Synthesis of pyrrolocarbazoles with N-substituted alkynyl-, alkylcyano- and alkylhydroxyl-groups

Alet E. van der Westhuyzen, Kathy Hadjegeorgiou, Ivan R. Green, Stephen C. Pelly, and Willem A. L. van Otterlo

Department of Chemistry and Polymer Science, University of Stellenbosch, Private Bag X1, Matieland, ZA-7602 Stellenbosch, South Africa
Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, PO Wits, 2050, Johannesburg, South Africa
Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322, USA

Email: wvo@sun.ac.za; stephen.c.pelly@emory.edu

Received 11-03-2020                Accepted 11-28-2020                Published on line 12-07-2020

Abstract

Due to their involvement in almost all stages of cellular life, kinase biomolecular catalysts have been linked to cancer development and, thus, remain attractive drug targets for cancer therapeutics. 6-(3'-Hydroxypropyl)-, 6-(2'-hydroxyethyl)-, 6-(2'-propynyl)- and 6-(3'-propanenitrile)-pyrrolo[3,4-c]carbazole-1,3(2H,6H)-diones were synthesized as potential small molecule EGFR kinase inhibitors. The pyrrolocarbazole compounds were synthesized by way of a Diels-Alder approach involving N-alkylated 2-vinyl-1H-indole and maleimide as starting materials followed by aromatization with MnO$_2$.

Keywords: Pyrrolocarbazole, kinase inhibitors, Diels-Alder, aromatization
Introduction

Over the past three decades, extensive research efforts have contributed to rapid developments in the field of oncology. Despite the apparent progress, cancer continues to be a worldwide leading cause of death. The need to develop new and less toxic treatments against a disease with the rather frustrating ability to remodel itself as drug-resistant variants is, thus, as important as ever.

The reversible phosphorylation of proteins is arguably one of the most general regulatory strategies adopted by eukaryotic cells and represents a key step in many crucial cellular processes. In this regard, protein kinases are enzymes that promote phosphorylation, i.e., the transfer of a phosphate group from ATP to a substrate protein. Due to the central involvement of kinases in almost all stages of cellular life (including growth factor signaling, cell cycle control, apoptosis and angiogenesis), these biocatalysts have been linked to cancer development and thus remain attractive drug targets for cancer therapeutics. The history concerning the development of kinase inhibitors has enjoyed much success; however, fundamental challenges, such as the lack of efficiency, drug resistance due to key amino acid mutations and inhibitor selectivity, persist. The development of effective long-term cancer treatments, including those which involve kinase inhibition, thus remains a pursuit of many researchers.

One of the most commonly selected kinase families targeted for the development of cancer therapeutics has been the receptor tyrosine kinases (RTKs), which include the epidermal growth factor receptors (EGFRs), the vascular endothelial growth factor receptors (VEGFRs) and the platelet-derived growth factor receptors (PDGFRs). Many of these cell-surface receptors are known to be mutated or overexpressed in cancer systems, which makes them attractive candidates as targets. For this particular project, we decided to focus on the EGFR family which consists of EGFR, human EGRF-related 2 (HER2) and the kinase-impaired HER3 and HER4. EGFR itself has been the target of many successful small-molecule drugs, including erlotinib, gefitinib, afatinib, the more recent osimertinib, and the more experimental brigatinib and icotinib. Even for the more recent compounds, the development of drug-resistant cancer cells is a serious limitation (see for instance, the exon 20 C797S mutation experienced by the 3rd generation inhibitor, osimertinib).

In terms of finding inspiration for new scaffolds which might provide the basis for kinase inhibitors with different and, hopefully, favourable characteristics, Nature continues to be one of the best sources of ideas. With this in mind, it was soon realized that staurosporine 1 is in fact a natural, potent kinase inhibitor, initially isolated from the bacterium Streptomyces staurosporeus, and has widely served as a structural muse for the design of protein kinase inhibitors with the overall aim of improved specificity and selectivity. Numerous staurosporine analogues have been evaluated against various human cancer cell lines, with some showing promising therapeutic activity. Staurosporine-inspired drug candidates have been in vogue, see for instance the staurosporin-inspired midostaurin 2 (Rydapt®, in clinic as a tyrosine kinase 3 (FLT3) inhibitor), CEP-2563 3 (phase 1) and endotecarin 4 (phase 3) depicted in Figure 1. The bisaryl maleimide derivative enzastaurin 5 could be considered an “open” form of staurosporine, but, unfortunately, it failed its phase III lymphoma clinical trial. Structurally simplified staurosporine-inspired pyrrolocarbazoles have also been considered as possible kinase inhibitors – examples include Chk 1 inhibitors 6 and PARP 1 inhibitors 7 – and these simplified staurosporine motifs were the basis for the design of new potential inhibitors described in this work.
Figure 1. Staurosporine 1, and examples of other important indolo- and pyrrolocarbazoles (see following references for reviews on clinically relevant staurosporin analogues\textsuperscript{9} and other relevant carbazoles\textsuperscript{10}).

It should be noted that the pyrrolocarbazole core, apart from its ubiquitous role in natural products\textsuperscript{11}, has seen frequent prior application in medicinal chemistry\textsuperscript{12}, with particular emphasis as kinase inhibitors. Examples include earlier work focused on protein kinase C\textsuperscript{13-14} the checkpoint kinase Wee1\textsuperscript{15} and Chk1\textsuperscript{16-20}, mixed lineage kinase (MLK)\textsuperscript{21} inhibitors, as well as other series with more generic anti-cancer applications\textsuperscript{22-23}. Similar scaffolds have also been identified as PARP-1 inhibitors\textsuperscript{24}.

In this project we envisaged the development of potential kinase inhibitors that would selectively suppress EGFR, an important therapeutic target (for other collaborative studies from our group involving this kinase see\textsuperscript{25-27}). Exploiting the attractive features demonstrated by the natural product staurosporine, the design considered was based on a staurosporine scaffold. It was our intention that the pyrrolocarbazole scaffold 8 could act as a driving portion and present a suitable platform to incorporate potentially electrophilic warheads (R) at a proper trajectory (Figure 2). Notably, the scaffold displaying the warhead at a particular distance and orientation, could result in a covalent interaction to cysteine 797 in the kinase-active site, a strategy utilized before in our research\textsuperscript{26,28}.

In terms of the synthetic strategy towards the desired substituted scaffolds, a Diels-Alder-oxidative aromatization approach was utilized. (For an excellent overview of the many synthetic approaches to the carbazole scaffold, please refer to the review by Knölker and co-workers\textsuperscript{11}). Approach A involved generating the pyrrolo[3,4-c]carbazole-1,3(2H,6H)-dione first, followed by selective acylation/alkylation of the carbazole nitrogen atom as shown in Figure 2. Alternatively, approach B would generate the desired compounds with the desired N-functionalizations already in place on the 2-vinylindole precursor 9b. It should be noted that the
Diels-Alder/aromatization strategy has been effectively utilized before to efficiently deliver substituted pyrrolocarbazoles (see the examples listed in the following references\textsuperscript{13-15,17-18,21-22,24} and the following examples which include related modifications\textsuperscript{29-32} with respect to the 2-vinylindole motif\textsuperscript{33}).

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure2.png}
\caption{Retrosynthetic analysis to afford pyrrolocarbazole skeletons 8 containing a group on the nitrogen atom of the resultant carbazole (Route B was eventually the successful one).}
\end{figure}

\section*{Results and Discussion}

The initial strategy focused on the synthesis of the known pyrrolo[3,4-c]carbazole-1,3(2H,6H)-dione scaffold 15 in order to use this compound in a divergent approach to obtain a small library of alkylated N-carbazole derivatives. To this end, commercially available ethyl 1H-indole-2-carboxylate 10 was converted into 1H-indole-2-carbaldehyde 12, via alcohol 11, through a reduction (LiAlH\textsubscript{4})-oxidation (MnO\textsubscript{2}) sequence. A Wittig reaction (MePPh\textsubscript{3}Br with nBuLi) involving carbaldehyde 12 readily afforded 2-vinyl-1H-indole 13, which gratifyingly underwent a Diels-Alder reaction as a neat mixture at 170 °C with maleimide to afford the fused indole 14a in quantitative yield. This compound was then oxidized into the fully-aromatized substituted carbazole scaffold 15 with DDQ in DMSO at 50 °C in 50% yield (Scheme 1).

Initial attempts to react 15 with acryloyl chloride in DMF at 0 °C to obtain N-acylated 16, and even after heating to 80 °C under N\textsubscript{2} for 48 h, did not indicate any evidence of N-substituted product 16 formation by TLC. In addition, treatment of 15 with NaH in DMF at RT under N\textsubscript{2} afforded a purple solution which turned a yellow color upon the drop-wise addition of acryloyl chloride with stirring at RT for 4 days, but still gave no new products (TLC). To address the regioselectivity issue between the two nitrogen atoms in 15, the known N-Boc-protected maleimide\textsuperscript{34} was reacted with diene 13 at 70 °C for 30 min to afford the expected adduct 14b in 59% yield. Attempts to react this latter adduct with acryloyl chloride, in DMF containing DIPEA (-5 to 60 °C for 2 days), only led to the cleavage of the Boc-protecting group. Aromatization of 14b with either DDQ or MnO\textsubscript{2} also resulted in the Boc group being cleaved. The unsuccessful work involving the Boc-protected compounds is not described further.
Scheme 1. Synthesis of pyrrolocarbazole dione 15 and attempted unsuccessful maleimide acylation/alkylations.

An alternative method at accessing N-substituted carbazoles involved the initial introduction of substituents on the nitrogen atom of the indole ring by the synthesis of N-alkylated 2-vinylindoles. These could, subsequently, be utilized as the starter dienes in the critical Diels-Alder cyclization step. To this end, ethyl and methyl 1H-indole-2-carboxylates 10 and 18, respectively (the latter readily obtained from carboxylic acid 17), were dissolved in DMF to which NaH was added, followed by (2-bromoethoxy)(tert-butyl)dimethylsilane (19) or (3-bromopropoxy)(tert-butyl)dimethylsilane (20) to afford 22 and 21, respectively, in reasonable yields (Scheme 2). Reduction of 22 and 21 was readily achieved by the use of LiAlH₄ in THF at 0 °C to afford 23a and 23b in excellent yields of 97% and 88%, respectively. It should be noted, however, that the reaction temperature needed to remain below room temperature in order to retain the ethoxy and propoxy silyl groups; at temperatures above room temperature these groups were cleaved.

MnO₂ was found to be the best oxidizing agent for the conversion of 23a and 23b into substituted 1H-indole-2-carbaldehydes 24a and 24b in respectable yields of 83% and 99%, respectively. Prior activation of the MnO₂ was necessary and achieved by placing a beaker of MnO₂ in an oven at 120 °C for 24 h. The oxidant, after the oxidation procedure, was readily removed by filtration and it was found that the aldehyde products were sufficiently pure to be used for conversion into the respective vinyl analogues without further chromatographic purification.

The Wittig protocol for conversion of the aldehydes into their corresponding vinyl analogues involved the initial generation of the methylene ylide, by treatment of MeP₂Ph₃ with nBuLi in dry THF at 0 °C, followed by the drop-wise addition of carbaldehydes 24a and 24b to afford the two alkylated 2-vinyl-1H-indoles 25a and 25b in yields of 79% and 55% respectively.
Scheme 2. Synthesis of \( N \)-alkylated 2-vinylindoles 25a and 25b.

The key Diels-Alder reaction to produce the additional 6-membered ring of the desired pyrrolocarbazole scaffold involved the cycloaddition of compounds 25a and 25b with maleimide. The reagents were heated together as a neat mixture and, after melting, they reacted to produce a solid adduct, which, in both cases, was purified chromatographically to afford the desired products 26a and 26b in reasonable yields of 78% and 91%, respectively, based on recovered starting material (brsm) (Scheme 3).

The target pyrrolocarbazoles 29a and 29b were prepared by a protocol involving the same steps, but in the opposite order, since it was found that this alternative sequence produced the best overall yields. Thus for pyrrolocarbazole 29a, adduct 26a was firstly treated with TBAF at 0 °C to remove the TBDMS protecting group to produce 27 in 86% yield, followed by the MnO\(_2\) oxidation in dioxane under reflux to form the desired aromatized product 29a in a yield of 53%. On the other hand, 29b was readily obtained by first oxidizing 26b with MnO\(_2\) in refluxing dioxane to form the aromatized carbazole 28 in 63% yield, followed by cleavage of the TBDMS protecting group with TBAF in THF at RT for 30 min, to afford the longer chain product 29b in 65% yield.

The propargyl group was introduced on the nitrogen atom of the previously synthesized 2-vinyl-1\(H\)-indole (13) by a nucleophilic substitution reaction employing Cs\(_2\)CO\(_3\) as a base, as per a literature procedure,\(^{37}\) to afford 30a in a moderate (45%) yield. We found the best way to introduce the cyanoethyl group on the nitrogen atom of indole 13, in order to obtain 30b, involved a Michael addition between the 2-vinyl-1\(H\)-indole (13) and acrylonitrile in the presence of DBU in acetonitrile, at RT for 8 h, which gave the desired product 30b in 84% yield [based on recovered starting material (brsm)], as shown in Scheme 4.

A Diels-Alder reaction between compound 30a and maleimide was successfully achieved in the same manner as described previously, but at a slightly lower reaction temperature of 160 °C. It should be noted that cycloadduct 31a was obtained in an acceptable yield of 73% (brsm) and, thus, in sufficient amounts to carry on with the syntheses. For the cycloaddition between diene 30b and maleimide, it was found that the addition of a Lewis acid, SnCl₂, produced the best results. Even under the best conditions available, however, unreacted starting material was still present which, fortunately, could easily be separated by chromatography. In this latter case, the cycloadduct 31b was obtained in an acceptable yield of 71% (calculated brsm).

Finally, aromatization of the cyclohexene ring of 31a and 31b, using an excess of MnO₂ in refluxing dioxane, afforded the desired substituted pyrrolocarbazoles 32a and 32b in yields of 72% and 30%, respectively. It should be noted that pyrrolocarbazoles 32a and 32b were found to be quite insoluble in most laboratory solvents which precluded their absolute purification by chromatography. Consequently, a trituration protocol for 32a and a recrystallization from DMF for 32b were employed to obtain the final
compounds in sufficient purity. The recrystallization from DMF, unfortunately, afforded 32b in a rather low yield.

\[ 13 \rightarrow 30a (R=CH_2CCH, 45\%) \rightarrow 30b (R=CH(CH_2)_2CN, 84\% \text{ brsm}) \rightarrow 31a (R=CH_2CCH, 73\% \text{ brsm}) \rightarrow 31b (R=CH(CH_2)_2CN, 71\% \text{ brsm}) \rightarrow 32a (R=CH_2CCH, 72\%) \rightarrow 32b (R=CH(CH_2)_2CN, 30\% \text{ brsm}) \]

**Scheme 4.** Synthesis of pyrrolocarbazoles 32a and 32b.

Initial biochemical evaluations on substituted pyrrolo[3,4-c]carbazole-1,3(2H,6H)-diones 29a,b and 32a,b were, unfortunately, underwhelming. These compounds were, thus, added to a small-molecule kinase library, and could represent starting points for future screening initiatives.

**Conclusions**

A set of four carbazole N-substituted pyrrolocarbazoles bearing the 6-(3'-hydroxypropyl)-, 6-(2'-hydroxyethyl)-, 6-(2'-propynyl)- and 6-(3'-propanenitrile)-fragments on their nitrogen atoms was prepared for evaluation as potential EGFR kinase inhibitors using Diels Alder cycloadditions and MnO₂ oxidative aromatizations to good effect. These compounds will be utilized as part of screening libraries for the identification of potential lead compounds in future high-throughput screenings.

**Experimental Section**

**General.** Purification of solvents and reagents: Ethyl acetate and hexane used for chromatographic purposes were distilled by means of conventional distillation procedures. Solvents used for reaction purposes were dried over an appropriate drying agent and distilled under nitrogen gas. Tetrahydrofuran, 1,4-dioxane, and diethyl ether were distilled from sodium wire using benzophenone as an indicator. Dimethylformamide and acetonitrile were distilled from calcium hydride.
Chromatography: Separation of compounds by column chromatography was performed using Merck silica gel (particle size 0.063–0.200 mm). Thin layer chromatography was performed using Merck silica gel 60 F_{254} coated on aluminium sheets. Compounds on TLC plates were viewed under UV light.

Spectroscopic and physical data: \(^1\)H and \(^{13}\)C NMR spectra were recorded on a Bruker ADVANCE 300 or Varian Gemini-300 spectrometer (\(^1\)H NMR at 300 MHz and \(^{13}\)C at 75 MHz). A Varian VXR-400 machine (\(^1\)H NMR at 400 MHz and \(^{13}\)C NMR at 101 MHz) or 600 MHz Varian Unity Inova (\(^1\)H NMR at 600 MHz and \(^{13}\)C NMR at 151 MHz) were also utilized. Spectra were recorded in deuterated chloroform (CDCl\(_3\)) and DMSO (DMSO-\(d_6\)) as indicated. Infra-red spectra were recorded using a Bruker Tensor 27 spectrometer. Melting points were measured using a Stuart SMP10 melting point machine. Mass spectra were recorded on a Thermo Electron DFS Magnetic Sector Mass Spectrometer (E.I. mode).

Other general procedures: Most reactions were carried out under nitrogen or argon and reaction vessels were dried in an oven. Removal of solvent in vacuo refers to removal of the solvent using a rotary evaporator followed by removal of trace amounts of solvent using a high vacuum pump.

\((1H\text{-Indol-2-yl})\text{methanol (11).}\) LiAIH\(_4\) (0.88 g, 23 mmol, 2.2 equiv.) was stirred in THF (10 mL) in a 250 mL two-neck round-bottom flask at 0 °C under N\(_2\). A solution of commercially available ethyl indole-2-carboxylate (10) (2.0 g, 10 mmol) in THF (10 mL) was then added drop-wise to the LiAIH\(_4\) solution. The ice bath was removed and the reaction mixture was stirred to 25 °C and stirred for 30 min. After cooling to 0 °C, H\(_2\)O (2 mL) was added drop-wise, followed by NaOH (1 M,aq., 5 mL) and again H\(_2\)O (6 mL) and the reaction mixture was stirred for 30 min at RT. The solution was filtered through Celite and washed with CH\(_2\)Cl\(_2\) (100 mL). The filtrate was washed with brine (100 mL) and the organic layer, after drying (MgSO\(_4\)) gave a residue which was purified by column chromatography (EtOAc/Hexane, 1:4) to afford 11 as an off-white solid (1.4 g, 93%) whose \(^1\)H NMR spectrum compared very well to the literature.\(^{38}\) \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.36 (s, 1H, NH), 7.59 (dd, J 7.9, 0.8 Hz, 1H, ArH), 7.33 (dd, J 8.1, 0.8 Hz, 1H, ArH), 7.19 (ddd, J 8.1, 7.1, 1.2 Hz, 1H, ArH), 7.14 – 7.08 (m, 1H, ArH), 6.40 (dd, J 2.0, 0.8 Hz, 1H, H-3), 4.80 (s, 2H, OCH\(_2\)), 1.99 (s, 1H, OH); \(R_f = 0.39\) (EtOAc/Hexane, 4:6).

\((1H\text{-Indole-2-carbaldehyde (12}.\)) MnO\(_2\) (8.41 g, 96.8 mmol, 10 equiv.) was added to a solution of 11 (1.42 g, 9.68 mmol) in freshly distilled MeCN (90 mL) and the mixture stirred at RT for 6 h. The MnO\(_2\) was then removed by filtration through Celite, followed by rinsing with EtOAc (50 mL) to afford an orange filtrate. Removal of the solvent afforded 12 as a yellow/orange solid (1.1 g, 76%) the \(^1\)H NMR spectrum of which corresponded to the literature.\(^{35,38}\) \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.86 (s, 1H, CHO), 9.36 (s, 1H, NH), 7.77 (ddd, J 8.1, 1.5, 0.9 Hz, 1H, ArH), 7.48 (dd, J 8.4, 1.2 Hz, 1H, ArH), 7.40 (ddd, J 8.4, 6.8, 1.5 Hz, 1H, ArH), 7.29 (dd, J 2.1, 0.9 Hz, 1H, H-3), 7.19 (ddd, J 8.1, 6.8, 1.2 Hz, 1H, ArH); \(R_f = 0.77\) (EtOAc/Hexane, 2:3).

\((2\text{-Vinyl-1H-Indole (13).}\)) Methyltriphenylphosphonium bromide (MePPh\(_3\)Br) (7.39 g, 20.7 mmol, 6 equiv.) and dry THF (140 mL) were added to a two-neck round-bottom flask under N\(_2\) in an ice bath and nBuLi (13.5 mL, 19.0 mmol, 5.5 equiv.) was added drop-wise to the solution at 0 °C. During this time, the color of the solution changed from white to a deep yellow. The ice bath was removed and the temperature increased to 30 °C. The solution was stirred for 30 min at this temperature and then cooled to 0 °C. Carbaldehyde 12 (0.500 g, 3.45 mmol) in THF (20 mL) was then added drop-wise to the methylenetriphenylphosphorane solution at 0 °C. The ice bath was removed and the mixture stirred overnight at RT under N\(_2\) after which diethylether (80 mL) was added and the reaction mixture was washed with H\(_2\)O (2 × 80 mL). The aqueous layer was collected and further extracted with Et\(_2\)O (2 × 50 mL). The organic layers were combined, washed with brine (200 mL), dried (MgSO\(_4\)) and the residue purified by chromatography (EtOAc/Hexane, 5:95) to afford 13 as an off-white solid (0.361 g, 74%), the \(^1\)H NMR spectrum of which compared well to that in the literature.\(^{35}\) \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.15 (s, 1H, NH), 7.58 (ddd, J 8.2, 1.1, 0.9 Hz, 1H, ArH), 7.33 (ddd, J 8.1, 1.5, 0.9 Hz, 1H, ArH), 7.19...
4,5,6,10c-Tetrahydropyrrolo[3,4-c]carbazole-1,3(2H,3aH)-dione (14a). A neat mixture of indole 13 (0.500 g, 3.50 mmol) and maleimide (0.407 g, 4.19 mmol, 1.2 equiv.) in a round-bottom flask (5 mL) was placed in an oil bath preheated to 170 °C and kept at this temperature for 1 h to form 14a as a brown, highly insoluble, solid (0.840 g, 100%) which was used without further purification. mp = 160 – 162 °C; ¹H NMR 300 MHz, DMSO-d₆ δ 10.95 (s, 1H, NH), 7.70 (d, J 7.2 Hz, 1H, ArH), 7.26 (d, J 7.4 Hz, 1H, ArH), 7.07 – 6.93 (m, 2H, ArH), 4.17 (d, J 8.1 Hz, 1H, H-10c), 3.50 – 3.42 (m, 1H, H-5/6), 3.17 (d, J 5.1 Hz, 1H, H-4), 2.77 – 2.66 (m, 1H, H-5/6), 2.33 – 2.22 (m, 1H, H-5/6), 1.88 – 1.73 (m, 1H, H-5/6); IR (ATR, cm⁻¹) 3382, 3222, 2961, 2943, 1703, 756, 745. HRMS calcd for C₁₇H₁₃N₂O₂²⁺ [M+H]⁺, 241.0977, found 241.0966; Rᵣ = 0.22 (MeOH/EtOAc/Hexane, 1:1:3).

Pyrrolo[3,4-c]carbazole-1,3(2H,6H)-dione (15). To a stirred solution of dione 14a (0.150 g, 0.630 mmol) in DMSO (7 mL) at 30 °C under N₂ was added DDQ (0.286 g, 1.26 mmol, 2 equiv.) after which the temperature was increased to 50 °C and stirring continued for 2 h. Water (10 mL) was then added drop-wise to form a precipitate which was filtered off and washed with Et₂O and dried under high vacuum to afford the aromatised product 15 as a brown solid (0.074 g, 50%). mp = 250 – 252 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 12.08 (s, 1H, NH), 11.12 (s, 1H, NH), 8.82 (d, J 8.0 Hz, 1H, ArH), 7.85 (d, J 8.2 Hz, 1H, ArH), 7.79 (d, J 8.2 Hz, 1H, ArH), 7.65 – 7.52 (m, 2H, ArH), 7.32 (ddd, J 8.2, 6.8, 1.3 Hz, 1H, ArH); ¹³C NMR (75 MHz, DMSO-d₆) δ 170.4 (CO), 170.3 (CO), 144.1 (ArC), 141.5 (ArC), 128.1 (ArC), 126.7 (ArCH), 124.7 (ArCH), 123.8 (ArC), 120.1 (ArCH), 120.0 (ArC), 119.42 (ArCH), 118.3 (ArC), 115.6 (ArCH), 111.6 (ArCH); IR (ATR, cm⁻¹) 3186, 3057, 1697, 1451, 740; HRMS calcd for C₁₄H₉N₂O₂⁺ [M+H]⁺, 237.0664, found 237.0659; Rᵣ = 0.84 (EtOAc).

Methyl 1H-indole-2-carboxylate (18). Into a two-neck round-bottom flask fitted with a condenser was placed methanol (130 mL) followed by commercially-available indole-2-carboxylic acid 17 (5.00 g, 31.0 mmol). The solution was saturated with HCl gas followed by heating under reflux for 24 h. The reaction mixture was treated with saturated aqueous sodium bicarbonate until effervescence ceased, concentrated in vacuo, and the residue extracted with EtOAc (3 × 100 mL). The organic phases were combined and washed with brine. Hexane was added until a slight cloudiness persisted, and the solution was cooled in an ice bath to precipitate 18 as a white powder (4.04 g, 74%). ¹H NMR (300 MHz, CDCl₃) δ 9.33 (s, 1H, NH), 7.69 (d, J 8.1 Hz, 1H, ArH), 7.42 (d, J 8.3 Hz, 1H, ArH), 7.31 (app. t, dd, J 7.6 Hz, 1H, ArH), 7.23 (s, 1H, ArH), 7.14 (app. t, dd, J 7.5 Hz, 1H, ArH), 3.95 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 162.8 (CO), 137.1 (ArC), 127.5 (ArC), 127.1 (ArC), 125.4 (ArCH), 122.7 (ArCH), 120.8 (ArCH), 112.0 (ArCH), 108.9 (ArCH), 52.1 (CH₃); IR (ATR, cm⁻¹) 3332, 1689, 1527, 1438, 1255; HRMS calcd for C₁₀H₁₀NO₂⁺ [M+H]⁺, 176.0712, found 176.0657; Rᵣ = 0.32 (20% EtOAc/Hexane).

Ethyl 1-[2'-[tert-butyldimethylsilyloxy]ethyl]-1H-indole-2-carboxylate (22). To a dry, two-neck round-bottom flask charged with commercially available ethyl indole-2-carboxylate 10 (1.5 g, 7.9 mmol) under argon was added dry DMF (10 mL) and the solution cooled to 0 °C in an ice bath. NaH (0.37 g, 9.5 mmol, 1.2 equiv.) was added in portions at 0 °C and the final mixture stirred for 10 min. (2-Bromoethoxy)(tert-butyl)dimethylsilane 19 (2.1 g, 8.7 mmol, 1.1 equiv.) in DMF (5 mL) was then added drop-wise to the reaction mixture and stirred at 40 °C, under N₂, overnight. The reaction mixture was cooled to RT, poured onto cold (5 °C) H₂O (50 mL) and extracted with EtOAc (50 mL). The organic layer was then washed with brine (80 mL), dried (MgSO₄), and the residue obtained was purified by chromatography (EtOAc/Hexane, 5:95) affording 22 as a clear liquid (0.27 g, 73%). ¹H NMR (300 MHz, CDCl₃) δ 7.60 (d, J 7.9 Hz, 1H, ArH), 7.44 (d, J 8.3 Hz, 1H, ArH), 7.22 – 7.28 (m, 2H, ArH), 7.08 (dd, J 10.9, 3.9 Hz, 1H, ArH), 4.64 (t, J 5.4 Hz, 2H, OCH₂), 4.32 (q, J 7.2 Hz, 2H, CH₂), 3.89 (t, J 5.4 Hz, 2H, NCH₂), 1.36 (t, J 7.2 Hz, 3H, CH₂CH₃), 0.70 (s, 9H, 3 × CH₃), -0.26 (s, 6H, 2 × CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 162.3 (CO), 140.2 (ArC), 127.7 (ArC), 126.0 (ArC), 124.9 (ArCH), 122.5 (ArCH), 120.6 (ArCH), 111.5 (ArCH), 110.8

Arkivoc 2020, v, 129-147
van der Westhuyzen, A. E. et al.
(ArCH), 63.2 (OCH₂), 60.6 (OCH₂), 47.0 (NCH₂), 25.9 (3 x CH₃), 18.3 (C(CH₃)₂), 14.5 (CH₃), −5.6 (2 x CH₃); IR (ATR, cm⁻¹) 2957, 2929, 2857, 1708, 1358, 1252, 1220, 1196, 1080; HRMS calcd for C₁₉H₃₀NO₃Si⁺ [M+H]⁺, 348.1995, found 348.2007; Rf = 0.88 (EtOAc/Hexane, 2:8).

Methyl 1-[3'-{ tert-butyldimethylsilyloxy}propyl]-1H-indole-2-carboxylate (21). Carboxylate 21 was synthesized in a similar manner to 22 using indole 18 (2.00 g, 11.4 mmol), sodium hydride (0.597 g, 14.8 mmol) and silyl compound 20 (3.22 g, 12.7 mmol) to provide indole 21 as a clear oil (2.73 g, 69%). ¹H NMR (300 MHz, CDCl₃) δ 7.66 (d, J = 8.0 Hz, 1H, ArH), 7.51 (d, J = 8.4 Hz, 1H, ArH), 7.35 – 7.30 (m, 2H, ArH), 7.14 (app. t, dd, J = 7.4 Hz, 1H, ArH), 4.66 (t, J = 7.1 Hz, 2H, OCH₂), 3.90 (s, 3H, CH₃), 3.63 (t, J = 5.8 Hz, 2H, NCH₂), 2.06 – 1.95 (m, 2H, CH₂), 0.94 (s, 9H, 3 x CH₃), 0.06 (s, 6H, 2 x CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 162.4 (CO), 139.4 (ArC), 127.0 (ArC), 125.8 (ArC), 124.9 (ArCH), 122.5 (ArCH), 120.5 (ArCH), 110.8 (ArCH), 110.6 (ArCH), 60.2 (OCH₂), 51.6 (OCH₃), 41.7 (NCH₂), 33.8 (CH₂), 25.9 (3 x CH₃), 18.3 (C(CH₃)₃), −5.4 (2 x CH₃); IR (ATR, cm⁻¹) 2953, 1713, 1463, 1246, 1192, 1140; HRMS calcd for C₁₉H₂₉NO₃Si [M⁺], 347.1917, found 347.1921; Rf = 0.13 (2% EtOAc/Hexane).

1-[2'-{ tert-butyldimethylsilyloxy}ethyl]-1H-indol-2-yl)methanol (23a). To a stirred slurry of LiAlH₄ (0.22 g, 5.8 mmol, 2 equiv.) in dry THF (10 mL) in a two-neck round-bottom flask under argon was added a solution of 22 (1.0 g, 2.9 mmol) in dry THF (10 mL) drop-wise at 0 °C. The reaction mixture was stirred for 15 min at 0 °C after which H₂O (2 mL), NaOH (1 M, aq., 5 mL) and more H₂O (6 mL) were successively added drop-wise and stirring continued at RT for 30 min. Filtration of the reaction mixture through Celite was followed by washing the filter plug with CH₂Cl₂ (50 mL). The filtrate was washed with brine (50 mL) and the organic layer was dried (MgSO₄) and the residue was purified by chromatography (EtOAc/Hexane, 2:8) affording 23a as a white solid (0.85 g, 97%).

Mp 66 – 68 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, J = 7.8 Hz, 1H, ArH), 7.40 (d, J = 8.0 Hz, 1H, ArH), 7.30 – 7.27 (m, 1H, ArH), 7.24 – 7.18 (m, 1H, ArH), 6.48 (s, 1H, ArH), 4.78 (s, 2H, OCH₂), 3.90 (t, J = 5.2 Hz, 2H, CH₂), 4.00 (t, J = 5.2 Hz, 2H, NCH₂), 3.23 (s, 1H, OH), 0.78 (s, 9H, 3 x CH₃), -0.13 (d, J = 3.0 Hz, 6H, 2 x CH₃); ¹³C NMR (105 MHz, CDCl₃) δ 139.7 (ArC), 137.0 (ArC), 127.9 (ArC), 121.9 (ArC), 121.2 (ArCH), 119.8 (ArCH), 109.5 (ArCH), 101.8 (ArCH), 62.2 (OCH₂), 57.0 (OCH₂), 45.7 (NCH₂), 25.9 (3 x CH₃), 18.5 (C(CH₃)₃), −5.7 (2 x CH₃). HRMS calcd for C₁₉H₂₉NO₂Si⁺ [M+H]⁺, 306.1889, found 306.1889; IR (ATR, cm⁻¹): 3258, 2926, 2854, 1251, 1111; Rf = 0.84 (EtOAc/Hexane, 4:6).

The compound 23b was synthesized in a similar manner to 23a making use of the following reagents: 21 (2.18 g, 6.28 mmol) and LiAlH₄ (0.238 g, 6.28 mmol) to produce alcohol 23b as a green-colored oil (1.77 g, 88%), which required no further purification and was used directly in the next reaction. ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 7.8 Hz, 1H, ArH), 7.35 (d, J = 8.2 Hz, 1H, ArH), 7.20 (app. t, dd, J = 7.6 Hz, 1H, ArH), 7.09 (app. t, dd, J = 7.4 Hz, 1H, ArH), 6.45 (s, 1H, ArH), 4.77 (s, 2H, OCH₂), 4.33 (t, J = 6.8 Hz, 2H, OCH₂), 3.59 (t, J = 5.5 Hz, 2H, NCH₂), 2.71 (s, 1H, OH), 2.08 – 1.96 (m, 2H, CH₂), 0.93 (s, 9H, 3 x CH₃), 0.08 (s, 6H, 2 x CH₃); ¹³C NMR (105 MHz, CDCl₃) δ 139.3 (ArC), 137.2 (ArC), 127.6 (ArC), 121.8 (ArCH), 120.9 (ArCH), 119.5 (ArCH), 109.8 (ArCH), 101.8 (ArCH), 59.7 (OCH₂), 57.0 (OCH₂), 39.8 (NCH₂), 32.7 (CH₂), 25.9 (3 x CH₃), 18.3 (C(CH₃)₃), −5.29 (2 x CH₃); IR (ATR, cm⁻¹): 3351, 2928, 1461, 1253, 1092; HRMS calcd for C₁₉H₂₉NO₂Si [M⁺], 319.1968, found 319.1897; Rf = 0.10 (10% EtOAc/Hexane).

1-[2'-{ tert-butyldimethylsilyloxy}ethyl]-1H-indole-2-carbaldehyde (24a). To a solution of alcohol 23a (2.9 g, 9.9 mmol) in dry MeCN (100 mL) in a two-neck round-bottom flask was added MnO₂ (8.4 g, 96 mmol, 10 equiv.) and the reaction mixture was stirred at RT under N₂ for 8 h. The reaction mixture was filtered through Celite and the plug washed with EtOAc (80 mL). The orange colored filtrate afforded carbaldehyde 24a as a light yellow oily solid (2.4 g, 83%), which required no further purification and was used directly in the next reaction. ¹H NMR (300 MHz, CDCl₃) δ 9.88 (s, 1H, CHO), 7.71 (d, J = 8.1 Hz, 1H, ArH), 7.52 (d, J = 8.5 Hz, 1H, ArH), 7.39 – 7.36 (m, 1H, ArH), 7.28 (s, 1H, ArH), 7.20 – 7.11 (m, 1H, ArH), 4.66 (t, J = 5.2 Hz, 2H, OCH₂), 3.95 (t, J = 5.2 Hz, 1H, ArH).
Hz, 2H, NCH₂), 0.73 (s, 9H, 3 × CH₃), -0.23 (s, 6H, 2 × CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 182.7 (CO), 141.5 (ArC), 135.4 (ArC), 126.9 (ArC), 126.4 (ArCH), 123.2 (ArCH), 121.0 (ArCH), 118.3 (ArCH), 111.9 (ArCH), 63.2 (OCH₂), 47.1 (NCH₂), 25.9 (3 × CH₃), 18.2 (C(CH₃)₃), -5.7 (2 × CH₃); IR (ATR, cm⁻¹) 2953, 2925, 2854, 2804, 2726, 1668, 1249; HRMS calcd for C₁₁H₂₆N₂O₅Si⁺ [M+H]⁺, 304.1733, found 304.1730; Rᵣ = 0.79 (EtOAc/Hexane, 2:8).

1-[3'-(tert-Butyldimethylsiloxy)propyl]-1H-indole-2-carbaldehyde (24b). The compound 24b was synthesized in a similar manner to 24a making use of the following reagents: alcohol 23b (1.00 g, 3.13 mmol) and MnO₂ (5.44 g, 62.6 mmol) to produce aldehyde 24b as a clear oil (1.00 g, 100%). ¹H NMR (300 MHz, CDCl₃) δ 9.87 (s, 1H, CHO), 7.72 (d, J 8.1 Hz, 1H, ArH), 7.52 (d, J 8.5 Hz, 1H, ArH), 7.40 (app. t, dd, J 7.3 Hz, 1H, ArH), 7.26 (s, 1H, ArH), 7.16 (app. t, dd, J 7.5 Hz, 1H, ArH), 4.64 (t, J 7.1 Hz, 2H, OCH₂), 3.62 (t, J 5.8 Hz, 2H, NCH₂), 2.04 – 1.93 (m, 2H, CH₂), 0.94 (s, 9H, 3 × CH₃), 0.06 (s, 6H, 2 × CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 182.5 (CO), 140.6 (ArC), 135.3 (ArC), 126.8 (ArCH), 126.2 (ArC), 123.3 (ArCH), 120.9 (ArCH), 117.9 (ArCH), 111.0 (ArCH), 60.0 (OCH₂), 41.7 (NCH₂), 33.7 (CH₂), 25.9 (3 × CH₃), 18.3 (C(CH₃)₃), -5.4 (2 × CH₃); IR (ATR, cm⁻¹) 2856, 1665, 1460, 1319, 1249, 1110; HRMS calcd for C₁₈H₃₇NO₅Si [M⁺], 317.1811, found, 317.1790; Rᵣ = 0.15 (2% EtOAc/Hexane).

1-[2'-(tert-Butyldimethylsiloxy)ethyl]-2-vinyl-1H-indole (25a). To a dry, two-neck round-bottom flask charged with MePPh₃Br (5.58 g, 15.6 mmol, 6 equiv.) under N₂ was added THF (80 mL) and the contents stirred at 0 °C for 10 min. n-BuLi (9.87 mL, 14.3 mmol, 5.5 equiv.) was then slowly added drop-wise to the mixture. The ice bath was removed and the reaction mixture was stirred for 30 min at 0 °C. Carbaldehyde (24a) (0.79 g, 2.6 mmol) in THF (15 mL) was added drop-wise to the methylenetriphenylphosphorane solution at 0 °C. The reaction mixture was stirred at RT for 8 h followed by dilution with Et₂O (100 mL) and washing of the organic phase with H₂O (2 × 100 mL). The combined aqueous layers were extracted with Et₂O (2 × 80 mL). The organic layers were combined, washed with brine (150 mL), dried (MgSO₄) and the residue was purified by chromatography (EtOAc/Hexane, 3:9) affording 25a as an opaque oil (0.62 g, 79%). ¹H NMR (400 MHz, CDCl₃) δ 7.49 (d, J 7.8 Hz, 1H, ArH), 7.23 (d, J 8.2 Hz, 1H, ArH), 7.09 (dd, J 8.2, 7.0 Hz, 1H, ArH), 7.03 – 6.98 (m, 1H, ArH), 6.77 (dd, J 17.4, 11.2 Hz, 1H, H-1'), 6.62 (s, 1H, ArH), 5.76 (dd, J 17.4, 1.3 Hz, 1H, trans H-2'), 5.26 (dd, J 11.2, 1.3 Hz, 1H, cis H-2'), 4.20 (t, J 6.1 Hz, 2H, OCH₂), 3.81 (t, J 6.1 Hz, 2H, NCH₂), 0.75 (s, 9H, 3 × CH₃), -0.21 (s, 6H, 2 × CH₃); ¹³C NMR (105 MHz, CDCl₃) δ 138.6 (ArC), 137.5 (ArC), 128.0 (ArC), 126.4 (C-1'), 121.7 (ArCH), 120.6 (ArCH), 119.9 (C-2'), 116.4 (ArCH), 109.6 (ArCH), 99.0 (ArCH), 62.3 (OCH₂), 45.6 (NCH₂), 26.0 (3 × CH₃), 18.4 (C(CH₃)₃), -5.6 (2 × CH₃); IR (ATR, cm⁻¹) 3052, 2926, 2854, 1251; HRMS calcd for C₁₁H₂₈N₂OSi⁺ [M+H]⁺, 302.1940, found 302.1941; Rᵣ = 0.75 (EtOAc/Hexane, 1:9).

1-[3'-(tert-Butyldimethylsiloxy)propyl]-2-vinyl-1H-indole (25b). Vinyl indole 25b was synthesised by a similar protocol as for 25a making use of the following reagents: MePPh₃Br (1.39 g, 3.89 mmol), nBuLi (2.35 mL, 3.29 mmol) and aldehyde 24b (0.953 g, 3.00 mmol) to afford diene 25b as an opaque oil (0.543 g, 55%). This compound was rather unstable during handling, and, after a sample was sent for ¹H NMR spectroscopy, the rest was used directly in the next reaction. ¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, J 7.8 Hz, 1H, ArH), 7.34 (d, J 8.2 Hz, 1H, ArH), 7.16 (app. t, dd, J 7.1 Hz, 1H, ArH), 7.07 (app. t, dd, J 7.1 Hz, 1H, ArH), 6.85 (dd, J 17.4, 11.2 Hz, 1H, H-1'), 6.69 (s, 1H, ArH), 5.83 (dd, J 17.4, 1.2 Hz, 1H, trans H-2'), 5.32 (dd, J 11.2, 1.2 Hz, 1H, cis H-2'), 4.28 (t, J 7.0 Hz, 2H, OCH₂), 3.59 (t, J 5.6 Hz, 2H, NCH₂), 1.99 – 1.88 (m, 2H, CH₂), 0.94 (s, 9H, 3 × CH₃), 0.07 (s, 6H, 2 × CH₃); Rᵣ = 0.59 (5% EtOAc/Hexane).

6-[2'-{(tert-Butyldimethylsiloxy)ethyl]-4,5,6,10c-tetrahydrodipyrrrolo[3,4-c]carbazole-1,3(2H,3aH)-dione (26a)

A neat mixture of vinyl indole 25a (0.190 g, 0.630 mmol) and maleimide (0.073 g, 0.76 mmol, 1.2 equiv.) was heated in an oil bath at 170 °C whilst stirring for 30 min. Purification of the crude product by chromatography (EtOAc/Hexane, 3:7) afforded the dione adduct (26a) as a light orange solid (0.155 g) and 0.040 g of indole 25a was recovered. Yield: 62% (78% brsm). Mp 140 – 142 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 10.95 (s, 1H, NH), 3.98 (t, J 6.7 Hz, 2H, NCH₂), 3.81 (t, J 6.7 Hz, 2H, OCH₂), 3.66 (t, J 6.7 Hz, 2H, CH₂), 1.99 – 1.88 (m, 2H, CH₂), 0.94 (s, 9H, 3 × CH₃), 0.07 (s, 6H, 2 × CH₃); Rᵣ = 0.59 (5% EtOAc/Hexane).
7.73 (d, J 7.6 Hz, 1H, ArH), 7.37 (d, J 7.9 Hz, 1H, ArH), 7.11 – 6.97 (m, 2H, ArH), 4.23 – 4.14 (m, 3H, CH & OCH_, 3.84 – 3.76 (m, 2H, NCH2), 3.52 – 3.39 (m, 1H, CH), 2.92 – 2.80 (m, 1H, CH2), 2.59 – 2.51 (m, 1H, CH2), 2.37 – 2.22 (m, 1H, CH2), 1.85 – 1.69 (m, 1H, CH2), 0.70 (s, 9H, 3 × CH3), -0.27 (s, 6H, 2 × CH3); C NMR (75 MHz, DMSO-d6) δ 180.3 (CO), 178.6 (CO), 136.5 (ArC), 136.1 (ArC), 126.3 (ArC), 120.7 (ArCH), 119.5 (ArCH), 118.8 (ArCH), 109.5 (ArCH), 102.8 (ArC), 61.8 (OCH2), 44.7 (NCH2), 40.7 (CH), 40.5 (CH), 25.7 (3 × CH3), 20.9 (C(CH3)2), 18.4 (CH2) 17.9 (CH2), -5.8 (2 × CH3); HRMS calcd for C22H23N2O3Si+ [M+H]+, 399.2104, found 399.2109; IR (ATR, cm⁻¹) 3181, 2951, 2928, 2854, 1700, 1250; Rf = 0.21 (20% EtOAc/Hexane).

6-[2'-Butylidimethylsilyl]propyl]-4,5,6,10c-tetrahydropyrrolo[3,4-c]carbazole-1,3(2H,3aH)-dione (26b)

Dione 26b was prepared by a similar pyrolysis protocol as for 26a using the following: diene 25b (0.534 g, 1.69 mmol) and maleimide (0.213 g, 2.19 mmol) affording a green, viscous oil which later solidified (0.633 g, 91%). mp = 131 – 132 °C (from dioxane/hexane); 1H NMR (300 MHz, DMSO-d6) δ 7.99 (s, 1H, NH), 7.93 – 7.90 (m, 1H, ArH), 7.33 – 7.31 (m, 1H, ArH), 7.21 – 7.12 (m, 2H, ArH), 4.33 (d, J 8.0, 1H, CH), 4.18 – 4.08 (m, 2H, CH2), 3.61 – 3.49 (m, 2H, CH2), 3.45 – 3.41 (m, 1H, CH), 2.88 – 2.83 (m, 1H, CH2), 2.71 – 2.66 (m, 1H, CH2), 2.61 – 2.54 (m, 1H, CH2), 1.97 – 1.84 (m, 3H, CH and CH2), 0.93 (s, 9H, 3 × CH3), 0.06 (s, 6H, 2 × CH3); 13C NMR (75 MHz, DMSO-d6) δ 179.0 (CO), 177.1 (CO), 136.4 (ArC), 135.8 (ArC), 126.4 (ArC), 121.6 (ArCH), 119.8 (ArCH), 119.7 (ArCH), 109.2 (ArCH), 102.2 (ArC), 59.5 (OCH2), 41.5 (NCH2), 41.1 (CH), 39.5 (CH), 33.1 (CH2), 25.9 (3 × CH3), 21.3 (CH2), 18.4 (CH2), 18.2 (C(CH3)2), -5.4 (2 × CH3); IR (ATR, cm⁻¹) 3325, 2937, 2937, 1701, 1463, 1340, 1164; HRMS: calcd for C22H23N2O3Si [M]+, 412.2182, found 412.2180; Rf = 0.37 (50% EtOAc/Hexane).

6-(2'-Hydroxyethyl)-4,5,6,10c-tetrahydropyrrolo[3,4-c]carbazole-1,3(2H,3aH)-dione (27). To a dry two-neck round-bottom flask containing diene 26a (0.256 g, 0.642 mmol) in THF (8 mL) in an ice bath was added in one portion TBAF-3H2O (1.01 g 3.21 mmol, 5 equiv.), followed by stirring at RT under N2 for 30 min. CH2Cl2 (20 mL) was added to the reaction mixture and the organic phase was washed with saturated aqueous NaHCO3 (20 mL). The aqueous layer was collected and extracted with CH2Cl2 (2 × 20 mL). The organic layers were combined and washed with brine (50 mL), dried (MgSO4) and the residue obtained purified by chromatography (EtOAc/Hexane, 7:3) to afford alcohol 27 as a yellow solid (0.155 g, 86%). Mp 166 – 169 °C; 1H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H, NH), 7.74 (d, J 7.5 Hz, 1H, ArH), 7.39 (d, J 7.9 Hz, 1H, ArH), 7.12 – 6.97 (m, 2H, ArH), 4.84 (s, 1H, OH), 4.24 – 4.10 (m, 3H, CH & OCH2), 3.66 – 3.57 (m, 2H, NCH2), 3.51 – 3.42 (m, 1H, CH), 2.93 – 2.80 (m, 1H, CH2), 2.60 – 2.52 (m, 1H, CH2), 2.35 – 2.24 (m, 1H, CH2), 1.90 – 1.73 (m, 1H, CH2); 13C NMR (75 MHz, DMSO-d6) δ 180.4 (CO), 178.7 (CO), 136.6 (ArC), 136.2 (ArC), 126.3 (ArC), 121.6 (ArCH), 119.8 (ArCH), 119.7 (ArCH), 109.2 (ArCH), 102.2 (ArC), 59.5 (OCH2), 41.5 (NCH2), 41.1 (CH), 39.5 (CH), 33.1 (CH2), 25.9 (3 × CH3), 21.3 (CH2), 18.4 (CH2), 18.2 (C(CH3)2), -5.4 (2 × CH3); IR (ATR, cm⁻¹) 3235, 2937, 1701, 1463, 1340, 1164; HRMS: calcd for C16H17N2O3Si [M]+, 285.1239, found 285.1246; IR (ATR, cm⁻¹) 3421, 1704; Rf = 0.39 (EtOAc/Hexane, 8:2).

6-(2'-Hydroxyethyl)pyrrolo[3,4-c]carbazole-1,3(2H,6H)-dione (29a) to afford aryl dione 29a as a yellow solid (0.098 g, 53%). Mp 322 – 324 °C; 1H NMR (300 MHz, DMSO-d6) δ 11.15 (s, 1H, NH), 8.87 (d, J 7.8 Hz, 1H, ArH), 8.01 (d, J 8.3 Hz, 1H, ArH), 7.84 (d, J 8.3 Hz, 1H, ArH), 7.75 (d, J 8.2 Hz, 1H, ArH), 7.62 (app. t, dd, J 7.6 Hz, 1H, ArH), 7.36 (app. t, dd, J 7.4 Hz, 1H, ArH), 4.90 (t, J 4.9 Hz, 1H, OH), 4.55 (d, J 4.4 Hz, 2H, OCH2), 3.82 (d, J 4.8 Hz, 2H, NCH2); 13C NMR (75 MHz, DMSO-d6) δ 171.0 (CO), 170.9 (CO), 145.3 (ArC), 142.9 (ArC), 128.7 (ArC), 127.3 (ArCH), 125.4 (ArC), 124.5 (ArC), 120.9 (ArCH), 120.4 (ArCH), 119.9 (ArCH), 118.7 (ArC), 115.2 (ArCH), 111.1 (ArCH), 60.2 (OCH2), 46.4 (NCH2); HRMS calcd for C16H13N2O3+ [M+H]+, 281.0926, found 281.0937; IR (ATR, cm⁻¹) 3372, 1710; Rf = 0.57 (EtOAc/Hexane, 8:2).
6-[3'-1H]NMR (300 MHz, CDCl$_3$) δ 6.32 (d, $J$ 17.5 Hz, 1H, ArH), 7.16 – 7.35 (m, 2H, ArH), 7.59 (s, 3 × CH$_3$), 8.23 (m, 2H, NCH$_2$), 8.39 (s, 9H, 3 × CH$_3$), 8.72 (s, 6H, 2 × CH$_3$); HRMS calc for C$_28$H$_{22}$O$_7$N$_2$Si 493.1545, found 493.1546; IR (ATR, cm$^{-1}$) 3383, 2951, 1710, 1266, 1064; R$_f$ = 0.63 (10% EtOAc/Hexane).

6-[2'-Propynyl]-2-vinyl-1H-indole (30a). To a two-neck round-bottom flask containing substituted indole 13 (0.505 g, 3.53 mmol) in dry DMF (80 mL) under argon was added Cs$_2$CO$_3$ (3.45 g, 10.6 mmol, 3 equiv.) and propargyl bromide (1.51 g, 10.6 mmol, 3 equiv.). The reaction mixture was stirred at 60 °C for 2 d under argon, cooled to RT and then diluted with EtOAc (50 mL) and washed with H$_2$O (3 × 50 mL). The organic layers were combined, washed with brine (150 mL) and dried over MgSO$_4$. The residue was purified by chromatography (EtOAc/Hexane, 5:95) to obtain indole product 30a as a yellow solid (0.29 g, 45%). The $^1$H NMR spectrum of 30a compared well to that in the literature.$^{10}$ $^1$H NMR (300 MHz, CDCl$_3$) δ 6.32 (d, $J$ 17.5 Hz, 1H, ArH), 7.16 – 7.35 (m, 2H, ArH), 7.59 (s, 3 × CH$_3$), 8.23 (m, 2H, NCH$_2$), 8.39 (s, 9H, 3 × CH$_3$), 8.72 (s, 6H, 2 × CH$_3$); HRMS calc for C$_28$H$_{22}$O$_7$N$_2$Si 493.1545, found 493.1546; IR (ATR, cm$^{-1}$) 3383, 2951, 1710, 1266, 1064; R$_f$ = 0.63 (10% EtOAc/Hexane, 1:9).

6-[2'-Propynyl]-4,5,6,10c-tetrahydropyrrolo[3,4-c]carbazole-1,3(2H,3aH)-dione (31a). A neat mixture of indole 30a (0.114 g, 0.629 mmol) and maleimide (0.092 g 0.94 mmol, 1.5 equiv.) was placed in an oil bath pre-heated to 160 °C. The mixture solidified within a few seconds. The reaction mixture was kept at this temperature for 30 min and the brown solid was washed with CH$_2$Cl$_2$ (40 mL) and this fraction was purified by chromatography (EtOAc/Hexane, 3:7) affording 0.048 g of adduct 31a as a light yellow solid, together with unreacted 30a (0.040 gm). The CH$_2$Cl$_2$ insoluble dark brown solid was pure adduct 31a (0.035g) for a total of 0.083 g (47% and 73% brsm). Mp 252 – 254 °C; $^1$H NMR (300 MHz, CDCl$_3$-d$_6$) δ 11.03 (s, 2H, NCH$_2$), 11.16 (s, 1H, NH), 8.61 (d, $J$ 7.8 Hz, 1H, ArH), 8.63 (d, $J$ 8.4 Hz, 1H, ArH), 8.75 (d, $J$ 8.3 Hz, 1H, ArH), 7.63 (app. t, dd, $J$ 7.7 Hz, 1H, ArH), 7.63 (app. t, dd, $J$ 7.4 Hz, 1H, ArH), 4.72 – 4.69 (m, 1H, OH), 4.56 (t, $J$ 6.8 Hz, 2H, OCH$_2$), 3.46 – 3.36 (m, 2H, NCH$_2$), 2.19 – 1.89 (m, 2H, CH$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 11.43 (OCH$_2$ masked by CDCl$_3$) δ 170.3 (CO), 170.2 (CO), 144.1 (ArC), 141.8 (ArC), 128.2 (ArC), 126.8 (ArC), 124.9 (ArC), 123.9 (ArC), 120.3 (ArC), 119.7 (ArC), 119.5 (ArC), 118.0 (ArC), 113.9 (ArC), 110.01 (ArC), 57.7 (OCH$_2$), 31.5 (CH$_2$); IR (ATR, cm$^{-1}$) 3437, 3155, 2943, 1710, 1448, 1313; HRMS calcul for C$_{28}$H$_{22}$N$_2$O$_2$Si 493.1545, found 493.1546; IR (ATR, cm$^{-1}$) 3383, 2951, 1710, 1266, 1064; R$_f$ = 0.63 (10% EtOAc/Hexane, 1:9).
1H, NH), 7.77 (d, J 7.6 Hz, 1H, ArH), 7.49 (d, J 7.9 Hz, 1H, ArH), 7.20 – 7.02 (m, 2H, ArH), 5.00 (s, 2H, NCH$_2$), 4.21 (d, J 7.7 Hz, 1H, CH), 3.54 – 3.42 (m, 1H, CH), 3.28 (s, 1H, CH), 2.93 – 2.81 (m, 1H, CH$_2$), 2.64 – 2.54 (m, 1H, CH$_2$), 2.39 – 2.24 (m, 1H, CH$_2$), 1.85 (dd, J 14.1, 9.1 Hz, 1H, CH$_2$); $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 180.7 (CO), 179.0 (CO), 136.3 (ArC), 136.1 (ArC), 126.8 (ArC), 121.7 (ArCH), 120.2 (ArCH), 119.8 (ArCH), 109.9 (ArCH), 104.4 (ArC), 79.9 (CCH), 75.2 (CCH), 41.1 (NCH$_2$), 40.9 (CH), 32.2 (CH), 21.4 (CH$_2$), 18.5 (CH$_2$); HRMS calcld for C$_{17}$H$_{15}$N$_2$O$_2$ $^+$ [M+H]$^+$, 279.1134, found 279.1126; IR (ATR, cm$^{-1}$) 3293, 1700; R$_f$ = 0.45 (EtOAc/Hexane, 4:8).

6-[2'-Propynyl]pyrrolo[3,4-c]carbazole-1,3(2H,6H)-dione (32a). To a two-neck round-bottom flask containing a solution of dione 31a (0.120 g, 0.43 mmol) in dry dioxane (15 mL) was added MnO$_2$ (0.825 g, 9.49 mmol, 22 equiv.) and the reaction mixture was stirred and heated under reflux for 8 h. The cooled reaction mixture was filtered through celite and the plug washed with dioxane (20 mL). The crude product obtained by removal of the solvent was triturated with CH$_2$Cl$_2$ and acetone to afford the aryl dione 32a as a yellow solid (0.092 g, 72%). mp = 278 – 280 $^\circ$C; $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 11.22 (s, 1H, NH), 8.87 (d, J 7.9 Hz, 1H, ArH), 8.08 (d, J 8.3 Hz, 1H, ArH), 7.90 (d, J 8.3 Hz, 1H, ArH), 7.83 (d, J 8.2 Hz, 1H, ArH), 7.67 (app. t, dd, J 7.6 Hz, 1H, ArH), 7.40 (app. t, dd, J 7.6 Hz, 1H, ArH), 5.46 (s, 2H, NCH$_2$), 3.56 (s, 1H, CCH); $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 170.1 (CO), 170.1 (CO), 143.6 (ArC), 141.3 (ArC), 128.4 (ArC), 126.9 (ArCH), 125.0 (ArC), 124.7 (ArC), 121.0 (ArCH), 119.8 (ArCH), 119.5 (ArC), 114.3 (ArCH), 110.3 (ArCH), 78.4 (CCH), 75.1 (CCH), 32.4 (CH$_2$); HRMS calcld for C$_{13}$H$_{11}$N$_2$O$_2$ $^+$ [M+H]$^+$, 275.0821, found 275.0316; IR (ATR, cm$^{-1}$) 3271, 1720, 1701; R$_f$ = 0.84 (EtOAc/Hexane, 7:3).

3-(2'-Vinyl-1H-indol-1'-yl)propanenitrile (30b). To a two-neck round-bottom flask containing a solution of disubstituted indole 13 (0.750 g, 5.24 mmol) in dry MeCN (20 mL) under argon, was added acrylonitrile (2.40 mL, 36.7 mmol, 7 equiv.), followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 20 drops). The reaction mixture was stirred at RT under argon for 8 h and then diluted with H$_2$O (30 mL) and extracted with EtOAc (30 mL). The organic layer was washed with brine (50 mL) and dried over MgSO$_4$. The crude product was purified by chromatography (EtOAc/Hexane, 1:9) to afford the propanenitrile 30b as an opaque solid (0.750 g), together with unreacted indole 13 (0.098 g). Yield: 73% (84% brsm). Mp 83 – 85 $^\circ$C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.59 (d, J 7.8 Hz, 1H, ArH), 7.29 – 7.20 (m, 2H, ArH), 7.16 – 7.11 (m, 1H, ArH), 6.76 (dd, J 17.3, 11.2, 1H, H-1'), 6.72 (s, 1H, ArH), 5.86 (d, J 17.3 Hz, 1H, trans H-2'), 5.44 (d, J 11.2 Hz, 1H, cis H-2'), 4.47 (t, J 7.2 Hz, 2H, NCH$_2$), 2.73 (t, J 7.2 Hz, 2H, CCH$_2$); $^{13}$C NMR (105 MHz, CDCl$_3$) $\delta$ 137.6 (ArC), 136.7 (ArC), 128.4 (ArC), 125.0 (C-1'), 122.6 (ArCH), 121.2 (ArCH), 120.8 (ArCH), 118.1 (CN), 117.1 (C-2'), 108.8 (ArCH), 100.8 (ArCH), 39.0 (NCH$_2$), 18.6 (CH$_2$); HRMS calcld for C$_{13}$H$_{12}$N$_2$ $^+$ [M+H]$^+$, 197.1079, found 197.1072; IR (ATR, cm$^{-1}$) 2247; R$_f$ = 0.22 (EtOAc/Hexane, 1:9).

3-{1',3'-Dixo-1',2',3',3'a',4',5'-hexahydropyrrolo[3,4-c]carbazol-6(10h)-yl}-propanenitrile (31b). To a solution of propanenitrile 30b (0.280 g, 1.43 mmol) in toluene (15 mL) under N$_2$ was added maleimide (0.208 g, 2.14 mmol, 1.5 equiv.) and SnCl$_2$ (0.005 g, 0.03 mmol, 0.02 equiv.), and the reaction mixture was heated with stirring under reflux for 16 h. Saturated NaHCO$_3$ (30 mL) was added to the cold mixture and extracted with CH$_2$Cl$_2$ (2 x 30 mL). The combined organic layers were then washed with brine (80 mL) and dried over MgSO$_4$. The residue was purified by chromatography (EtOAc/Hexane, 1:1). This led to the recovery of propanenitrile 30b (0.050 g), followed by the product 31b as a yellow solid (0.243 g). Yield: 58% (71% brsm). Mp 160 – 162 $^\circ$C; $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 11.02 (s, 1H, NH), 7.76 (d, J 7.5 Hz, 1H, ArH), 7.51 (d, J 8.0 Hz, 1H, ArH), 7.17 – 7.02 (m, 2H, ArH), 4.43 (t, J 6.3 Hz, 2H, NCH$_2$), 4.21 (d, J 8.0 Hz, 1H, CH), 3.54 – 3.43 (m, 1H, CH), 2.92 (t, J 6.3 Hz, 2H, CCH$_2$), 2.88 – 2.82 (m, 1H, CH$_2$), 2.67 – 2.55 (m, 1H, CH$_2$), 2.38 – 2.25 (m, 1H, CH$_2$), 1.90 – 1.75 (m, 1H, CH$_2$); $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 180.3 (CO), 178.5 (CO), 135.9 (ArC), 135.7 (ArC), 126.5 (ArC), 121.1 (ArCH), 119.7 (ArCH), 119.4 (CN), 118.9 (ArCH), 109.5 (ArCH), 103.7 (ArC), 40.6 (CH), 38.7 (CH$_2$), 20.6 (m, 3H, NCH$_2$); HRMS calcld for C$_{13}$H$_{11}$N$_2$O$_2$ $^+$ [M+H]$^+$, 275.0316, found 275.0314; IR (ATR, cm$^{-1}$) 3271, 1720, 1701; R$_f$ = 0.84 (EtOAc/Hexane, 7:3).
38.0 (CH), 21.1 (CH₂), 18.2 (CH₂), 18.0 (CH₂); HRMS calcd for C₁₇H₁₆N₃O₂⁺ [M+H]⁺, 294.1243, found 294.1253; IR (ATR, cm⁻¹) 2246, 1703; Rᵣ = 0.21 (EtOAc/Hexane, 6:4).

3-{1',3'-Dioxo-2,3-dihydropyrrolo[3,4-c]carbazol-6(1H)-yl}propanenitrile (32b). To a two-neck round-bottom flask containing a solution of propanenitrile 31b (0.490 g, 1.67 mmol) in dry dioxane (20 mL), and under argon, was added MnO₂ (3.20 g, 36.8 mmol, 22 equiv.). The reaction mixture was stirred and heated under reflux for 8 h. The cooled mixture was filtered through celite and the residue purified by recrystallization from DMF to afford the aromatized product 32b as a yellow solid (0.145 g, 30%). M p 298 – 300 °C; ¹H NMR (300 MHz, DMSO-d₆) δ 11.21 (s, 1H, NH), 8.88 (d, J 7.8 Hz, 1H, ArH), 8.16 (d, J 8.3 Hz, 1H, ArH), 7.88 (d, J 8.5 Hz, 2H, ArH), 7.69 – 7.60 (m, 1H, ArH), 7.44 – 7.35 (m, 1H, ArH), 4.89 (t, J 6.3 Hz, 2H, NCH₂), 3.10 (t, J 6.3 Hz, 2H, CCH₂); ¹³C NMR (75 MHz, DMSO-d₆) δ 170.1 (CO), 170.1 (CO), 143.8 (ArC), 141.4 (ArC), 128.3 (ArC), 126.8 (ArCH), 124.9 (ArC), 124.5 (ArC), 120.9 (ArCH), 120.0 (ArCH), 119.6 (ArCH), 118.7 (CN), 118.3 (ArC), 114.4 (ArCH), 110.3 (ArCH), 38.6 (NCH₂), 17.0 (CCH₂); HRMS calcd for C₁₇H₁₃N₃O₂⁺ [M+H]⁺, 290.0930, found 290.0928; IR (ATR, cm⁻¹): 2251, 1716, 1697; Rᵣ = 0.32 (EtOAc/Hexane, 6:4).

Acknowledgements

AEvdW would like to acknowledge the South African National Research Foundation (NRF, Pretoria, South Africa) and Stellenbosch University (SU) for financial support during her PhD studies. WvO, SCP and IRG thank the NRF (CPRR and Incentive funding – Grant UIDs 93528, 109465 and 113322), and Stellenbosch University (Faculty and Departmental support) for research support. SCP also thanks School of Chemistry and Faculty of Science, University of the Witwatersrand for support. Central Analytical Facilities (CAF), Stellenbosch, and Mass and NMR Spectroscopy services at University of Witwatersrand, are also acknowledged for support in characterizing compounds.

Supplementary Material

The ¹H, ¹³C NMR spectra of Diels-Alder products (26b, 27, 31a, and 31b) and novel substituted pyrrolocarbazoles (28, 29a, 29b, 32a and 32b) are available in the online supplementary information file.

References

https://doi.org/10.1016/j.ejmech.2011.11.040
https://doi.org/10.1016/S1040-8428(00)00058-5
https://doi.org/10.1021/cr300410v
https://doi.org/10.1039/c1cc15851a
https://doi.org/10.1039/b923848b
https://doi.org/10.1080/14756366.2019.1640692
https://doi.org/10.1021/cr200447s
https://doi.org/10.3390/molecules200813496
https://doi.org/10.1039/C4QO00228H
https://doi.org/10.1016/S0040-4039(99)01142-9
https://doi.org/10.1021/jm0512591
https://doi.org/10.1021/jo4020672
https://doi.org/10.1021/jm070664k
https://doi.org/10.1016/j.bmc.2008.02.061
https://doi.org/10.1016/j.ejmech.2007.03.026
https://doi.org/10.1016/j.bmc.2010.09.042
https://doi.org/10.1021/jm051074u
   https://doi.org/10.1016/S0968-0896(03)00308-0
   https://doi.org/10.1016/j.bmcl.2005.10.099
   http://dx.doi.org/10.520/EJC152901
   https://doi.org/10.1002/cbic.201000352
   https://doi.org/10.1021/jm901877j
   https://doi.org/10.1002/anie.201502142
   https://doi.org/10.1021/ie00084a020
   https://doi.org/10.1021/ic00244a020
   https://doi.org/10.1039/C6CC00633G
   https://doi.org/10.1016/j.tet.2017.09.025
   https://doi.org/10.1002/ejoc.201700120
   https://doi.org/10.1021/ja062355+
   https://doi.org/10.1002/jlcr.2929
   https://doi.org/10.1002/cjoc.201200672

https://doi.org/10.1021/jm060126s

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)