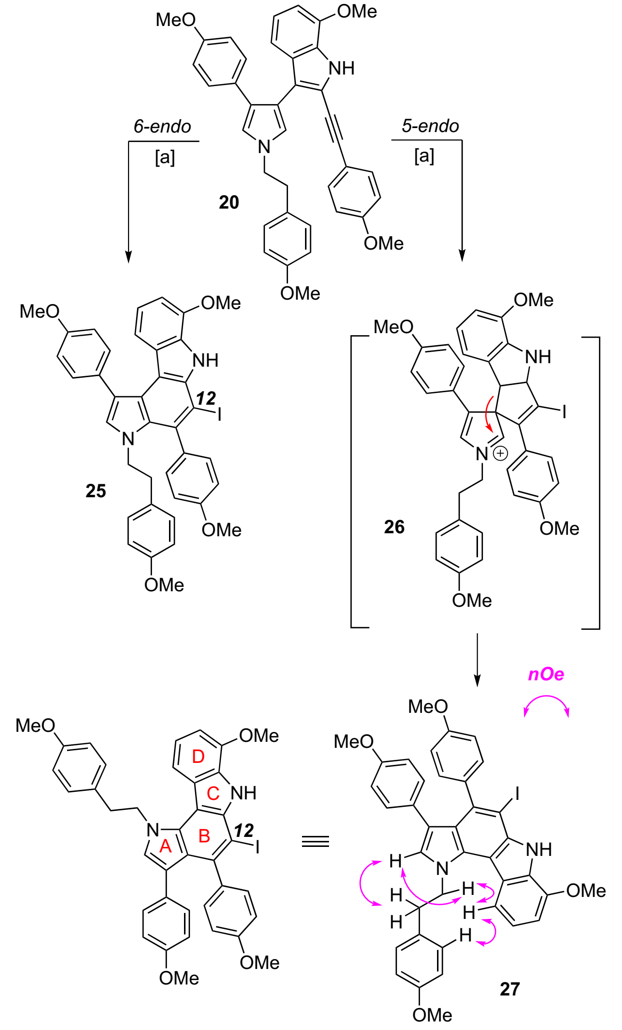
The NMR data allow one fragment consisting of ring A and its substituents and another of rings C, D, and part of B together with their substituents to be identified; they showed that the iodide must definitely be on ring B. The connectivities determined by HMBC spectra ($^{13}C,^{1}H$ and $^{15}N,^{1}H$) revealed *no* significant differences from those determined for the major product **25**. However, not all the connectivities in the center of the core can be determined using HMBC spectra because correlations corresponding to those from H-12 in **24** are missing—in particular, the connectivities in ring B to the ring junction AB are not defined. Thus, these data are also consistent with the orientation of the pyrrole A-ring in



Scheme 4. Attempted Friedel–Crafts acylation of **21** induces a 3→2 aryl shift: (a) *p*-$MeOC_6H_4COCl$, $SnCl_4$, 1,2-dichloroethane, reflux, 64%.

27 relative the remainder of the core being the '*reverse*' of that in **25**. This structural assignment was nicely confirmed by the observed NOEs (Scheme 5).

This unexpected outcome may be rationalized by assuming that activation of the alkyne in **20** by the I^+ equivalent engenders two competing cyclization modes. Whereas the regular 6-*endo* process leads to the expected product **25**, a 5-*endo* cyclization gives rise to iminium cation **26**, which generates **27** by a subsequent Wagner–Meerwein-like rearrangement. Though unusual, this process follows the reactivity pattern that is also expressed in the acid catalyzed aryl shift described above (**21**→**24**).



Scheme 5. (a) [I(pyridine)$_2$]BF$_4$, TfOH, CH$_2$Cl$_2$, −60 °C, 67% (**25** and **27**).

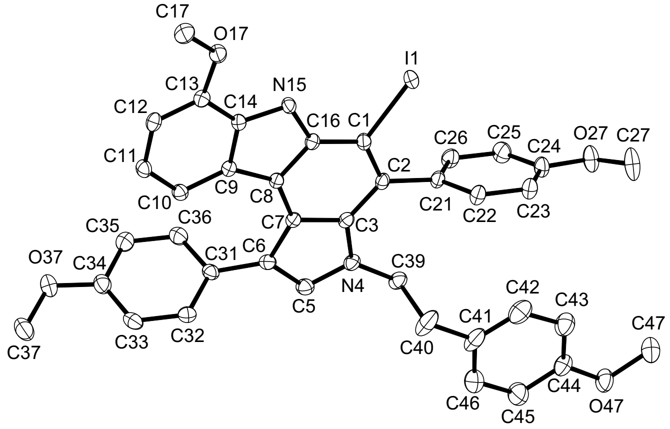
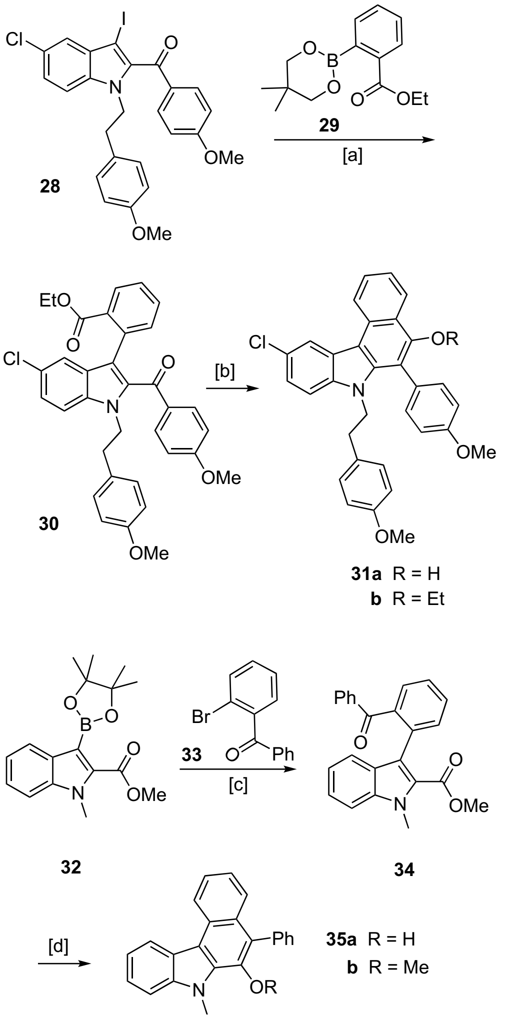


Figure 2. Molecular structure of compound **25** in the solid state. Anisotropic displacement parameters are shown at the 50% probability level.

2.2. Reductive closure of the B-ring and non-canonical McMurry-type reactions

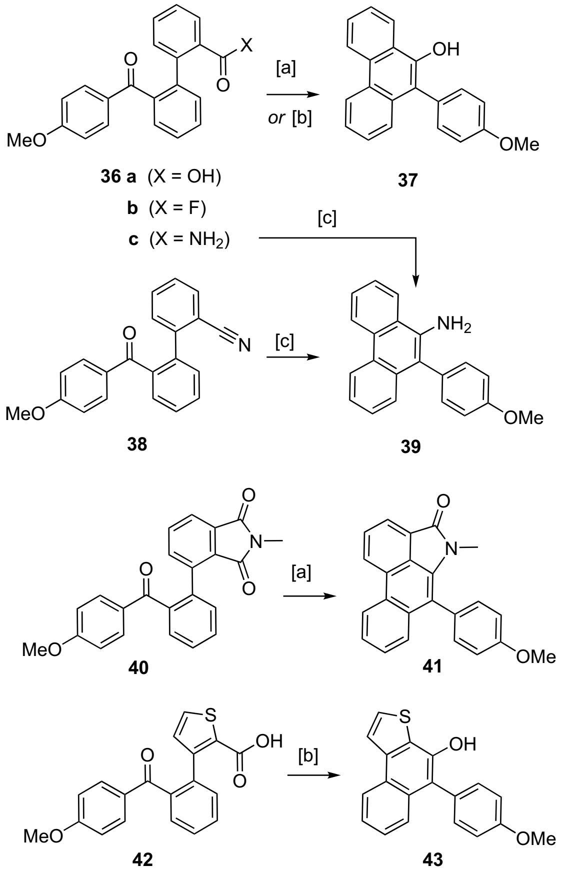
Next, we investigated if the B-ring of the dictyodendrin core could be forged by reductive oxo-ester cyclization. This plan was inspired by the remarkable efficiency with which the indole subunit of these targets could be generated from suitable keto-amide precursors with the aid of low-valent titanium. Even though titanium-mediated oxo-ester coupling reactions per se are known in the literature,[19,25,26] it seems that such transformations have never been used for the formation of substituted phenol derivatives.[27]

To probe this new entry into phenol derivatives, two suitable model compounds were prepared by Suzuki reaction[28] of **28** with **29** and **32** with **33**, respectively (Scheme 6, for the preparation of the building blocks, see the Experimental section). Gratifyingly, the resulting keto-esters **30** and **34** underwent productive ring closure when exposed to low-valent titanium in the presence of excess pyridine to buffer the reaction mixture. In both cases the corresponding free phenols **31a** and **35a** (R=H) were formed as the major products.



Scheme 6. (a) Pd(PPh$_3$)$_4$ (5 mol %), K$_3$PO$_4$, 1,4-dioxane, 100 °C, 36%; (b) TiCl$_3$/2KC$_8$, DME, pyridine, reflux, 79% (**31a**/**31b**=25:1); (c) Pd(PPh$_3$)$_4$ (5 mol %), K$_3$PO$_4$, 1,4-dioxane, 100 °C, 92%; (d) TiCl$_3$/2KC$_8$, DME, pyridine, reflux, 89% (**35a**/**35b**=5:1).

Based on these promising results, the investigation into arene ring formation by reductive coupling was extended to other unconventional substrate types. As can be seen from the results compiled in Scheme 7, various biaryl derivatives bearing a ketone and either a free carboxylic acid, acyl fluoride, amide, lactam or nitrile cleanly reacted to the corresponding substituted phenanthrene derivatives when exposed to low-valent titanium, independent of whether it is generated from TiCl$_3$ and KC$_8$ or via the operationally more convenient 'instant procedure' (TiCl$_3$/Zn, without pre-reduction);[15] notably, product **41** closely resembles the aristolactam alkaloids (Fig. 3).[29] Collectively, these results show that the formation of substituted aromatic rings provides sufficient



Scheme 7. (a) $TiCl_3/2KC_8$, DME, reflux, 89% (**36a**→**37**), 85% (**36b**→**37**); 86% (**40**→**41**); (b) $TiCl_3$, Zn, DME, reflux, 86% (**36a**→**37**), 90% (**36b**→**37**), 85% (**42**→**43**); (c) (i) $TiCl_3$, Zn, DME, reflux; (ii) ETDA workup, 58% (**36c**→**39**), 90% (**38**→**39**).

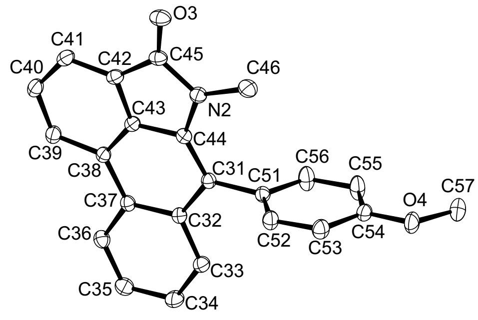


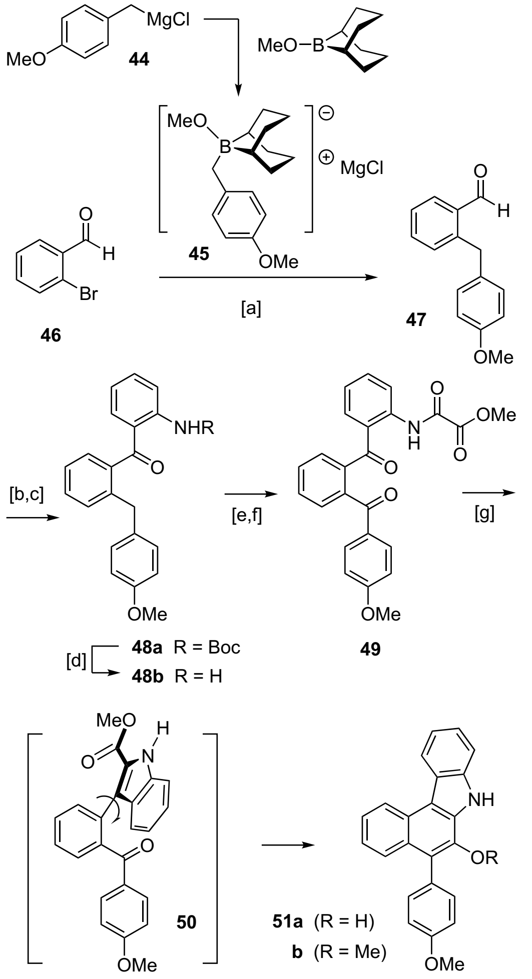
Figure 3. Molecular structure of compound **41** in the solid state. Anisotropic displacement parameters are shown at the 50% probability level.

driving force for highly 'non-canonical' McMurry reactions[19] which involve functional groups that were previously considered inert toward low-valent titanium.[30]

2.3. McMurry cascade

Since the results summarized above had shown that the B- as well as the C-ring of the dicytodendrin core can be formed in a reductive mode, an attempt was made to combine these transformations into a one-pot cyclization cascade. This requires four different carbonyl groups in close proximity to engage into two well orchestrated coupling events effected by the very same reagent.

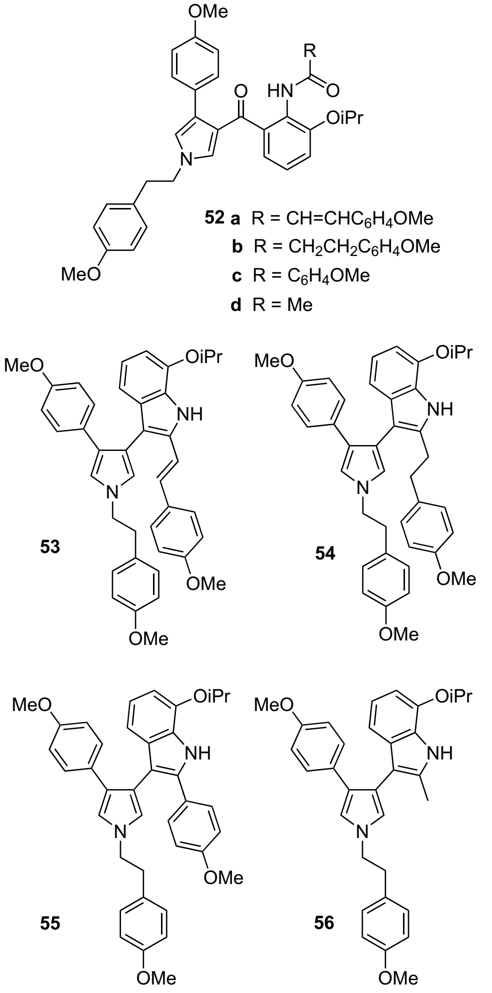
This concept was probed by the model study shown in Scheme 8. Chemoselective benzylation of 2-bromo benzaldehyde **46** via the 9-MeO-9-BBN variant[31] of the Suzuki coupling afforded product **47**,[31] which was readily transformed into compound **49**. Treatment of this polycarbonyl derivative with excess titanium–graphite in refluxing DME for 40 min gave the desired carbazole **51** in 54% yield. If the reaction was quenched prematurely after only 25 min, indole **50** was the only product that could be isolated from the mixture (70%). Although these results show that polycarbonyl derivatives are amenable to chemo- and regioselective coupling cascades,[32] it becomes evident that reductive indole formation is considerably faster than the subsequent closure of the phenol ring. For the latter process to occur, the *ortho*,*ortho*′-disubstituted biaryl unit in, e.g., **50** must become planar, with the two carbonyl groups on the same side, before productive C–C-bond formation can occur; the barrier inherent to this rotation probably translates into a kinetic handicap.



Scheme 8. (a) **45**, $Pd(OAc)_2$ (1 mol %), *S*-Phos (2 mol %), DMF/THF, 110 °C; (b) *N*-Boc-2-bromoaniline, MeLi, THF, 78 °C, then *tert*-BuLi, 63% (over both steps); (c) TPAP (5 mol %), NMO, MS 3 Å, CH_2Cl_2, 88%; (d) aq HCl, EtOH, reflux, quant.; (e) MeOOC-C(O)Cl, pyridine, CH_2Cl_2, −20 °C, 93%; (f) CrO_3, HOAc, 93%; (g) $TiCl_3/2KC_8$, DME, reflux, 25 min: **50** (70%)+**51** (3%); 40 min: **51** (**a**/**b**=9:1, 54%).

2.4. Peripheral modifications

In addition to the dictyodendrin analogues mimicking the condensed pyrrolocarbazole core of the natural products, several derivatives with a formally open B-ring were prepared for biological testing (**53**–**56**). Their syntheses were straightforward, requiring nothing but acylation of the common pyrrole precursor **17b** (R=*i*-Pr)[7] followed by treatment of the resulting oxo-amide derivatives **52** with $TiCl_3/2KC_8$ under standard conditions. Although not fully optimized, the yields were good to excellent in all cases but one, showing the robustness of this reductive approach to indoles (Scheme 9).



Scheme 9. Dictyodendrin analogues with formally cleaved B-ring generated by reductive cyclization of keto-amides **52a–d**. Reagents and conditions: $TiCl_3/2KC_8$, DME, reflux, **53** (73%), **54** (20%), **55** (89%), **56** (77%).

3. Investigation of the DNA-cleaving Properties

Together with the samples of the natural products themselves and their immediate precursors, our synthesis campaign afforded more than 30 dictyodendrin-like compounds for biological investigations. Whereas a detailed profiling of the individual products is still in progress, the preliminary data indicate a low inherent toxicity of prototype members of the series against HeLa as well as HepG2 cancer cells. This constitutes an important prerequisite for possible monitoring of cancer growth inhibition by downregulation of telomerase activity.

Previous investigations from this laboratory had shown that polyhydroxylated pyrroles can induce single- and even double strand cleavage in supercoiled plasmid DNA under oxidative conditions.[10,33,34] As the dictyodendrins are supposed to target DNA, it was appropriate to study whether they are also able to damage this bio-macromolecule in a similar fashion. The gel depicted in Figure 4 illustrates this property and establishes a strong correlation between observed DNA damage and the peripheral methylation pattern of the compounds. Specifically, dictyodendrin B (**2**, lane 9) and E (**5**, lane 4),[7] as well as the dictyodendrin E analogue **58** devoid of the sulfate moiety (lane 6)[7] relax the supercoiled plasmid DNA of the bacteriophage ΦX174 (form **I**) within 1.5 h at 37 °C to the nicked form **II** in the presence of $Cu(OAc)_2$ and *n*-butylamine; even small amounts of linear DNA (form **III**) generated by double strand cleavage are visible. As expected, comparison of lanes 9 and 10 show that the presence of Cu(2+) is essential for triggering such oxidative stress. Dictyodendrin C, in sulfated (**3**) or unsulfated form (**65**),[7] also shows an appreciable effect (Fig. 4, lane 7 and Fig. 5, lane 10). Importantly, however, no noticeable DNA cleavage was exerted by their fully protected congeners **57** and **59** (lanes 5 and 8).

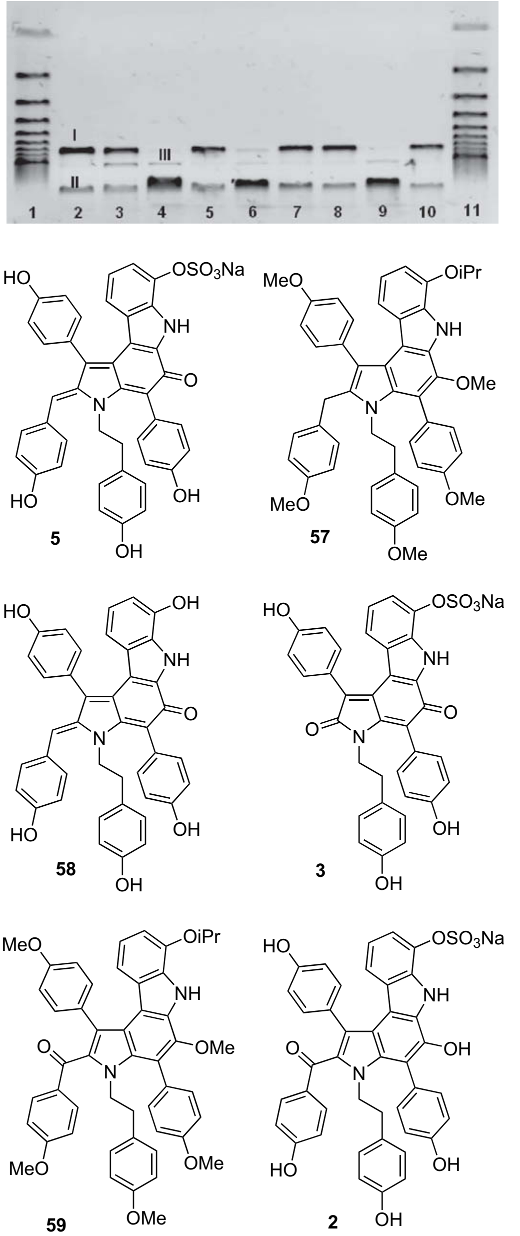


Figure 4. Agarose gel electrophoresis showing the extent of DNA cleavage by different dictyodendrins and derivatives thereof in the presence of $Cu(OAc)_2$ and $BuNH_2$ after an incubation time of 1.5 h at 37 °C. Lane 1: DNA marker (500 base pairs molecular weight difference); lane 2: native DNA (band I: supercoiled DNA; band II: nicked DNA (single strand cleavage)); lane 3: linear DNA produced by cleavage of the parent DNA with the restriction endonuclease *Xho I* (band **III**); lane 4: DNA+compound **5**+Cu^{II}+$BuNH_2$; lane 5: DNA+compound **57**+Cu^{II}+$BuNH_2$; lane 6: DNA+compound **58**+Cu^{II}+$BuNH_2$; lane 7: DNA+compound **3**+Cu^{II}+$BuNH_2$; lane 8: DNA+compound **59**+Cu^{II}+$BuNH_2$; lane 9: DNA+compound **2**+Cu^{II}+$BuNH_2$; lane 10: DNA+compound **5** without Cu^{II}+$BuNH_2$; lane 11: DNA marker (500 base pairs molecular weight difference).

This conclusion was confirmed by the gel depicted in Figure 5, wherein selected analogues were screened. Even compound **63**,[7] in which all but one of the phenolic groups are methylated, still constitutes a potent DNA damaging agent in combination with Cu(2+) (lane 7), whereas all fully protected compounds are devoid

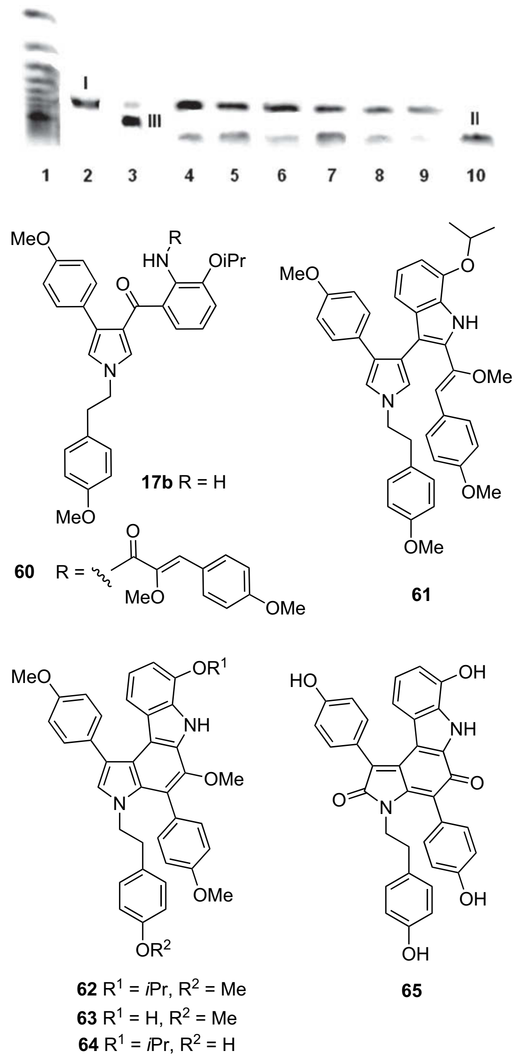


Figure 5. Agarose gel electrophoresis showing the extent of DNA cleavage by different dictyodendrins analogues in the presence of $Cu(OAc)_2$ and $BuNH_2$ after an incubation time of 1.5 h at 37 °C; band I: supercoiled DNA; band II: nicked DNA (single strand cleavage); band III: linear DNA produced by cleavage of the parent DNA with the restriction endonuclease *Xho I*; lane 1: DNA marker (500 base pairs molecular weight difference); lane 2: native DNA; lane 3: linear DNA (band **III**); lane 4: DNA+compound **60**+Cu^{II}+$BuNH_2$; lane 5: DNA+compound **61**+Cu^{II}+$BuNH_2$; lane 6: DNA+compound **62**+Cu^{II}+$BuNH_2$; lane 7: DNA+compound **63**+Cu^{II}+$BuNH_2$; lane 8: DNA+compound **17b**+Cu^{II}+$BuNH_2$; lane 9: DNA+compound **64**+Cu^{II}+$BuNH_2$; lane 10: DNA+compound **65**+Cu^{II}+$BuNH_2$.

of any appreciable activity. This strong correlation with the nuclease-like activity can be rationalized by assuming a Cu(2+)-mediated oxidation of the phenol to the corresponding *o*-quinone with concomitant release of H_2O_2 which, in turn, undergoes metal-assisted cleavage to diffusible oxygen radicals as the ultimately DNA-damaging agents.[35] In any case, we conclude that the naturally occurring dictyodendrins and synthetic analogues are endowed with potent DNA cleavage properties, but that these can be effectively switched off by per-alkylation of the peripheral phenolic sites.

4. Experimental

4.1. General

All reactions were carried out under Ar in flame-dried glassware. The solvents used were purified by distillation over the drying agents indicated and transferred under Ar: THF, Et_2O, 1,4-dioxane (Mg/anthracene), CH_2Cl_2, Et_3N, CH_3CN, DMSO,(CaH_2), hexane, toluene, 1,4-dioxane, DME (Na/K), DMF (Desmodur 15, dibutyl tin dilaurate), MeOH, EtOH (Mg). Flash chromatography (FC): Merck silica gel 60 (230–400 mesh) or CombiFlash (Teledyne Isco). NMR: Spectra were recorded on Bruker DPX 300, AMX 300, AV 400 and DMX 600 spectrometers in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: $\delta_C\equiv77.0$ ppm; residual $CHCl_3$: $\delta_H\equiv7.26$ ppm; CD_2Cl_2: $\delta_C\equiv53.8$ ppm; residual $CHDCl_2$: $\delta_H\equiv5.32$ ppm; CD_3OD $\delta_C\equiv49.0$ ppm; residual CHD_2OD: $\delta_H\equiv3.30$ ppm; acetone-d_6: $\delta_C\equiv29.8$ ppm; residual acetone-d_5: $\delta_H\equiv2.05$ ppm, C_6D_6: $\delta_C\equiv128.0$ ppm; residual C_6D_5H: $\delta_H\equiv7.15$ ppm; DMSO-d_6: $\delta_C\equiv39.5$ ppm; residual DMSO-d_5: $\delta_H\equiv2.49$ ppm). ^{15}N NMR spectra were calibrated against external CH_3NO_2. The coupling constants (J) were not averaged. The proton spectra of the *para*-disubstituted phenyl groups are of AA′XX′ spin systems. The splitting of signals of greatest intensity is quoted as the value of the coupling constant $^3J_{(AX)}$, assuming that $^5J_{(AX')}$ is zero. Where indicated, the signal assignments are unambiguous; the numbering scheme is arbitrary and shown in the inserts. The assignments are based upon 1D and 2D spectra recorded using the following pulse sequences from the Bruker standard pulse program library: DEPT; COSY (*cosygs* and *cosydqtp*); HSQC (invietgssi) optimized for $^1J_{C,H}$=145 Hz; HMBC (*inv4gslplrnd*) for correlations via $^nJ_{C,H}$; HSQC-TOCSY (invietgsml) using an MLEV17 mixing time of 120 ms; IR: Magna IR750 (Nicolet) or Spectrum One (Perkin–Elmer) spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}; MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: ESQ3000 (Bruker), accurate mass determinations: Bruker APEX III FT-MS (7 T magnet) or Mat 95 (Finnigan). Melting points: Büchi melting point apparatus B-540 (corrected). Elemental analyses: H. Kolbe, Mülheim/Ruhr. All commercially available compounds (Fluka, Lancaster, Aldrich) were used as received. For the preparation of compounds **2**, **3**, **5**, **15b**–**17b** and **57**–**65**, see Ref. 7.

4.1.1. *(2E)-3-Methoxy-2-nitrophenyl-3-(4-methoxyphenyl)-2-propenone (**15a**, R=Me)*

Sodium (161 mg, 7.00 mmol) was dissolved in MeOH (10 mL) before *p*-methoxybenzaldehyde (2.50 mL, 21.2 mmol) and ketone **14a** (2.70 g, 14.2 mmol) were added. The mixture was stirred at 70 °C for 2 h before it was slowly cooled to ambient temperature. The resulting precipitate was filtered off, successively washed with water (20 mL) and MeOH (20 mL), and dried under high vacuum to give chalcone **15a** as a pale yellow solid (3.42 g, 77%); mp=151–152 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=7.57–7.50 (m, 4H), 7.28–7.26 (m, 2H), 7.01–6.90 (m, 3H), 3.96 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=189.6, 162.2, 151.5, 147.1, 134.3, 131.5, 130.6, 126.8, 121.5, 120.4, 115.4, 114.5, 56.8, 55.4; IR (film): 3007, 2939, 2841, 1663, 1642, 1587, 1571, 1539, 1511, 1475, 1454, 1436, 1306, 1292, 1258, 1173, 1026, 852, 830, 794 cm^{-1}; MS (EI): *m/z* (%): 313 (17) [M^+], 177 (14), 161 (10), 135 (35), 121 (100), 90 (11), 76 (18), 65 (8); HRMS (EI) *m/z*: calcd for $C_{17}H_{15}NO_5$+Na [$(M+Na)^+$]: 336.0847, found: 336.0850.

4.1.2. *(3-Methoxy-2-nitrophenyl){4-(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)ethyl]1H-pyrrol-3-yl}methanone (**16a**, R=Me)*

A solution of tosylmethylisocyanide (TosMIC, 1.76 g, 9.00 mmol) and chalcone **15a** (1.42 g, 4.50 mmol) in THF (20 mL) was added to a stirred suspension of NaH (0.65 g, 27 mmol) in dry THF (10 mL) at −30 °C. The mixture was stirred at −30 °C for 1 h and at ambient temperature for 2 h. After completion of the reaction, 2-bromoethyl-4-methoxybenzene (3.87 g, 18.0 mmol) was introduced and the mixture refluxed for 2 h. For work up, the reaction was quenched with water (20 mL) and the product extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent followed by flash chromatography of the residue (EtOAc/hexanes, 1:1) afforded pyrrole **16a** as a pale yellow solid (1.98 g, 90%); mp=61–62 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.36–7.26 (m, 3H), 7.04 (m, 1H), 6.93 (m, 2H), 6.88 (m, 1H), 6.81–6.77 (m, 4H), 6.73 (d, J=2.3 Hz, 1H), 6.55 (d, J=2.3 Hz, 1H), 3.96 (t, J=6.9 Hz, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 3.74 (s, 3H), 2.92 (t, J=6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=186.1, 158.3, 158.2, 151.0, 139.3, 136.0, 131.0, 130.9, 129.7, 129.6, 129.4, 126.8, 126.5, 121.6, 121.0, 120.3, 114.4, 113.9, 113.1, 56.5, 55.0, 51.7, 36.6; IR (KBr): 3122, 3001, 2940, 2837, 1644, 1610, 1577, 1536, 1514, 1503, 1473, 1453, 1382, 1289, 1247, 1179, 1035, 834, 790 cm^{-1}; MS (EI): m/z (%): 486 (100) [M$^+$], 335 (9), 322 (20), 264 (11), 189 (8), 160 (13), 121 (57), 105 (12), 77 (9); HRMS (EI) m/z: calcd for $C_{28}H_{26}N_2O_6$+Na [(M+Na)$^+$]: 509.1688, found: 509.1684.

*4.1.3. (2-Amino-3-methoxyphenyl){4-(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)ethyl]1H-pyrrol-3-yl}methanone (**17a**, R=Me)*

Compound **16a** (5.20 g, 10.7 mmol) was added to a suspension of Pd/C (10% w/w, 2.27 g) in EtOAc (30 mL) and the resulting mixture was stirred under an atmosphere of H_2 until TLC control indicated complete consumption of the substrate. For work up, the catalyst was filtered off through a short pad of silica which was carefully rinsed with EtOAc, the combined filtrates were evaporated and the residue was purified by flash chromatography (hexanes/EtOAc, 2:1) to give product **17a** as a yellow solid (4.12 g, 84%); mp=56–57 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.29 (m, 2H), 7.12 (dd, J=8.1, 1.2 Hz, 1H), 6.92 (m, 2H), 6.83–6.75 (m, 5H), 6.60 (dd, J=10.2, 2.3 Hz, 2H), 6.43 (dd, J=8.0, 7.9 Hz, 1H), 6.05 (s, 2H), 3.92 (t, J=6.8 Hz, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 2.89 (t, J=6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=193.0, 158.2, 157.8, 146.7, 140.4, 129.5, 129.4, 129.0, 128.2, 127.3, 126.3, 125.0, 121.7, 120.2, 119.8, 113.7, 113.5, 113.3, 112.1, 55.4, 54.9, 54.9, 51.3, 36.7; IR (film): 3484, 3358, 3120, 3033, 3000, 2935, 2835, 1613, 1582, 1543, 1513, 1453, 1440, 1246, 1224, 1178, 1036, 833, 776, 745 cm^{-1}; MS (EI): m/z (%): 456 (53) [M$^+$], 335 (100), 307 (14), 212 (5), 186 (9), 162 (8), 121 (19), 91 (4); HRMS (EI) m/z: calcd for $C_{28}H_{29}N_2O_4$ [(M+H)$^+$]: 457.2127, found: 457.2126.

*4.1.4. Compound **19***

Chloro-*N*,*N*-2-trimethylpropenylamine (1.0 mL, 7.6 mmol)[18] was added to a solution of 3-(4-methoxyphenyl)-2-propynoic acid (689 mg, 3.90 mmol) in CH_2Cl_2 (8 mL) and the resulting mixture stirred for 2 h. Because of the instability of the resulting acid chloride **18**, amine **17a** (880 mg, 1.93 mmol) was directly added to this mixture at −30 °C and stirring continued for 15 min at this temperature. At this point, pyridine (1 mL) was introduced and the mixture allowed to reach ambient temperature. After 1 h, the reaction was quenched with water (10 mL), the aqueous layer was extracted with EtOAc (3×10 mL), the combined organic phases were dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 1:1) to afford amide **19** as a beige solid (829 mg, 70%); mp=115–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.40 (s, 1H), 7.44–7.36 (m, 4H), 7.16 (t, J=8.0 Hz, 1H), 7.04–6.95 (m, 4H), 6.85–6.95 (m, 7H), 6.58 (m, 1H), 4.00 (m, 2H), 3.88 (s, 3H), 3.78 (s, 9H), 2.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=190.1, 160.9, 158.5, 158.3, 154.2, 134.3, 131.8, 129.6, 129.5, 127.0, 127.0, 126.3, 123.4, 121.9, 121.2, 121.0, 114.0, 113.4, 112.1, 82.7, 56.1, 55.2, 55.1, 51.8, 36.8, 19.1; IR (film): 3006, 2936, 2837, 2206, 1768, 1713, 1645, 1604, 1580, 1512, 1464, 1441, 1286, 1249, 1168, 1033, 834, 752 cm^{-1}; MS (EI) m/z (%): 614 (100) [M$^+$], 582 (11), 482 (88), 453 (39), 361 (24), 334 (36), 306 (10), 238 (6), 176 (28), 159 (58), 135 (52), 121 (29); HRMS (EI) m/z: calcd for $C_{38}H_{34}N_2O_6$+Na [(M+Na)$^+$]: 637.2314, found: 637.2302.

*4.1.5. Amide **52a***

Prepared analogously from **17b** as a pale yellow solid (81%); mp=164–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.11 (br s, 1H), 7.55 (d, J=15.7 Hz, 1H), 7.44 (d, J=8.7 Hz, 2H), 7.36 (d, J=8.6 Hz, 2H), 7.09 (dd, J=8.0, 7.8 Hz, 1H), 7.02–6.95 (m, 4H), 6.92 (d, J=2.5 Hz, 1H), 6.89–6.78 (m, 6H), 6.57 (d, J=2.5 Hz, 1H), 6.37 (d, J=15.6 Hz, 1H), 4.54 (sept, J=6.0 Hz, 1H), 4.02 (t, J=7.1 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 2.98 (t, J=7.1 Hz, 2H), 1.33 (d, J=6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=190.5, 164.3, 160.8, 158.5, 158.3, 152.1, 141.0, 137.0, 131.5, 129.7, 129.7, 129.7, 129.4, 127.7, 127.3, 127.1, 125.7, 125.3, 122.0, 121.2, 121.0, 118.6, 116.2, 114.1, 114.1, 113.4, 71.3, 55.3, 55.2, 55.2, 51.8, 36.9, 22.1; IR (KBr): 3251, 3119, 2974, 2933, 2835, 1675, 1629, 1603, 1577, 1513, 1464, 1248, 1174, 1112, 1033, 921, 827, 778 cm^{-1}; MS (EI) m/z (%): 644 (61) [M$^+$], 484 (18), 467 (31), 363 (47), 334 (12), 321 (10), 176 (9), 161 (100), 135 (22), 121 (9), 105 (5); HRMS (ESI) calcd for $C_{40}H_{40}N_2O_6$+Na [(M+Na)$^+$]: 667.2779, found: 667.2776.

*4.1.6. Amide **52b***

Prepared analogously from **17b** as a colorless foam (84%); ^{1}H NMR (300 Hz, $CDCl_3$): δ=7.72 (br s, 1H), 7.38 (d, J=9.0 Hz, 2H), 7.13–6.80 (m, 12H), 6.76 (d, J=8.6 Hz, 2H), 6.60 (d, J=2.3 Hz, 1H), 4.52 (sept, J=6.0 Hz, 1H), 4.03 (dd, J=7.3, 7.0 Hz, 2H), 3.80 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 3.00 (t, J=7.1 Hz, 2H), 2.92–2.81 (m, 2H), 2.56–2.45 (m, 2H), 1.31 (d, J=6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.4, 170.4 (br), 158.6, 158.3, 157.9, 152.1, 137.5 (br), 133.1, 131.5, 129.8, 129.7, 129.6, 129.2, 127.2, 127.1, 125.5 (br), 125.3, 121.8, 121.2, 121.0, 115.8, 114.1, 113.8, 113.4, 71.1, 55.2, 55.2, 55.2, 51.8, 38.6 (br), 36.9, 30.7, 22.1; IR (KBr): 3251, 3121, 3030, 2974, 2933, 2834, 1683, 1632, 1612, 1579, 1549, 1513, 1464, 1384, 1300, 1246, 1178, 1034, 921, 828, 779 cm^{-1}; MS (EI) m/z (%): 646 (100) [M$^+$], 587 (6), 484 (12), 467 (16), 441 (7), 363 (48), 339 (32), 321 (31), 292 (11), 280 (8), 186 (16), 178 (19), 162 (15), 135 (31), 121 (78), 105 (9); HRMS (ESI) calcd for $C_{40}H_{42}N_2O_6$+Na [(M+Na)$^+$]: 669.2935, found: 669.2936. Anal. Calcd for $C_{40}H_{42}N_2O_6$ (646.8): C 74.28, H 6.55, N 4.33; found: C 74.17, H 6.63, N 4.24.

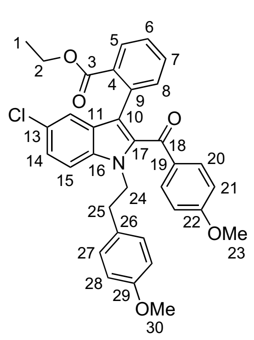
*4.1.7. Amide **52c***

Prepared analogously from **17b** as a colorless foam (91%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.55 (br s, 1H), 7.78 (d, J=8.8 Hz, 2H), 7.34 (d, J=8.8 Hz, 2H), 7.09 (dd, J=8.3, 7.3 Hz, 1H), 7.04–6.95 (m, 4H), 6.94 (d, J=2.3 Hz, 1H), 6.88 (d, J=8.8 Hz, 2H), 6.82 (d, J=8.6 Hz, 2H), 6.81 (d, J=8.4 Hz, 2H), 6.55 (d, J=2.3 Hz, 1H), 4.53 (sept, J=6.1 Hz, 1H), 4.00 (t, J=7.1 Hz, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 2.96 (t, J=7.1 Hz, 2H), 1.31 (d, J=6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=190.8, 165.0, 162.2, 158.6, 158.2, 152.0, 136.6, 131.3, 129.7, 129.6, 129.4, 127.3, 127.2, 127.0, 126.4, 125.0, 122.4, 121.3, 120.9, 116.5, 114.1, 113.6, 113.4, 71.4, 55.4, 55.2, 55.2, 51.8, 36.9, 22.1; IR (KBr): 3422, 3122, 2974, 2933, 2835, 1677, 1640, 1607, 1513, 1249, 1032, 834, cm^{-1}; MS (EI): m/z (%): 618 (44) [M$^+$], 497 (12), 467 (26), 307 (5), 135 (100), 107 (6), 77 (6); HRMS (ESI) calcd for $C_{38}H_{38}N_2O_6$+Na [(M+Na)$^+$]: 641.2622, found: 641.2614. Anal. Calcd for $C_{38}H_{38}N_2O_5$ (618.7): C 73.77, H 6.19, N 4.53; found: C 73.58, H 6.16, N 4.45.

*4.1.8. Amide **52d***

Prepared analogously from **17b** as a colorless foam (90%); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.75 (br s, 1H), 7.38 (d, J=8.8 Hz, 2H), 7.12–7.03 (m, 1H), 7.03–6.90 (m, 4H), 6.89–6.80 (m, 5H), 6.60 (d, J=2.5 Hz, 1H), 4.53 (sept, J=6.1 Hz, 1H), 4.01 (t, J=7.1 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 2.98 (t, J=7.1 Hz, 2H), 1.99 (s, 3H), 1.33 (d, J=6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=190.4, 168.4, 158.5, 158.3, 152.2, 137.6, 131.6, 129.7, 129.6, 129.6, 127.1, 127.0, 125.5, 125.3, 121.7, 121.1, 121.0, 115.9, 114.1, 113.3, 71.1, 55.2, 55.1, 51.8, 36.8, 23.2, 22.0; IR (KBr): 3260 (br), 3121, 2975, 2934, 2835, 1683, 1635, 1613, 1513, 1503, 1464, 1384, 1246, 1033, 832, 778 cm^{-1}; MS (EI) m/z (%): 526 (100) [M$^+$], 467 (37), 441 (8), 405 (7), 363 (31), 321 (26), 307 (19), 292 (8), 186 (16), 135 (23), 121 (17), 105 (6); HRMS (ESI) calcd for $C_{32}H_{34}N_2O_5$+Na [(M+Na)$^+$]: 549.2360, found: 549.2365.

4.1.9. *Representative procedure for the synthesis of cyclization precursors via Suzuki coupling: preparation of compound **30***



A mixture of iodide **28** (546 mg, 1.00 mmol), boronic ester **29** (530 mg, 2.02 mmol),[36] dry K_3PO_4 (850 mg, 4.00 mmol), and $Pd(PPh_3)_4$ (116 mg, 0.100 mmol) in 1,4-dioxane (5 mL) was stirred at 100 °C for 22 h. Sodium hydroxide (41.3 mg, 1.03 mmol) and ethanol (0.83 mL) were added and the mixture was stirred for 1 h until GC/MS indicated complete hydrolysis of excess boronic ester **29**. At this point, water (30 mL) was added, the aqueous layer was extracted with EtOAc (3×20 mL), the combined organic phases were washed with aq satd NH_4Cl and brine, dried (Na_2SO_4), filtered and evaporated, and the residue was purified by flash chromatography (EtOAc/hexanes, 1:10→1:5) to provide compound **30** as an orange foam (201 mg, 36%). ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.72 (dd, J=7.7, 1.5 Hz, 1H, H-5), 7.68 (d, J=8.9 Hz, 2H, H-20), 7.36 (dd, J=2.0, 0.4 Hz, 1H, H-12), 7.31 (dd, J=8.8, <1 Hz, 1H, H-15), 7.26 (dd, J=8.8, 2.0 Hz, 1H, H-14), 7.21 (td, J=7.5, 1.5 Hz, 1H, H-7), 7.17 (td, J=7.6, 1.5 Hz, 1H, H-6), 7.06–7.04 (m, 1H, H-8), 7.01 (d, J=8.6 Hz, 2H, H-27), 6.69 (d, J=8.7 Hz, 2H, H-28), 6.55 (d, J=8.9 Hz, 2H, H-21), 4.70 (ddd, J=14.4, 8.3, 6.7 Hz, 1H, H-24a), 4.54 (ddd, J=14.4, 8.4, 6.3 Hz, 1H, H-24b), 4.18 (dq, J=10.8, 7.1 Hz, 1H, H-2a), 4.10 (dq, J=10.8, 7.1 Hz, 1H, H-2b), 3.72 (s, 3H, H-23), 3.68 (s, 3H, H-30), 3.08 (ddd, J=13.8, 8.2, 6.3 Hz, 1H, H-25a), 3.02 (ddd, J=13.7, 8.2, 6.8 Hz, 1H, H-25b), 1.09 (t, J=7.1 Hz, 3H, H-1); ^{13}C NMR (150 MHz, $CDCl_3$): δ=188.6 (C-18), 167.8 (C-3), 163.2 (C-22), 158.3 (C-29), 135.8 (C-16), 134.0 (C-17), 133.9 (C-9), 133.0 (C-8), 132.5 (C-20), 131.5 (C-4), 131.1 (C-7), 130.8 (C-19), 130.2 (C-26), 129.9 (C-5), 129.8 (C-27), 127.5 (C-11), 127.0 (C-6), 126.3 (C-13), 125.1 (C-14), 121.6 (C-10), 120.2 (C-12), 114.0 (C-28), 112.9 (C-21), 111.5 (C-15), 61.1 (C-2), 55.3 (C-23), 55.1 (C-30), 46.4 (C-24), 36.0 (C-25), 13.9 (C-1); ^{15}N NMR (60.8 MHz, $CDCl_3$, CH_3NO_2): δ=−242.7; IR (film): 3062, 2957, 2935, 2837, 1719, 1634, 1598, 1573, 1512, 1475, 1464, 1354, 1286, 1251, 1164, 1110, 1067, 1032, 965, 843, 824, 800, 779, 765, 722 cm^{-1}; MS (EI) m/z (%): 567 (37) [M$^+$], 446 (21), 433 (19), 400 (12), 362 (13), 360 (38), 134 (35), 121 (100), 91 (6), 77 (8); HRMS (ESI) calcd for $C_{34}H_{30}ClNO_5$+Na [(M+Na)$^+$]: 590.1705, found: 590.1708. Anal. Calcd for $C_{34}H_{30}ClNO_5$ (568.1): C 71.89, H 5.32, N 2.47; found: C 69.48, H 5.42, N 2.40.

4.1.10. *Methyl 3-iodo-1H-indole-2-carboxylate*

KOH (884 mg, 24.5 mmol) was added to solution of methyl indole-2-carboxylate (853 mg, 4.87 mmol) in DMF (4.5 mL) at 0 °C and the resulting mixture was stirred for 10 min before a solution of iodine (1.30 g, 5.12 mmol) in DMF (5.2 mL) was added over 7 min. Stirring was continued for 1.5 h at this temperature before the mixture was poured into aq satd NH_4Cl (50 mL) and $Na_2S_2O_3$ (50 mL) to precipitate the product. The solid material was filtered off, washed with water (10 mL) and dried under high vacuum to give the title compound as an off-white powder (1.29 g, 88%); mp=156–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.45 (br s, 1H), 7.60–7.55 (m, 1H), 7.43–7.34 (m, 2H), 7.28–7.20 (m, 1H), 4.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.3, 136.2, 131.4, 127.1, 126.7, 123.6, 121.7, 112.0, 66.2, 52.1; IR (KBr): 3310, 2949, 2845, 1699, 1691, 1508, 1434, 1334, 1255, 1205, 770, 742 cm^{-1}; MS (EI): m/z (%): 301 (94) [M$^+$], 269 (100), 241 (8), 215 (8), 114 (53), 88 (17), 62 (8); HRMS (ESI) calcd for $C_{10}H_8INO_2$+Na [(M+Na)$^+$]: 323.9492, found: 323.9490. Anal. Calcd for $C_{10}H_8INO_2$ (301.1): C 39.89, H 2.68, N 4.65; found: C 39.98, H 2.74, N 4.61.

4.1.11. *Methyl 3-iodo-1-methyl-1H-indole-2-carboxylate*

Methyl 3-iodo-1*H*-indole-2-carboxylate (500 mg, 1.66 mmol) was added in small portions to a suspension of NaH (59.9 mg, 2.50 mmol) in DMF (3.3 mL) at 0 °C. After the evolution of hydrogen had ceased, MeI (210 μL, 3.37 mmol) was introduced and the resulting mixture stirred for 1 h at ambient temperature. Addition of water (15 mL) precipitated the crude material which was filtered off and washed with water. Recrystallization from Et_2O afforded the title compound as a white solid (390 mg, 74%); mp=74–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.57 (ddd, J=8.1, 1.1, <1 Hz, 1H), 7.40 (ddd, J=8.3, 6.7, 1.2 Hz, 1H), 7.34 (ddd, J=8.5, 1.0, 0.9 Hz, 1H), 7.27–7.20 (m, 1H), 4.07 (s, 3H), 3.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=161.8, 139.0, 130.3, 128.8, 126.1, 124.0, 121.5, 110.4, 66.6, 51.6, 33.0; IR (KBr): 3017, 2949, 2837, 1706, 1501, 1461, 1433, 1371, 1221, 1160, 1105, 744 cm^{-1}; MS (EI) m/z (%): 315 (100) [M$^+$], 284 (17), 256 (6), 215 (7), 158 (10), 129 (13), 114 (9), 89 (15); HRMS (ESI) calcd for $C_{11}H_{10}INO_2$+Na [(M+Na)$^+$]: 337.9648, found: 337.9650. Anal. Calcd for $C_{11}H_{10}INO_2$ (315.1): C 41.93, H 3.20, N 4.45; found: 41.80, H 3.20; N 4.42.

4.1.12. *Compound **32***

A solution of indole methyl 3-iodo-1-methyl-1*H*-indole-2-carboxylate, pinacolborane (140 μL, 0.965 mmol), Et_3N (270 μL, 1.91 mmol) and $[(dppf)PdCl_2]\cdot CH_2Cl_2$ (15.8 mg, 0.193 mmol) in 1,4-dioxane (3.2 mL) was stirred for 8.5 h at 100 °C. For work-up, the mixture was diluted with EtOAc (20 mL), the combined organic phases were washed with water, aq satd NH_4Cl (2×10 mL), and brine (2×10 mL), dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 8:1) to give compound **32** as colorless crystals (177 mg, 88%); mp=91–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.87 (dt, J=8.1, 1.0 Hz, 1H), 7.40–7.30 (m, 2H), 7.17 (ddd, J=8.0, 6.3, 1.6 Hz, 1H), 4.02 (s, 3H), 3.92 (s, 3H), 1.43 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=163.1, 139.6, 131.0, 124.7, 123.4, 120.9, 110.1, 83.5, 51.6, 31.7, 25.0; IR (KBr): 3054, 2978, 2945, 1711, 1611, 1528, 1469, 1388, 1300, 1250, 1226, 1144, 1108, 978, 858, 745 cm^{-1}; MS (EI) m/z (%): 315 (100) [M$^+$], 257 (81), 242 (59), 214 (22), 198 (72), 184 (80), 171 (23), 156 (21), 115 (25); HRMS (ESI) calcd for $C_{17}H_{22}BNO_4$+Na [(M+Na)$^+$]: 338.1534, found: 338.1531. Anal. Calcd for $C_{17}H_{22}BNO_4$ (315.2): C 64.78, H 7.04, N 4.44; found: C 64.71, H 6.95, N 4.35.

4.1.13. *Compound **34***

A mixture containing compound **32** (300 mg, 0.952 mmol), 2-bromo benzophenone (**33**, 379 mg, 1.45 mmol), anhydrous K_3PO_4 (612 mg, 2.88 mmol) and $Pd(PPh_3)_4$ (54.2 mg, 46.9 μmol) in 1,4-dioxane (4.8 mL) was stirred at 100 °C for 7.5 h. For work up, the mixture was diluted with EtOAc (30 mL) before it was washed with water and brine (15 mL each), the organic layer was dried over Na_2SO_4 and evaporated, and the residue purified by flash chromatography (hexanes/EtOAc, 10:1) to give product **34** as a white solid (323 mg, 92%); mp=118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.70 (ddd, J=7.6, 1.5, 0.5 Hz, 1H), 7.62 (td, J=7.6, 1.5 Hz, 1H), 7.54–7.46 (m, 2H), 7.43–7.39 (m, 1H), 7.37–7.33 (m, 2H), 7.29 (ddd, J=8.5, 6.9, 1.2 Hz, 1H), 7.21–7.14 (m, 3H), 7.09 (ddd, J=8.0, 6.9, 1.1 Hz, 1H), 7.00–6.94 (m, 1H), 3.82 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.4, 162.3, 140.1, 138.1, 137.8, 134.3, 131.6, 131.4, 130.2, 129.0, 128.7, 127.1, 127.1, 126.9, 125.5, 125.2, 122.6, 121.6, 120.8, 109.8, 51.4, 31.7; IR (film): 3396, 3291, 3058, 3031, 2953, 1709, 1658, 1599, 1537, 1467, 1440, 1333, 1318, 1287, 1264, 1247, 1200, 1111, 968, 945, 935, 920, 808, 766, 746, 708 cm^{-1}; MS (EI) *m*/*z* (%): 369 (34) [M$^+$], 310 (100); HRMS (ESI) calcd for $C_{24}H_{19}NO_3$+Na [(M+Na)$^+$]: 392.1257, found: 392.1254. Anal. Calcd for $C_{24}H_{19}NO_3$ (369.4): C 78.03, H 5.18, N 3.79; found: C 77.94, H 5.24, N 3.70.

The following compounds were prepared analogously:

4.1.14. Acid **36a**

Off-white foam; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.84 (d, *J*=9.1 Hz, 2H), 7.80–7.76 (m, 1H), 7.56–7.44 (m, 3H), 7.39–7.30 (m, 3H), 7.08–7.04 (m, 1H), 6.90 (d, *J*=8.8 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=189.4, 170.2, 164.5, 140.4, 139.3, 137.6, 133.4, 132.7, 130.9, 130.8, 130.6, 129.7, 129.2, 129.1, 128.6, 128.0, 127.3, 113.9, 55.6; IR (film): 3012, 2970, 2840, 1737, 1724, 1689, 1649, 1593, 1574, 1508, 1366, 1253, 1229, 1217, 1150, 1023, 929, 844, 749 cm^{-1}; MS (EI) *m*/*z* (%): 332 (8) [M$^+$], 287 (100), 271 (5), 197 (26), 181 (5), 152 (8), 135 (23), 107 (5) 77 (8); HRMS (ESI) calcd for $C_{21}H_{16}O_4$+Na [(M+Na)$^+$]: 355.0941, found: 355.0941. Anal. calcd for $C_{21}H_{16}O_4$ (332.3): C 75.89, H 4.85; found: C 75.77, H 4.82.

4.1.15. Acid **42**

White foam; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.67 (d, *J*=8.8 Hz, 2H), 7.56–7.35 (m, 5H), 6.96 (d, *J*=4.8 Hz, 1H), 6.74 (d, *J*=8.8 Hz, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.2, 166.2, 163.4, 147.8, 139.2, 134.9, 132.5, 132.4, 131.3, 130.6, 130.0, 129.7, 128.5, 127.6, 127.2, 113.3, 55.4; IR (film): 3600 (br), 1658, 1598, 1509, 1421, 1293, 1259, 1152, 933, 847, 785, 766 cm^{-1}; MS (EI) *m*/*z* (%): 338 (39) [M$^+$], 293 (100), 203 (99), 187 (8), 135 (52), 92 (13), 77 (20); HRMS (ESI) calcd for $C_{19}H_{14}O_4S$+Na [(M+Na)$^+$]: 361.0505, found: 361.0505. Anal. Calcd for $C_{19}H_{14}O_4S$ (338.4): C 67.44, H 4.17; found: C 67.32, H 4.22.

4.1.16. Amide **36c**

Yellow solid; mp=158–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.89 (d, *J*=8.8 Hz, 2H), 7.70 (dd, *J*=7.8, 0.8 Hz, 1H), 7.54–7.31 (m, 6H), 7.23–7.18 (m, 1H), 6.96 (d, *J*=9.1 Hz, 2H), 6.93 (d, *J*=7.6 Hz, 1H), 5.37–5.19 (br s, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.5, 171.5, 164.3, 141.0, 138.2, 136.3, 133.1, 131.0, 130.3, 129.7, 129.5, 128.7, 128.3, 128.0 (2C), 127.9, 126.9, 113.9, 55.6; IR (film): 3333 (br), 3184 (br), 3059, 3962, 2931, 2840, 1666, 1646, 1593, 1575, 1509, 1317, 1305, 1293, 1256, 1151, 931, 754, 730 cm^{-1}; MS (EI): *m*/*z* (%): 331 (<1) [M$^+$], 287 (69) [M$^+$−$CONH_2$], 196 (100), 135 (10); HRMS (ESI) calcd for $C_{21}H_{17}NO_3$+Na [(M+Na)$^+$]: 354.1101, found: 354.1103. Anal. Calcd for $C_{21}H_{17}NO_3$ (331.4): C 76.12, H 5.17, N 4.23; found: C 76.04, H 5.11, N 4.05.

4.1.17. Compound **38**

Yellow solid; mp=119–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.68 (d, *J*=8.8 Hz, 2H), 7.62 (ddd, *J*=7.4, 7.3, 2.0 Hz, 1H), 7.60–7.51 (m, 3H), 7.51–7.48 (m, 1H), 7.48–7.43 (m, 1H), 7.35–7.32 (m, 1H), 7.29 (td, *J*=7.6, 1.3 Hz, 1H), 6.82 (d, *J*=8.8 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.0, 163.5, 144.3, 139.5, 137.4, 132.9, 132.4, 132.1, 131.0, 130.6, 130.3, 130.1, 129.1, 128.4, 127.7, 118.2, 113.5, 112.1, 55.4; IR (film): 3061, 2966, 2936, 2840, 2225, 1656, 1597, 1575, 1509, 1468, 1436, 1420, 1291, 1259, 1177, 1151, 1027, 930, 846, 761 cm^{-1}; MS (EI) *m*/*z* (%): 313 (38) [M$^+$], 177 (6), 151 (7), 135 (100), 107 (6), 92 (9), 77 (12); HRMS (ESI) calcd for $C_{21}H_{15}NO_2$+Na [(M+Na)$^+$]: 336.0995, found: 336.0995. Anal. Calcd for $C_{21}H_{15}NO_2$ (313.3): C, 80.49, H 4.82, N 4.47; found: C 80.33, H 4.92, N 4.41.

4.1.18. Compound **40**

Yellow solid; mp=159–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.73–7.66 (m, 3H), 7.62–7.47 (m, 5H), 7.45–7.40 (m, 1H), 6.78 (d, *J*=8.8 Hz, 2H), 3.81 (s, 3H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.0, 168.0, 167.8, 160.4, 139.0, 139.0, 136.3, 136.2, 133.1, 132.6, 132.5, 130.8, 130.3, 130.0, 129.2, 128.2, 128.0, 122.2, 113.3, 55.4, 23.7; IR (film): 3452, 3016, 2970, 2947, 2841, 1768, 1738, 1706, 1655, 1595, 1575, 1436, 1378, 1253, 1151, 1004, 929, 739 cm^{-1}; MS (EI) *m*/*z* (%): 371 (24) [M$^+$], 236 (100), 207 (6), 157 (6), 135 (32), 77 (6); HRMS (ESI) calcd for $C_{23}H_{17}NO_4$+Na [(M+Na)$^+$]: 394.1050, found: 394.1051.

4.1.19. Acid fluoride **36b**

Cyanuric fluoride (0.53 mL, 6.2 mmol) was added dropwise to a solution of acid **36a** (407 mg, 1.22 mmol) in CH_2Cl_2 (12 mL) and pyridine (110 μL, 1.36 mmol) at 0 °C. The mixture was stirred at ambient temperature for 3 h before the reaction was quenched with water (5 mL) and the mixture diluted with CH_2Cl_2 (10 mL). The organic phase was washed several times with water until it became clear, dried (Na_2SO_4), filtered, and evaporated to provide the title compound as a colorless oil (382 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.94 (dd, *J*=7.8, 1.3 Hz, 1H), 7.69 (d, *J*=8.8 Hz, 2H), 7.56–7.43 (m, 4H), 7.41–7.36 (m, 1H), 7.35–7.29 (m, 2H), 6.82 (d, *J*=8.8 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=195.9, 163.5, 156.6 (d, J_{CF}=347 Hz), 144.1 (d, J_{CF}=4.4 Hz), 139.6, 138.3, 133.7, 132.5, 132.2 (d, J_{CF}=2.9 Hz), 131.9 (d, J_{CF}=1.8 Hz), 130.4, 130.1, 129.9, 128.8, 127.8, 127.6, 123.9 (d, J_{CF}=57.6 Hz), 113.4, 55.4; ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$): δ=30.1; IR (film): 3062, 2965, 2936, 2841, 1814, 1654, 1598, 1575, 1509, 1315, 1290, 1258, 1229, 1177, 1152, 1023, 998, 930, 847, 755 cm^{-1}; MS (EI): *m*/*z* (%): 334 (30) [M$^+$], 287 (100), 199 (7), 170 (11), 135 (58), 77 (12); HRMS (ESI) calcd for $C_{21}H_{15}FO_3$+Na [(M+Na)$^+$]: 357.0897, found: 357.0901.

*4.1.20. 2-(4-Methoxybenzyl)benzaldehyd (**47**)*

A solution of *p*-methoxybenzylmagnesium chloride (0.55 M in THF, 24.0 mL 13.2 mmol) was added over 10 min to a solution of 9-MeO-9-BBN (1.80 mL, 13.4 mmol) in THF (25 mL) at −78 °C. Once the addition was completed, the mixture was stirred at ambient temperature for 30 min before the resulting solution of borate **45** was diluted with DMF (100 mL) and degassed by two freeze–thaw cycles. Aldehyde **46** (1.50 mL, 12.9 mmol) was added, followed by $Pd(OAc)_2$ (29.1 mg, 0.130 mmol) and *S*-Phos (106 mg, 0.258 mmol),[37] and the resulting mixture was stirred at 110 °C for 5 h until GC/MS indicated complete conversion of the substrate. The mixture was diluted with *tert*-butyl methyl ether (200 mL), the organic layer was washed with water (200 mL) and brine (3×100 mL), dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography (EtOAc/hexanes, 1:20) to provide the title compound as a pale yellow oil (2.28 g, 78%) Even though some boron impurities were visible by ^{1}H NMR, the material was used in the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.27 (s, 1H), 7.85 (dd, *J*=7.7, 1.4 Hz, 1H), 7.52 (td, *J*=7.5, 1.5 Hz, 1H), 7.40 (td, *J*=7.5, <1 Hz, 1H), 7.28–7.24 (m, 1H), 7.06 (d, *J*=8.7 Hz, 2H), 6.82 (d, *J*=8.7 Hz, 2H), 4.39 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.4, 158.1, 143.5, 133.9, 133.9, 132.4, 131.9, 131.5, 129.7, 126.9, 114.0, 55.2, 37.1; IR (film): 2932, 2835, 2753, 1696, 1611, 1599, 1511, 1301, 1247, 1178, 1035, 843, 818, 773, 755 cm^{-1}; MS (EI) *m*/*z* (%): 226 (100) [M$^+$], 209 (95), 195 (35), 181 (12), 178 (13), 165 (45), 152 (23), 121 (11), 118 (37), 90 (31), 77 (12), 51 (7); HRMS (ESI) calcd for $C_{15}H_{14}O_2$+Na [(M+Na)$^+$]: 249.0886, found: 249.0888.

4.1.21. Compound **48a**

MeLi (1.64 M in Et_2O, 9.0 mL, 14.8 mmol) was added over 7 min to a solution of *N*-(*tert*-butoxycarbonyl)-2-bromoaniline (4.01 g, 14.7 mmol) in THF (75 mL) at −78 °C and the mixture was stirred for 15 min. *tert*-BuLi (2.87 M in pentanes, 10.0 mL, 28.7 mmol) was then added dropwise and the mixture was stirred for 80 min before a solution of aldehyde **47** (2.27 g, 10.0 mmol) in THF (25 mL) was added over 25 min. The resulting mixture was stirred for 25 min before the reaction was carefully quenched with water (10 mL) at

−78 °C and the mixture allowed to reach ambient temperature. The mixture was diluted with brine (100 mL), the aqueous phase was extracted with *tert*-butyl methyl ether (3×100 mL), the combined organic layers were dried (Na_2SO_4), filtered, and evaporated, and the residue was purified by flash chromatography (EtOAc/hexanes, 1:12→1:3+1% Et_3N) to provide *tert*-butyl-2-(hydroxy(2-(4-methoxybenzyl)phenyl)methyl)phenylcarbamate as a white foam (3.41 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.76 (d, J=7.9 Hz, 1H), 7.57 (d, J=7.3, 1.8 Hz, 1H), 7.36–7.24 (m, 4H), 7.14 (dd, J=7.2, 1.6 Hz, 1H), 6.98–6.90 (m, 3H), 6.83 (dd, J=7.7, 1.6 Hz, 1H), 6.77 (d, J=8.8 Hz, 1H), 6.77 (d, J=8.8 Hz, 2H), 6.06 (br s, 1H), 3.79 (br s, 2H), 3.76 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=158.0, 153.8, 139.7, 138.4, 137.0, 132.5, 132.1, 130.7, 129.6, 128.7, 128.1, 128.0, 126.9, 126.8, 123.9, 122.6, 114.0, 80.5, 70.4, 55.2, 37.8, 28.3; IR (film): 3391, 2978, 2933, 2835, 1726, 1704, 1611, 1588, 1512, 1450, 1392, 1368, 1302, 1246, 1159, 1026, 837, 759, 739 cm^{-1}; MS (EI): *m*/*z* (%): 401 (2) [$(M-H_2O)^+$], 345 (100), 300 (71), 269 (28), 237 (25), 225 (28), 208 (75), 165 (20), 121 (12), 57 (99), 41 (26), 29 (16); HRMS (ESI) calcd for $C_{26}H_{29}NO_4$+Na [$(M+Na)^+$]: 442.1989; found: 442.1987.

TPAP (141 mg, 0.402 mmol)[38] was added to a mixture containing this alcohol (3.39 g, 8.07 mmol), carefully dried NMO (1.42 g, 12.1 mmol, dried by aceotropic distillation with toluene and drying in high vacuum) and molecular sieves 3 Å (6.7 g) in CH_2Cl_2 (160 mL), and the resulting suspension was stirred for 3 h at ambient temperature. For work-up, the mixture was adsorbed on silica, which was loaded on top of a flash column packed with silica. The product was eluted with EtOAc/hexanes (1:10), giving compound **48a** as a colorless oil which solidified on standing (2.96 g, 88%); mp=78–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.72 (br s, 1H), 8.46 (dd, J=8.6, 1.0 Hz, 1H), 7.48 (ddd, J=7.5, 7.4, 1.7 Hz, 1H), 7.42–7.37 (m, 1H), 7.28–7.23 (m, 2H), 7.20 (dd, J=8.0, 1.6 Hz, 2H), 6.94 (d, J=8.8 Hz, 2H), 6.85–6.80 (m, 1H), 6.70 (d, J=8,6 Hz, 2H), 3.93 (s, 2H), 3.71 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=202.2, 158.0, 153.1, 142.4, 139.8, 139.7, 135.0, 134.6, 132.2, 130.5, 130.2, 130.0, 127.9, 125.7, 122.1, 120.5, 119.0, 113.8, 80.7, 55.2, 38.2, 28.3; IR (film): 3275, 3065, 2978, 2932, 2835, 1730, 1636, 1605, 1581, 1512, 1448, 1392, 1367, 1249, 1150, 832, 753 cm^{-1}; MS (EI): *m*/*z* (%): 417 (21) [M^+], 361 (52), 317 (50), 299 (97), 224 (100), 208 (56), 181 (21), 165 (12), 152 (10), 120 (11), 57 (54), 41 (17); HRMS (ESI) calcd for $C_{26}H_{27}NO_4$+Na [$(M+Na)^+$]: 440.1832, found: 440.1837. Anal. Calcd for $C_{26}H_{27}NO_4$ (417.5): C 74.80, H 6.52, N 3.35; found: C 74.65, H 6.41, N 3.28.

*4.1.22. 2-Amino-2′-(4-methoxybenzyl)benzophenone (**48b**)*

A suspension of **48a** (2.88 g, 6.91 mmol) in ethanol (30 mL) and aq HCl (2 M, 30 mL) was refluxed for 1.5 h. The resulting yellow solution was cooled to 0 °C before aq NaOH (2 M, 35 mL) was added. The mixture was extracted with *tert*-butyl methyl ether (3×100 mL) and the combined organic phases where washed with brine (20 mL), dried (Na_2SO_4) and evaporated to provide the title compound as a yellow oil which was used without further purification (2.24 g, quant.). ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.34 (ddd, J=7.6, 7.2, 1.8 Hz, 1H), 7.27–7.22 (m, 3H), 7.20 (dq, J=7.8, 0.5 Hz, 1H), 7.15 (dd, J=8.1, 1.3 Hz, 1H), 7.00 (d, J=8.7 Hz, 2H), 6.73 (d, J=8.7 Hz, 2H), 6.68 (dd, J=8.3, 0.7 Hz, 1H), 6.48 (ddd, J=8.1, 7.1, 1.1 Hz, 1H), 6.42–6.28 (br s, 2H), 3.88 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=201.1, 157.9, 151.1, 140.5, 139.1, 134.9, 134.7, 132.5, 130.2, 130.1, 129.2, 127.3, 125.6, 118.5, 116.7, 115.5, 113.7, 55.2, 38.0; IR (film): 3472, 3343, 3061, 3024, 2997, 2954, 2929, 2849, 2835, 1724, 1616, 1582, 1547, 1511, 1478, 1450, 1301, 1248, 1035, 934, 840, 754 cm^{-1}; MS (EI) *m*/*z* (%): 317 (86) [M^+], 299 (69), 266 (8), 224 (100), 209 (20), 181 (28), 165 (12), 152 (12), 120 (19), 92 (11), 65 (9); HRMS (ESI) calcd for $C_{21}H_{19}NO_2$+Na [$(M+Na)^+$]: 340.1308, found: 340.1305. Anal. Calcd for $C_{21}H_{19}NO_2$ (317.4): C 79.47, H 6.03, N 4.41; found: C 79.33, H 6.09, N 4.32.

*4.1.23. Compound **49***

MeO_2CCOCl (350 µL, 3.80 mmol) was added to a solution of aniline **48b** (996 mg, 3.14 mmol) in CH_2Cl_2 (30 mL) and pyridine (1.3 mL, 16.1 mmol) at −20 °C and the resulting mixture was stirred for 30 min before the reaction was quenched with water (60 mL). The product was extracted with CH_2Cl_2 (3×40 mL), the combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (EtOAc/hexanes, 1:2) to provide the corresponding amide as a white foam (1.18 g, 93%). ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.71 (dd, J=8.4, 1.0 Hz, 1H), 7.59–7.55 (m, 1H), 7.43 (td, J=7.5, 1.5 Hz, 1H), 7.31–7.23 (m, 5H), 7.03 (ddd, J=7.9, 7.4, 1.1 Hz, 1H), 6.85 (d, J=8.8 Hz, 2H), 6.63 (d, J=8.7 Hz, 2H), 4.00 (s, 3H), 3.94 (s, 2H), 3.68 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=202.2, 160.7, 157.9, 154.8, 140.1, 139.1 (2C), 134.9, 134.3, 131.9, 130.7, 130.4, 130.2, 128.2, 125.9, 123.9, 123.6, 120.8, 113.7, 55.1, 53.9, 38.5; IR (film): 3232, 3064, 3007, 2954, 2909, 2836, 1765, 1737, 1714, 1642, 1582, 1602, 1523, 1512, 1450, 1437, 1292, 1255, 1163, 1034, 936, 838, 765 cm^{-1}; MS (EI) *m*/*z* (%): 403 (38) [M^+], 385 (100), 325 (36), 316 (26), 300 (38), 236 (10), 224 (11), 208 (75), 197 (14), 194 (10), 181 (15), 165 (17), 152 (13), 146 (14); HRMS (ESI) calcd for $C_{24}H_{22}NO_5$ [$(M+H)^+$]: 404.1492, found: 404.1491. Anal. calcd for $C_{24}H_{21}NO_5$ (403.4): C 71.45, H 5.25, N 3.47; found: C 71.35, H 5.36, N 3.39.

A solution of CrO_3 (345 mg, 3.45 mmol) in acidic acid (2.7 mL) and water (1.6 mL) was added to a solution of this amide (499 mg, 1.24 mmol) in acidic acid (12.4 mL) and the resulting mixture stirred for 7 h before water (50 mL) was introduced and the product extracted with EtOAc (2×40 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (EtOAc/hexanes, 1:1.5→1:0) to provide compound **49** as an off-white solid (477 mg, 93%); mp=135–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=12.0 (br s, 1H), 8.55 (d, J=8.3 Hz, 1H), 7.70–7.58 (m, 4H), 7.56–7.49 (m, 3H), 7.36 (dd, J=7.8, 1.5 Hz, 1H), 7.08–7.03 (m, 1H), 6.81 (d, J=8.8 Hz, 2H), 3.96 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=200.0, 194.7, 163.6, 160.5, 154.4, 140.4, 139.5, 138.2, 134.7, 133.5, 132.2, 130.8, 130.7, 130.3, 129.6, 128.9, 124.9, 123.8, 120.8, 113.7, 55.4, 53.8; IR (film): 3456, 3282, 2971, 2864, 1734, 1641, 1598, 1582, 1524, 1451, 1421, 1366, 1301, 1291, 1269, 1257, 1229, 1217, 1150, 1113, 937, 762 cm^{-1}; MS (EI) *m*/*z* (%): 417 (26) [M^+], 358 (61), 250 (100), 135 (20), 77 (6); HRMS (ESI) calcd for $C_{24}H_{19}NO_6$+Na [$(M+Na)^+$]: 440.1105, found: 440.1104. Anal. Calcd for $C_{24}H_{19}NO_6$ (417.4): C 69.06, H 4.59, N 3.36; found: C 68.94, H 4.51, N 3.28.

*4.1.24. Representative procedure for reductive carbonyl coupling reactions. Preparation of indole **20***

CAUTION: KC_8 is pyrophoric and must be handled with care under Ar! Dry DME (30 mL) was carefully added to a mixture of $TiCl_3$ (301 mg, 1.95 mmol) and KC_8 (527 mg, 3.90 mmol)[39] at 0 °C under Ar and the resulting suspension was refluxed for 1.5 h. A solution of ketoamide **19** (150 mg, 0.24 mmol) in dry DME (5 mL) was then introduced and the mixture was refluxed until TLC indicated complete conversion of the substrate (ca. 1.5 h). After reaching ambient temperature, the mixture was filtered through a plug of Celite layered on silica, which was carefully rinsed with EtOAc/toluene (1:1, 120 mL), and the combined filtrates were evaporated. Purification of the residue by flash chromatography (EtOAc/hexanes, 1:4) yielded indole **20** as a pale yellow solid (83 mg, 59%). ^{1}H NMR (400 MHz, C_6D_6): 8.11 (s, 1H), 7.50 (m, 2H), 7.36 (m, 2H), 7.33 (m, 1H), 6.98 (t, J=7.9 Hz, 1H), 6.87 (m, 1H), 6.80 (m, 2H), 6.75–6.70 (m, 4H), 6.64–6.62 (m, 3H), 6.42 (m, 1H), 3.57 (t, J=7.1 Hz, 2H), 3.43 (s, 3H), 3.31 (s, 3H), 3.24 (s, 3H), 3.18 (s, 3H), 2.67 (t, J=7.1 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6): δ=160.0, 159.0, 158.1, 146.0, 133.3, 130.8, 130.3, 130.0, 129.7, 128.9, 127.4, 125.0, 122.0, 120.6, 119.1, 118.7, 116.9, 116.1, 114.7, 114.6, 114.3, 114.3, 114.1, 103.5, 94.0, 82.4, 54.9, 54.8, 54.7, 54.6, 51.5, 37.4; IR (film): 3342, 3000, 2957, 2934, 2836, 2206, 1606, 1578, 1546, 1512, 1462, 1441, 1289, 1248, 1177, 1095, 1031, 832, 785 cm^{-1}; MS (EI) m/z (%): 582 (100) [M^{+}], 461 (17), 448 (15), 446 (10); HRMS (EI) m/z: calcd for $C_{38}H_{34}N_2O_4$: 582.2518; found: 582.2523.

4.1.25. *Representative procedure for reductive arene syntheses via the 'instant method': preparation of compound **39***

A suspension containing nitrile **38** (46.6 mg, 0.149 mmol), $TiCl_3$ (334 mg, 2.17 mmol) and zinc dust (288 mg, 4.40 mmol) in DME (15 mL) was stirred under reflux until TLC showed complete consumption of the substrate. For work up, the filtrate was evaporated, the residue suspended in EtOAc (20 mL) and the suspension vigorously stirred with a solution of Na_4EDTA (1 M in water, 20 mL) for 20 min. The mixture was extracted with EtOAc (2×20 mL), the combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and evaporated, and the residue was purified by flash chromatography (EtOAc/hexanes, 1:6) to provide aniline **39** as a white solid (40.0 mg, 90%); mp=175–176 °C (Ref. 40: 179–181 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.79–8.76 (m, 1H), 8.67–8.63 (m, 1H), 7.98–7.95 (m, 1H), 7.73–7.64 (m, 2H), 7.47–7.38 (m, 2H), 7.36–7.32 (m, 3H), 7.13 (d, J=8.8 Hz, 2H), 4.04 (br, 2H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.1, 137.0, 133.5, 132.3, 130.6, 129.7, 126.7, 126.5, 126.5, 125.8, 125.2, 125.1, 123.3, 123.1, 122.4, 121.6, 117.8, 114.9, 55.3; IR (KBr): 3441, 3363, 3073, 3004, 2953, 2898, 2833, 1622, 1605, 1588, 1573, 1508, 1493, 1433, 1398, 1283, 1245, 1175, 1103, 1031, 844, 814, 755, 723 cm^{-1}; MS (EI): m/z (%): 299 (100) [M^{+}], 284 (15), 254 (10), 239 (7); HRMS (EI) calcd for $C_{21}H_{17}NO$: 299.1310; found: 299.1308. The analytical data are consistent with those previously reported.[41]

The following products were prepared analogously:

4.1.26. *Compound **31a***

White solid; mp >165 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.70 (d, J=8.3 Hz, 1H), 8.50 (d, J=2.0 Hz, 1H), 8.40 (dd, J=8.3, 0.8 Hz, 1H), 7.56 (ddd, J=8.3, 7.1, 1.3 Hz, 1H), 7.51 (ddd, J=8.2, 6.9, 1.0 Hz, 1H), 7.45 (d, J=8.6 Hz, 2H), 7.34 (dd, J=8.6, 2.0 Hz, 1H), 7.28 (d, J=8.7 Hz, 1H), 7.15 (d, J=8.6 Hz, 2H), 6.73 (d, J=8.8 Hz, 2H), 6.66 (d, J=8.8 Hz, 2H), 5.46 (s, 1H), 4.00–3.90 (m, 5H), 3.77 (s, 3H), 2.65–2.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.6, 158.3, 149.4, 138.0, 137.2, 132.8, 130.0, 129.7, 129.4, 127.9, 125.6, 124.9, 124.6, 123.7, 123.0, 122.8, 122.6, 120.7, 120.2, 115.6, 113.8, 110.1, 109.1, 108.7, 55.5, 55.3, 45.6, 34.5; IR (film): 3515, 3068, 3030, 3003, 2954, 2933, 2835, 1622, 1608, 1576, 1512, 1305, 1247, 1217, 1176, 1150, 1032, 873, 822, 761 cm^{-1}; MS (EI) m/z (%): 507 (100) [M^{+}], 386 (61), 351 (91), 135 (7). Anal. Calcd for $C_{32}H_{26}ClNO_3$ (508.0): C 75.66, H 5.16, N 2.76; found: C 75.56, H 5.20, N 2.71.

4.1.27. *Compound **31b***

Formed as minor by-product during the titanium-mediated cyclization of oxo-ester **30**; this compound can be separated form the major product **31a** by flash chromatography using hexanes/EtOAc (4:1) as the eluent. White solid; mp=148–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.76 (d, J=8.3 Hz, 1H), 8.56 (d, J=1.3 Hz, 1H), 8.28 (d, J=8.3 Hz, 1H), 7.79–7.72 (m, 1H), 7.57–7.45 (m, 3H), 7.42–7.32 (m, 2H), 7.09 (d, J=8.6 Hz, 2H), 6.74–6.62 (m, 4H), 4.08–3.99 (m, 2H), 3.94 (s, 3H), 3.84–3.70 (m, 5H), 2.65–2.53 (m, 2H), 1.14 (t, J=7.2 Hz, 3H); IR (KBr): 3069, 2932, 2835, 1610, 1569, 1512, 1471, 1447, 1348, 1303, 1286, 1246, 1176, 1096, 1078, 1033, 822, 764 cm^{-1}; MS (EI) m/z (%): 535 (79) [M^{+}], 414 (8), 385 (100), 350 (13), 135 (29); HRMS (ESI) calcd for $C_{34}H_{30}ClNO_3$+Na [(M+Na)$^{+}$]: 558.1806; found: 558.1813.

4.1.28. *Compound **35b***

The crude product consists of a ~5:1 mixture of phenol **35a** and methyl ether **35b** which could not be separated by flash chromatography. This mixture was reacted with MeI and NaH in DMF to generate pure **35b**, which was isolated by flash chromatography (hexanes/EtOAc, 10:1→2:1) as a beige solid; mp=216–219 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.85 (d, J=8.1 Hz, 1H), 8.63 (d, J=8.1 Hz, 1H), 7.71–7.46 (m, 9H), 7.42 (ddd, J=8.0, 6.9, 1.0 Hz, 1H), 7.35 (ddd, J=8.3, 7.0, 1.2 Hz, 1H), 4.29 (s, 3H), 3.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=144.5, 140.9, 136.6, 132.1, 131.4, 130.0, 129.2, 128.2, 127.7, 127.3, 126.9, 125.6, 124.4, 123.6, 123.0, 123.0, 122.0, 120.1, 117.3, 109.4, 61.5, 31.5; IR (KBr): 3060, 3029, 2957, 2930, 2828, 1610, 1577, 1554, 1519, 1498, 1476, 1379, 1294, 1262, 1080, 1005, 769, 745, 702 cm^{-1}; MS (EI) m/z (%): 337 (100) [M^{+}], 322 (17), 307 (12), 294 (29), 278 (13), 153 (7), 139 (5); HRMS (EI) calcd for $C_{24}H_{19}NO$: 337.1367; found: 337.1465. Anal. Calcd for $C_{24}H_{19}NO$ (337.4): C 85.43, H 5.68, N 4.15; found: C 80.91, H 5.45, N 3.60.

4.1.29. *10-(4-Methoxyphenyl)phenanthren-9-ol (**37**)*

Mp=198–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.75 (m, 1H), 8.68 (d, J=8.1 Hz, 1H), 8.42–8.39 (m, 1H), 7.75–7.65 (m, 2H), 7.53–7.43 (m, 3H), 7.41 (d, J=8.7 Hz, 2H), 7.16 (d, J=8.7 Hz, 2H), 5.52 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.9, 146.4, 132.9, 132.7, 131.0, 127.1, 126.8, 126.6, 126.4, 126.1, 125.4, 125.0, 123.9, 123.0, 122.6, 122.5, 116.9, 115.3, 55.4; IR (KBr): 3480, 3074, 3025, 2966, 2937, 2839, 1605, 1596, 1509, 1494, 1449, 1296, 1246, 1208, 1184, 1072, 1021, 854, 763, 727 cm^{-1}; MS (EI) m/z (%): 300 (100) [M^{+}], 285 (7), 271 (8), 257 (9); HRMS (EI) calcd for $C_{21}H_{16}O_2$: 300.1150, found: 300.1147. Anal. Calcd for $C_{21}H_{16}O_2$ (300.4): C 83.98, H 5.37; found: C 83.88, H 5.31.

4.1.30. *Compound **41***

Yellow solid; recrystallization from EtOAc provided a crystal suitable for X-ray structure analysis; mp=156–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.63 (d, J=7.8 Hz, 1H), 8.58 (dd, J=8.1, 0.8 Hz, 1H), 8.13 (dd, J=7.1, 0.5 Hz, 1H), 7.84 (dd, J=8.0, 7.2 Hz, 1H), 7.58–7.44 (m, 3H), 7.36 (d, J=8.8 Hz, 2H), 7.07 (d, J=8.6 Hz, 2H), 3.94 (s, 3H), 2.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.6, 159.7, 135.7, 134.4, 132.2, 128.7, 127.4, 127.4, 127.1, 126.8, 126.3, 125.9, 125.3, 123.6, 122.8, 119.3, 113.9, 55.4, 28.6; IR (KBr): 2943, 2834, 1702, 1638, 1624, 1605, 1512, 1475, 1454, 1295, 1247, 1020, 841, 760, 717 cm^{-1}; MS (EI) m/z (%): 339 (100) [M^{+}], 294 (5); HRMS (ESI) calcd for $C_{23}H_{17}NO_2$+Na [(M+Na)$^{+}$]: 362.1151, found: 362.1151. Anal. Calcd for $C_{23}H_{17}NO_2$ (339.4): C 81.40, H 5.05, N 4.13; found: C 81.34, H 5.10, N 4.06.

4.1.31. *Compound **43***

Mp=202–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.33 (d, J=8.1 Hz, 1H), 8.02 (d, J=5.3 Hz, 1H), 7.64 (d, J=5.3 Hz, 1H), 7.54–7.44 (m, 2H), 7.43–7.36 (m, 3H), 7.15 (d, J=8.3 Hz, 2H), 5.56 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.9, 145.5, 137.6, 132.7, 132.5, 128.3, 126.5, 125.7, 125.6, 125.3, 123.7, 123.7, 122.4, 116.5, 115.2, 55.4; IR (KBr): 3467, 3100, 3068, 3029, 2966, 2937, 2839, 1607, 1555, 1513, 1476, 1450, 1441, 1245, 1211, 1182, 1020, 838, 767, 734 cm^{-1}; MS (EI): m/z (%): 306 (100) [M^{+}], 291 (11), 234 (6); HRMS (EI) calcd for $C_{19}H_{14}O_2S$: 306.0715, found: 306.0712. Anal. Calcd for $C_{19}H_{14}O_2S$ (306.4): C 74.48, H 4.61; found: 74.36, H 4.53.

4.1.32. *Compound **50***

Formed as a yellow foam by cyclization of **49** after a reaction time of 25 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.79 (br s, 1H), 7.68–7.64 (m, 1H), 7.60 (td, J=7.5, 1.5 Hz, 1H), 7.55–7.41 (m, 5H), 7.28–7.20 (m, 2H), 7.08 (ddd, J=8.1, 6.3, 1.5 Hz, 1H), 6.55 (d, J=8.8 Hz, 2H), 3.72 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.5, 162.8, 161.9, 140.4, 135.4, 132.9, 131.7, 131.6, 130.5, 129.9, 129.0, 128.3, 127.4, 125.7, 123.3, 122.4, 121.7, 120.9, 112.7, 111.5, 55.4, 51.3; IR (film): 3330, 3059, 2951, 2839, 1700, 1649, 1596, 1575, 1508, 1479, 1452, 1443, 1420, 1330, 1315, 1291, 1246, 1176, 1148, 930, 844, 730 cm^{-1}; MS (EI) m/z (%): 385 (58) [M^{+}], 326 (100), 310 (11), 282 (6), 250 (10), 135 (30), 77 (5); HRMS (ESI) calcd for $C_{24}H_{19}NO_4$+Na [(M+Na)$^+$]: 408.1206, found: 408.1211. Anal. Calcd for $C_{24}H_{19}NO_4$ (385.4): C 74.79, H 4.97, N 3.63; found: C 74.62, H 4.87, N 3.73.

4.1.33. Compound *51a*

Formed as a pale yellow solid by cyclization of **49** after a reaction time of 40 min; mp >228 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6): δ=11.60 (br s, 1H), 8.97–8.95 (m, 1H), 8.71 (d, *J*=8.1 Hz, 1H), 8.56 (d, *J*=8.1 Hz, 1H), 7.69 (d, *J*=8.1 Hz, 1H), 7.50 (ddd, *J*=8.1, 6.8, 1.0 Hz, 1H), 7.45–7.39 (m, 2H), 7.35–7.25 (m, 4H), 7.13 (d, *J*=8.6 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=158.5, 140.4, 138.6, 132.6, 130.7, 129.7, 128.0, 125.6, 125.6, 125.1, 123.8, 123.6, 123.3, 122.6, 121.4, 119.8, 119.6, 114.7, 114.0, 112.0, 55.1; IR (KBr): 3426, 3059, 3014, 2964, 2935, 2836, 1607, 1535, 1512, 1453, 1326, 1286, 1256, 1243, 1174, 1116, 1026, 828, 761, 748 cm^{-1}; MS (EI) *m*/*z* (%): 339 (100) [M$^+$], 324 (6), 267 (6); HRMS (ESI) calcd for $C_{23}H_{17}NO_2$+Na [(M+Na)$^+$]: 362.1151, found: 362.1157. Anal. Calcd for $C_{23}H_{17}NO_2$ (339.4): C 81.40, H 5.05, 4.13; found: C 81.31, H 5.11, N 4.05. Small amounts of the corresponding methyl ether **51b** were formed as a by-product which analyzed as follows: ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.78 (d, *J*=9.3 Hz, 1H), 8.67 (br s, 1H), 8.58 (d, *J*=7.8 Hz, 1H), 7.74 (d, *J*=8.3 Hz, 1H), 7.66–7.60 (m, 2H), 7.51–7.34 (m, 5H), 7.09 (d, *J*=8.6 Hz, 2H), 3.93 (s, 3H), 3.64 (s, 3H); IR (KBr): 3374, 3057, 3002, 2958, 2935, 2835, 1607, 1531, 1512, 1455, 1370, 1289, 1244, 1174, 1032, 1003, 834, 766, 750, 743 cm^{-1}; MS (EI) *m*/*z* (%): 353 (100) [M$^+$], 338 (26), 310 (12), 307 (21), 295 (6), 161 (7); HRMS (ESI) calcd for $C_{24}H_{19}NO_2$+Na [(M+Na)$^+$]: 376.1308; found: 376.1307.

4.1.34. Compound *53*

Pale yellow solid; ^{1}H NMR (400 MHz, CD_2Cl_2): δ=8.40 (br s, 1H), 7.22 (d, *J*=8.8 Hz, 2H), 7.17 (d, *J*=8.8 Hz, 2H), 7.10 (d, *J*=8.6 Hz, 2H), 6.88–6.81 (m, 8H), 6.76 (d, *J*=16.7 Hz, 1H), 6.70–6.61 (m, 4H), 4.76 (sept, *J*=6.1 Hz, 1H), 4.16 (t, *J*=7.1 Hz, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.66 (s, 3H), 3.11 (t, *J*=7.1 Hz, 2H), 1.46 (d, *J*=6.1 Hz, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=159.6, 158.9, 158.0, 144.1, 133.0, 131.2, 131.0, 130.6, 130.1, 129.7, 128.6, 128.3, 127.7, 125.4, 124.4, 122.5, 120.2, 119.2, 117.3, 114.4, 114.3, 114.1, 113.9, 113.1, 113.0, 105.5, 70.8, 55.6, 55.6, 55.5, 52.0, 37.7, 22.5; IR (KBr): 3431 (br), 3032, 2973, 2931, 2834, 1605, 1576, 1545, 1513, 1462, 1248, 1175, 1114, 1032, 957, 929, 832, 784 cm^{-1}; MS (EI) *m*/*z* (%): 612 (100) [M$^+$], 449 (5), 135 (8), 121 (9); HRMS (ESI) calcd for $C_{40}H_{40}N_2O_4$+Na [(M+Na)$^+$]: 635.2880, found: 635.2881.

4.1.35. Compound *54*

Yellow solid; ^{1}H NMR (400 MHz, CD_2Cl_2): δ=7.96 (br s, 1H), 7.09 (d, *J*=8.8 Hz, 2H), 7.06 (d, *J*=8.6 Hz, 2H), 6.93 (d, *J*=8.6 Hz, 2H), 6.87–6.74 (m, 7H), 6.68 (d, *J*=8.8 Hz, 2H), 6.60–6.54 (m, 1H), 6.39 (d, *J*=2.3 Hz, 1H), 4.68 (sept, *J*=6.1 Hz, 1H), 4.10 (t, *J*=7.1 Hz, 2H), 3.75 (s, 3H), 3.75 (s, 3H), 3.70 (s, 3H), 3.06 (t, *J*=7.1 Hz, 2H), 2.80–2.72 (m, 2H), 2.68–2.60 (m, 2H), 1.39 (d, *J*=6.1 Hz, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=158.9, 158.8, 157.9, 143.9, 135.5, 134.0, 131.2, 131.1, 130.1, 130.0, 129.7, 128.3, 127.0, 124.4, 122.0, 119.8, 118.6, 114.5, 114.3, 114.1, 113.9, 112.5, 109.1, 104.2, 70.7, 55.5, 55.5, 55.5, 51.9, 37.7, 34.7, 29.1, 22.5; IR (KBr): 3443 (br), 3031, 2973, 2932, 2834, 1611, 1576, 1545, 1512, 1454, 1246, 1177, 1115, 1034, 832, 782 cm^{-1}; MS (EI) *m*/*z* (%): 614 (100) [M$^+$], 493 (82), 451 (26), 329 (11), 135 (26), 121 (16), 105 (5); HRMS (ESI) calcd for $C_{40}H_{42}N_2O_4$+Na [(M+Na)$^+$]: 637.3037, found: 637.3034.

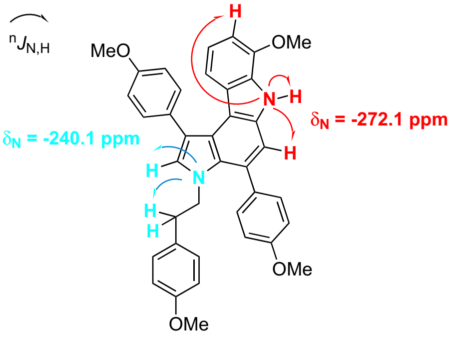
4.1.36. Compound *55*

Yellow solid; ^{1}H NMR (400 MHz, CD_2Cl_2): δ=8.41 (br s, 1H), 7.41 (d, *J*=8.8 Hz, 2H), 7.09–7.01 (m, 4H), 6.93–6.76 (m, 7H), 6.67–6.62 (m, 1H), 6.58 (d, *J*=8.8 Hz, 2H), 6.50 (d, *J*=2.4 Hz, 1H), 4.76 (sept, *J*=6.1 Hz, 1H), 4.11 (t, *J*=6.9 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.67 (s, 3H), 3.04 (t, *J*=6.9 Hz, 2H), 1.45 (d, *J*=6.1 Hz, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=159.2, 158.8, 157.7, 144.3, 134.3, 132.7, 131.1, 130.1, 129.7, 128.6, 128.0, 127.4, 126.3, 124.7, 122.1, 120.3, 118.8, 114.7, 114.2, 114.1, 113.7, 112.8, 108.9, 104.7, 70.8, 55.6, 55.5, 55.4, 52.0, 37.7, 22.5; IR (KBr): 3422 (br), 3033, 2973, 2933, 2834, 1612, 1577, 1534, 1512, 1493, 1452, 1441, 1248, 1178, 1115, 1034, 832, 784 cm^{-1}; MS (EI) *m*/*z* (%): 586 (100) [M$^+$], 544 (8), 423 (14), 135 (5); HRMS (ESI) calcd for $C_{38}H_{38}N_2O_4$+Na [(M+Na)$^+$]: 609.2724, found: 609.2717.

4.1.37. Compound *56*

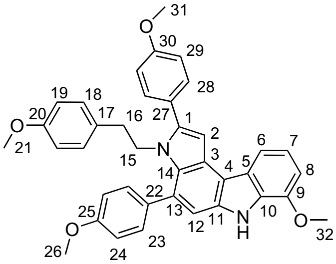
Colorless foam; ^{1}H NMR (400 MHz, CD_2Cl_2): δ=8.12 (br s, 1H), 7.12 (d, *J*=8.8 Hz, 2H), 7.09 (d, *J*=8.6 Hz, 2H), 6.88–6.83 (m, 4H), 6.82 (d, *J*=2.4 Hz, 1H), 6.69 (d, *J*=8.8 Hz, 2H), 6.61–6.55 (m, 2H), 4.72 (sept, *J*=6.1 Hz, 1H), 4.13 (t, *J*=7.2 Hz, 2H), 3.79 (s, 3H), 3.72 (s, 3H), 3.09 (t, *J*=7.2 Hz, 2H), 2.05 (s, 3H), 1.42 (d, *J*=6.1 Hz, 6H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=158.9, 157.8, 143.8, 131.8, 131.2, 131.1, 130.1, 130.1, 128.2, 127.0, 124.3, 121.8, 119.8, 118.7, 114.7, 114.3, 113.9, 112.3, 108.9, 103.9, 70.6, 55.6, 55.5, 51.9, 37.7, 22.5, 12.4; IR (KBr): 3386, 3032, 2973, 2932, 2834, 1611, 1576, 1545, 1513, 1501, 1462, 1245, 1033, 833, 781 cm^{-1}; MS (EI) *m*/*z* (%): 494 (100) [M$^+$], 452 (12), 373 (6), 331 (27), 135 (5); HRMS (ESI) calcd for $C_{32}H_{34}N_2O_3$+Na [(M+Na)$^+$]: 517.2462, found: 517.2454.

4.1.38. Compound *21*



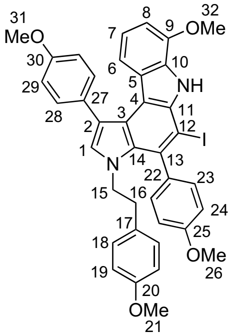
$AgSbF_6$ (50 mg, 5 mol %) was added to a solution of $(Ph_3P)AuCl$ (70 mg, 5 mol %) in CH_2Cl_2 (40 mL) at 0 °C and the resulting mixture stirred at this temperature for 10 min before a solution of compound **20** (180 mg, 0.3 mmol) in CH_2Cl_2 (10 mL) was introduced. After stirring for 2 min, the mixture was filtered through a pad of silica, the filtrate was evaporated, and the residue purified by flash chromatography (hexanes/EtOAc, 5:1) to give product **21** as a pale yellow solid (120 mg, 67%). ^{1}H NMR (600 MHz, acetone-d_6): δ=10.27 (s, 1H, NH), 7.51 (m, 2H, H-23), 7.39 (m, 2H, H-28), 7.31 (s, 1H, H-12), 7.11 (s, 1H, H-1), 7.07 (m, 2H, H-24), 7.02 (m, 2H, H-29), 6.76 (d, *J*=7.8 Hz, 1H, H-8), 6.69 (m, 2H, H-19), 6.65 (m, 2H, H-18), 6.64 (m, 1H, H-7), 6.32 (d, *J*=7.8 Hz, 1H, H-6), 3.99 (m, 2H, H-15), 3.95 (s, 3H, H-32), 3.89 (s, 3H, H-31), 3.88 (s, 3H, H-26), 3.70 (s, 3H, H-21), 2.58 (m, 2H, H-16); ^{13}C NMR (150 MHz, acetone-d_6): δ=160.3 (C-25), 159.8 (C-30), 159.2 (C-20), 146.4 (C-9), 136.2 (C-11), 134.5 (C-22), 132.7 (C-28), 131.9 (C-23), 131.3 (C-27), 131.2 (C-17), 130.7 (C-10), 130.5 (C-18), 130.2 (C-1), 129.5 (C-14), 126.8 (C-13), 124.9 (C-5), 123.9 (C-3), 118.6 (C-7), 118.1 (C-6), 117.9 (C-2), 114.8 (C-4), 114.4 (C-24), 114.3 (C-19), 114.1 (C-29), 110.6 (C-12), 104.6 (C-8), 55.7 (C-31), 55.7 (C-32), 55.7 (C-26), 55.4 (C-21), 51.1 (C-15), 37.4 (C-16); ^{15}N NMR (60.8 MHz, acetone-d_6): −240.1, −272.1 ppm; IR (KBr): 2997, 2959, 2917, 1849, 1610, 1574, 1547, 1513, 1503, 1462, 1441, 1417, 1246, 1175, 1032, 837 cm^{-1}; MS (EI) *m*/*z* (%): 582 (100) [M$^+$], 461 (73), 446 (11), 430 (23), 121 (7); HRMS (EI) *m*/*z*: calcd for $C_{38}H_{35}N_2O_4$ [(M+H)$^+$]: 583.2596; found: 583.259.

4.1.39. Compound **24**



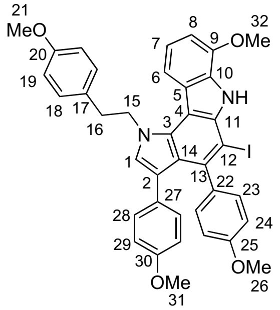
A solution of substrate **21** (11 mg, 2 μmol) and $SnCl_4$ (2 μL, 2.1 μmol) in 1,2-dichloroethane (1.5 mL) was stirred at 80 °C for 2 h. The reaction was diluted with CH_2Cl_2 (5 mL) before it was quenched at ambient temperature with satd aq $NaHCO_3$ (5 mL). A standard extractive work up followed by flash chromatography (EtOAc/hexanes, 1:4) of the crude material afforded compound **24** as a colorless solid (7 mg, 64%). ^1H NMR (600 MHz, acetone-d_6): δ=10.28 (s, 1H, NH), 7.91 (d, J=7.8 Hz, 1H, H-6), 7.62 (m, 2H, H-23), 7.48 (m, 2H, H-28), 7.29 (s, 1H, H-12), 7.15 (m, 1H, H-7), 7.14 (m, 1H, H-2), 7.11 (m, 2H, H-24), 7.06 (m, 2H, H-29), 6.94 (d, J=7.8 Hz, 1H, H-8), 6.56 (m, 2H, H-19), 6.29 (m, 2H, H-18), 4.02 (m, 5H, H-15, H-32), 3.90 (s, 3H, H-26), 3.87 (s, 3H, H-31), 3.66 (s, 3H, H-21), 2.19 (m, 2H, H-16); ^{13}C NMR (150 MHz, acetone-d_6): 160.5 (C-30), 160.2 (C-25), 159.1 (C-20), 146.9 (C-9), 144.2 (C-1), 135.9 (C-11), 134.8 (C-22), 131.8 (C-23), 131.7 (C-28), 131.1 (C-17), 131.0 (C-14), 130.6 (C-10), 130.1 (C-18), 127.2 (C-13), 126.9 (C-27), 125.5 (C-5), 124.6 (C-3), 119.9 (C-7), 114.7 (C-29), 114.6 (C-6), 114.5 (C-24), 114.4 (C-4), 114.3 (C-19), 110.1 (C-12), 105.3 (C-8), 102.7 (C-2), 55.8 (C-26), 55.8 (C-32), 55.7 (C-31), 55.3 (C-21), 48.2 (C-15), 36.0 (C-16); IR (film): 2950, 2925, 2899, 2832, 1609, 1577, 1512, 1457, 1439, 1421, 1281, 1244, 1175, 1083, 1030, 834, 793, 753, 734 cm^{-1}; MS (EI) m/z (%): 582 (96) [M^+], 461 (100), 430 (22), 121 (6); HRMS (EI) calcd for $C_{38}H_{35}N_2O_4$ [$(M+H)^+$]: 583.2596, found: 583.2591.

4.1.40. Compounds **25** and **27**



Trifluoromethanesulfonic acid (15 μL, 0.16 mmol) was added to a solution of [I(pyridine)$_2$]BF_4 (67 mg, 0.18 mmol) in CH_2Cl_2 (3.5 mL) and the resulting mixture was stirred for 15 min at ambient temperature before it was cooled to −40 °C. A solution of compound **20** (87 mg, 0.15 mmol) in CH_2Cl_2 (2.5 mL) was introduced and stirring continued for 30 min before the mixture was allowed to reach ambient temperature. The reaction was quenched with aq satd $Na_2S_2O_3$ (5 mL), the organic layer was washed with water, dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc, 4:1) to give a mixed fraction containing products **25** and **27** (71 mg, 67%). Analytically pure samples were obtained by preparative HPLC which showed the following analytical and spectroscopic properties: Compound **25**: ^1H NMR (600 MHz, acetone-d_6): δ=9.01 (s, 1H, NH), 7.40 (m, 2H, H-23), 7.38 (m, 2H, H-28), 7.17 (m, 2H, H-24), 7.14 (s, 1H, H-1), 7.04 (m, 2H, H-29), 6.84 (d, J=7.8 Hz, 1H), 6.82 (m, 2H, H-18), 6.75 (m, 2H, H-19), 6.71 (dd, J=7.8, 8.2 Hz, 1H, H-7), 6.24 (d, J=8.2 Hz, 1H, H-6), 3.99 (s, 3H, H-32), 3.94 (s, 3H, H-26), 3.91 (s, 3H, H-31), 3.77 (m, 2H, H-15), 3.73 (s, 3H, H-21), 2.70 (m, 2H, H-16); ^{13}C NMR (150 MHz, acetone-d_6): δ=160.8 (C-25), 160.0 (C-30), 159.3 (C-20), 146.4 (C-9), 138.7 (C-11), 137.0 (C-27), 136.0 (C-22), 132.8 (C-28), 132.8 (C-23), 131.2 (C-17), 131.0 (C-1), 130.7, 130.6 (C-14, C-18), 130.1 (C-13), 129.7 (C-10), 125.8 (C-5), 123.7 (C-3), 119.8 (C-7), 118.4 (C-6), 117.5 (C-2), 114.8 (C-4), 114.7 (C-24), 114.4 (C-19), 114.2 (C-29), 105.4 (C-8), 81.4 (C-12), 55.9 (C-32), 55.8 (C-26), 55.7 (C-31), 55.4 (C-21), 50.6 (C-15), 37.8 (C-16); IR (film): 2962, 1571, 1511, 1454, 1401, 1357, 1316, 1258, 1241, 1170, 1014, 797, 729, 657 cm^{-1}; MS (EI): m/z (%): 708 (100) [M^+], 587 (19), 460 (28), 445 (6), 300 (5), 254 (10), 135 (8); HRMS (EI) m/z: calcd for $C_{38}H_{33}IN_2O_4$+Na [$(M+Na)^+$]: 731.1382, found: 731.1386.

4.1.41. Compound **27**



^1H NMR (600 MHz, acetone-d_6): δ=9.22 (s, 1H, NH), 8.03 (d, J=8.3 Hz, 1H, H-6), 7.24 (dd, J=8.1 Hz, 1H, H-7), 7.09 (m, 2H, H-18), 7.07 (d, J=7.9 Hz, 1H, H-8), 6.90 (s, 1H, H-1), 6.87 (m, 2H, H-23), 6.85 (m, 2H, H-19), 6.63 (m, 2H, H-28), 6.56 (m, 2H, H-24), 6.46 (m, 2H, H-29), 5.05 (d, J=7.5 Hz, 2H, H-15), 4.09 (s, 3H, H-32), 3.77 (s, 3H, H-21), 3.74 (s, 3H, H-26), 3.71 (s, 3H, H-31), 3.28 (d, J=7.5 Hz, 2H, H-16); ^{13}C NMR (150 MHz, acetone-d_6): δ=159.8 (C-25), 159.5 (C-20), 158.2 (C-30), 147.1 (C-9), 139.0 (C-13), 138.8 (C-11), 135.5 (C-22), 132.7 (C-23), 132.1 (C-14), 131.5 (C-28), 131.0 (C-17), 130.8 (C-18), 129.5 (C-10), 129.4 (C-27), 128.1 (C-1), 123.9 (C-5), 123.2 (C-3), 121.2 (C-7), 119.9 (C-2), 116.4 (C-6), 114.7 (C-19), 113.3 (C-24), 113.2 (C-29), 108.2 (C-4), 105.7 (C-8), 77.9 (C-12), 56.1 (C-32), 55.5 (C-21), 55.4 (C-26), 55.4 (C-31), 52.4 (C-15), 37.8 (C-16); IR (film): 2950, 2925, 2832, 1607, 1565, 1511, 1462, 1454, 1400, 1364, 1318, 1284, 1243, 1173, 1103, 1062, 1033, 827, 804, 778, 721 cm^{-1}; HRMS (EI) m/z: calcd for $C_{38}H_{33}IN_2O_4$+Na [$(M+Na)^+$]: 731.1382, found: 731.1386.

4.2. DNA cleavage assay

A solution of purified scDNA (2 μL of a stock solution containg ca. 400 μg mL^{-1}) [ΦX174 RF1 DNA, purchased from MBI Fermentas GmbH, St. Leon-Rot, Germany; the EDTA contained in the commercial sample was removed according to the Qiaex II protocol for desalting and concentrating DNA by using a Qiaex II Gel Extraction Kit] was incubated at 37 °C for 1.5 h with the respective dictyodendrin derivative (2 μL of a 2 mM stock solution), $Cu(OAc)_2$ (2 μL of a 1 mM stock solution), n-butylamine (2 μL of a 20 mM stock solution), aq NaCl (3 μL of a 0.5 mM stock solution) in water (complemented to give a total volume of 20 μL). The mixture was quenched with loading buffer (BioRad laboratories) and the DNA resolved by electrophoresis (Powerpac 300, BioRad) (85 V, 1 h) on a 0.8% agarose gel (containing ethidium bromide) in tris/boronic acid buffer (BioRad). The bands detected by UV were analyzed and processed using the Bio Doc II software (Biometra).

4.3. X-ray crystal structure analysis of 21

$2(C_{38}H_{34}N_2O_4)\cdot C_4H_8O_2$, M_r=1253.45 g mol^{-1}, colorless plate, crystal size 0.24×0.21×0.04 mm, monoclinic, space group $P2_1/n$, a=19.1139(2) Å, b=16.5476(2) Å, c=20.7068(3) Å, β=96.5220(10)°, V=6506.95(14) Å^3, T=100 K, Z=4, D_{calcd}=1.279 g cm^3, λ=0.71073 Å, μ(Mo Kα)=0.084 mm^{-1}, semi-empirical absorption correction (T_{min}=0.95, T_{max}=1.00), Nonius KappaCCD diffractometer, $3.01<\theta<30.97°$, 94,787 measured reflections, 20,639 independent reflections, 12,819 reflections with $I>2\sigma(I)$, structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1=0.080 [$I>2\sigma(I)$], wR_2=0.118, 857 parameters, H atoms riding, S=0.997, residual electron density 0.6/−0.4 e Å^{-3}.

4.4. X-ray crystal structure analysis of 25

$C_{38}H_{33}IN_2O_4$, M_r=708.56 g mol^{-1}, colorless plate, crystal size 0.07×0.05×0.02 mm, monoclinic, space group $P2_1/c$, a=10.09510(10) Å, b=23.1367(3) Å, c=13.7023(2) Å, β=92.9810(10)°, V=3196.08(7) Å^3, T=100 K, Z=4, D_{calcd}=1.473 g cm^3, λ=0.71073 Å, μ(Mo Kα)=1.046 mm^{-1}, semi-empirical absorption correction (T_{min}=0.99, T_{max}=1.00), Nonius KappaCCD diffractometer, $2.98<\theta<30.97°$, 86,412 measured reflections, 10,167 independent reflections, 8026 reflections with $I>2\sigma(I)$, structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1=0.039 [$I>2\sigma(I)$], wR_2=0.088, 415 parameters, H atoms riding, S=1.048, residual electron density 3.0/−1.0 e Å^{-3}.

4.5. X-ray crystal structure analysis of 41

$C_{23}H_{17}NO_2$, M_r=339.38 g mol^{-1}, yellow block, crystal size 0.13×0.12×0.12 mm, triclinic, space group $P-1$, a=6.76770(10) Å, b=9.6890(2) Å, c=27.6343(6) Å, α=96.5490(10)°, β=95.2090(10)°, γ=108.0680(10)°, V=1696.11(6) Å^3, T=100 K, Z=4, D_{calcd}=1.329 g cm^3, λ=0.71073 Å, μ(Mo Kα)=0.085 mm^{-1}, semi-empirical absorption correction (T_{min}=0.72, T_{max}=0.86), Nonius KappaCCD diffractometer, $2.92<\theta<33.16°$, 40,537 measured reflections, 12,778 independent reflections, 9803 reflections with $I>2\sigma(I)$, structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1=0.066 [$I>2\sigma(I)$], wR_2=0.199, 473 parameters, H atoms riding, S=1.056, residual electron density 0.8/−1.0 e Å^{-3}.

CCDC 719,450–719,652 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.ca.ac.uk/data_request/cif.

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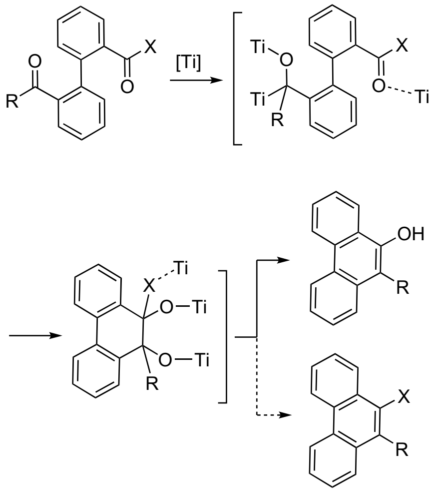
during the actual reaction. This assumption is in line with the proposed mechanism which is thought to involve a two electron reduction of the ketone followed by nucleophilic attack of the resulting carbonyl dianion equivalent onto the adjacent –C(O)X group. For a detailed study on the two-electron reduction mechanism, see Ref. 15a.



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