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# Recent progress in the chemistry and applications of indolocarbazoles

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**Contents**



## 1. Introduction

The indolocarbazoles constitute a family of condensed heterocyclic compounds featuring an indole unit fused to one of the benzenoid rings of a carbazole moiety. Five isomers are recognized, namely indolo[2,3-*a*]carbazole (**1**), indolo[3,2-*a*]carbazole (**2**), indolo[3,2-*b*]carbazole (**3**), indolo[2,3-*b*]carbazole (**4**) and indolo[2,3-*c*]carbazole (**5**), which are distinguished by the position and orientation of the indole–carbazole ring fusion (Fig. 1).

Much of the remarkable progress in this field has been inspired by the interesting biological effects displayed by numerous natural products incorporating the indolo[2,3-*a*]carbazole skeleton.[1] One of the most intensely studied members belonging to this class, the microbial alkaloid K-252a (**6**), isolated from a culture broth of a *Nocardiopsis* sp.,[2,3] was at an early stage recognized as a potent inhibitor of protein kinase C.[4,5] Additionally, K-252a has also proven to be a formidable challenge for total synthesis.[6] Likewise, several derivatives of the isomeric system indolo[3,2-*b*]carbazole (**3**) display striking biological activity,[7] as may be illustrated by 6-formylindolo[3,2-*b*]carbazole (**7**), which is a powerful ligand for the aromatic hydrocarbon receptor (also known as the aryl hydrocarbon receptor, AhR) (Fig. 2).[8]

The advances in indolocarbazole chemistry have been previously summarized in a comprehensive review focusing on carbazole and indolocarbazole synthesis,[9] as well as an account detailing the chemistry and biological aspects of indolocarbazoles, excluding the rich group of natural indolo[2,3-*a*]pyrrolo[*c*]carbazole derivatives

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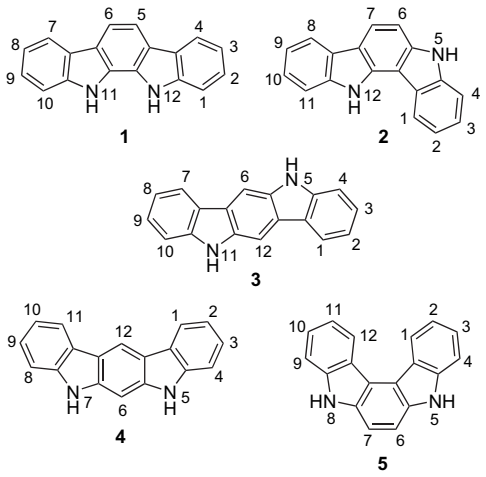


**Figure 1.**

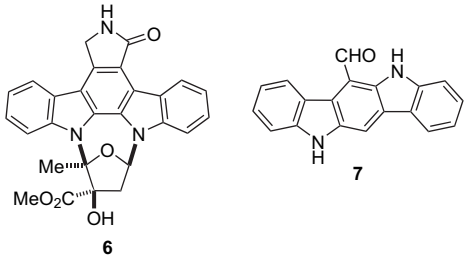


**Figure 2.**

and their synthetic analogues with carbohydrate moieties.[7] As the chemistry and biology of indolo[2,3-*a*]pyrrolo[*c*]carbazole derivatives have been discussed thoroughly over the years,[1,9–13] and will without doubt receive further treatment as demonstrated by a recent contribution summarizing the most recent achievements,[14] this topic will not be covered in this review. In addition, specialized accounts detailing the occurrence, biosynthesis, and biological effects of indolo[2,3-*a*]carbazole alkaloids,[15,16] as well as the production of indolo[2,3-*a*]carbazole derivatives through biochemical engineering[16,17] have appeared. Despite all these significant contributions, there is a need for a general overview of the field, particularly with respect to the numerous new emerging trends, such as the applications of materials based on indolocarbazoles. Moreover, the continuous development and refinement of the synthetic methods toward indolocarbazoles have eluded in-depth coverage since the year 2000. Hence, this review will summarize the literature since that time, emphasizing the aspects concerning the fundamental chemistry, applications, and biological effects of indolocarbazoles, thereby serving as an update on our previous coverage of the subject.[7] Since many of the potentially useful applications of these systems are subject to patents or patent applications, selected examples from the patent literature will also be included.

## 2. Indolo[2,3-*a*]carbazoles

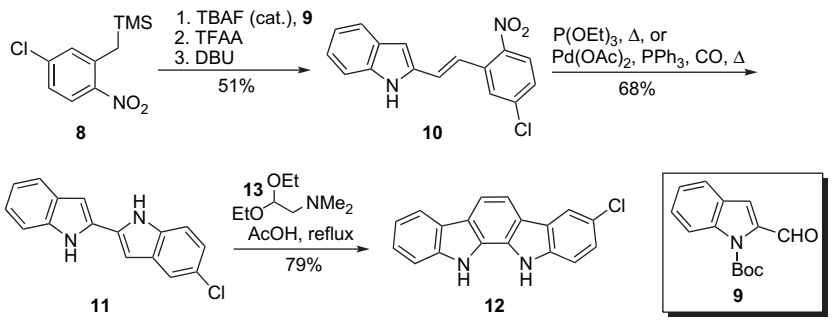
### 2.1. Synthesis and reactions

Many new approaches to indolo[2,3-*a*]carbazoles have emerged in recent years, allowing preparation of derivatives, which were previously accessible only with great difficulty. Most of the available routes rely either on direct formation of the indolocarbazole skeleton by indole ring synthesis, elaboration of bisindole precursors by construction of the central carbocyclic ring, or a combination of these strategies. Modification of the existing indolo[2,3-*a*]carbazole scaffolds using well-established functional-group transformations enables synthesis of structurally more complex derivatives. Each of these general strategies is particularly suitable for certain classes of derivatives and the method of choice depends strongly on the final target. Apart from the synthetic aspects concerning indolo[2,3-*a*]carbazoles, selected examples of the biological effects of these compounds will also be provided.

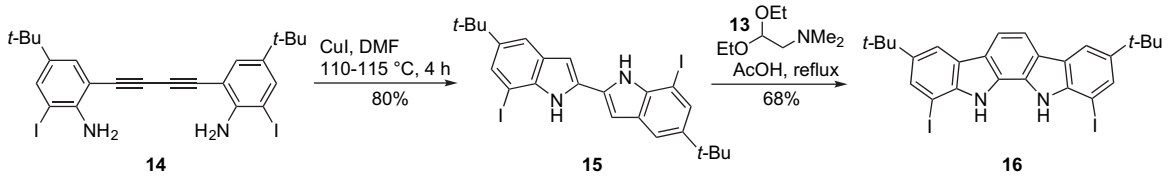
Unsymmetrically substituted indolo[2,3-*a*]carbazoles have previously been rather cumbersome to prepare.[7] A new valuable and elegant contribution to this field offers access to such products from readily available starting materials (Scheme 1). In a representative example, reaction of the nitrobenzene derivative **8**[18] with the indole-2-carboxaldehyde **9** in the presence of TBAF, followed by base-induced elimination, gave the styrene **10**, which was subsequently annulated to the 2,2′-biindolyl **11** under Cadogan[19] conditions. This material could finally be converted into the natural product, tjipanazole I[20] (**12**), by heating with *N*,*N*-dimethylacetaldehyde diethyl acetal **13** in acetic acid,[21] by analogy with a procedure originally developed for conversion of 2,3′-biindolyl into indolo[3,2-*a*]carbazole.[22]

Cyclization using the reagent **13** has also been employed en route to molecular clefts capable of coordinating anions by hydrogen-bonding interactions. In this case, double copper-mediated cyclization of the diyne **14**, which is available in three steps from 2-(*tert*-butyl)aniline via iodination, Sonogashira coupling with trimethylsilylacetylene, and copper-induced homocoupling of an intermediate 2-(alkynyl)aniline, gave the 2,2′-biindolyl **15** (Scheme 2). Eventually, formation of the indolocarbazole **16** took place upon heating of **15** with **13** in acetic acid.[23]

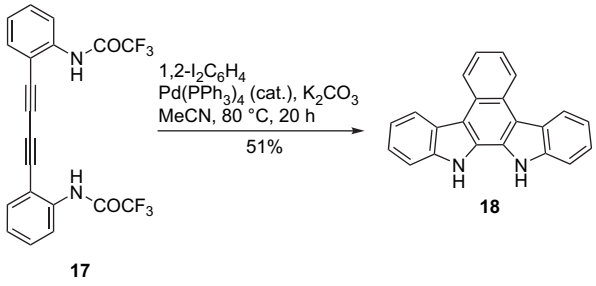
The related diyne **17** has been used as a starting material for palladium-catalyzed annulation with 1,2-diiodobenzene, which provided a direct route to the fused indolo[2,3-*a*]carbazole **18** in moderate yield, featuring the formation of two indole units and a central benzene ring (Scheme 3).[24]



**Scheme 1.**

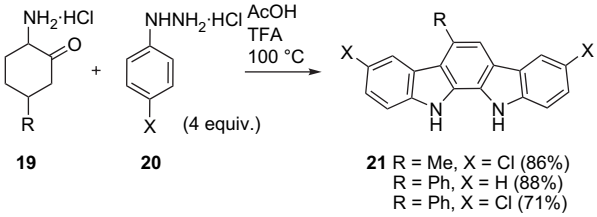



Scheme 2.



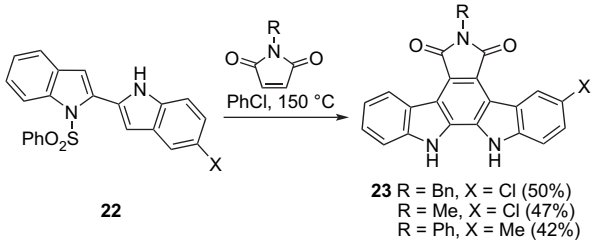

Scheme 3.

An extensive set (16 examples) of indolo[2,3-*a*]carbazoles have been prepared by the Fischer indole synthesis, as illustrated by exposure of the substituted 2-aminocyclohexanone derivatives **19** to the hydrazine hydrochlorides **20** in a medium consisting of acetic acid and trifluoroacetic acid, which led to the formation of the products **21** (Scheme 4). Similarly, application of 2-aminocyclohexanone hydrochloride in combination with suitable hydrazine derivatives gave the corresponding symmetric indolo[2,3-*a*]carbazoles.[25] The intensely studied indolo[2,3-*a*]pyrrolo[*c*]carbazole alkaloid, arcyriaflavin A,[26] has been prepared by a rather complex stepwise approach involving Fischer methodology and Cadogan annulation,[19] also affording one of its methoxy derivatives,[27] whereas double Fischer indolization between cyclohexane-1,2-dione and substituted hydrazines served as a tool for the construction of a series of symmetric 3,8- or 1,10-disubstituted indolo[2,3-*a*]carbazoles.[28]



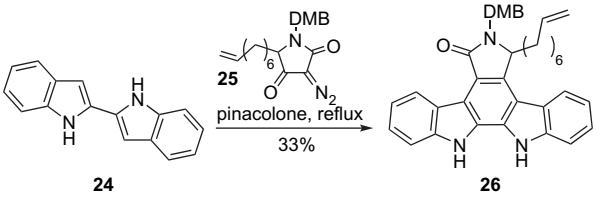

Scheme 4.

Previous attempts to effect cycloaddition reactions between 2,2′-biindolyls and acetylenes have enjoyed relatively little success, as only low yields of indolo[2,3-*a*]carbazoles could be obtained, and it has also been suggested that the products are formed via a stepwise process involving an initial Michael addition, followed by annulation of the resulting intermediate, rather than a concerted [4+2] electrocyclization.[7] However, this issue has been addressed by heating the mono-protected 2,2′-biindolyls **22**[21] with maleimides in a sealed vessel, which afforded the indolo[2,3-*a*]pyrrolo[*c*]carbazole derivatives **23**. A plausible rationale accounting for this outcome has also been suggested, involving an initial Michael addition, followed by a cyclization step, which is probably facilitated by the phenylsulfonyl group, and a final dehydrogenation with concomitant loss of the *N*-substituent (Scheme 5).[29] Moreover, it has previously been reported that some other *N*-substituted 2,2′-biindolyls, e.g., *N*-glucopyranosyl derivatives, participate in reactions with dimethyl acetylenedicarboxylate in refluxing nitrobenzene, affording the corresponding indolo[2,3-*a*]carbazoles in low-to-moderate yields.[30]




Scheme 5.

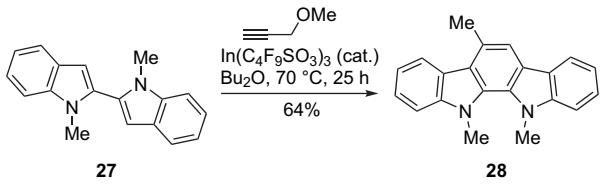
Treatment of 2,2′-biindolyl[31] (**24**) with the diazo compound **25** (DMB=3,4-dimethoxybenzyl) according to a previously established protocol[6] furnished a moderate yield of the system **26** (Scheme 6). The series of events leading to this outcome has been suggested to involve sequential C–H insertion, electrocyclization, and aromatization.[32] By applying a stepwise approach, exposure of 2,2′-biindolyl (**24**) to *N*-benzoyltetramic acid in the presence of $BF_3 \cdot OEt_2$ gave a 3-alkenyl-2,2′-biindolyl intermediate, which could thereafter be converted into the aglycone of the indolo[2,3-*a*]pyrrolo[*c*]carbazole alkaloid, staurosporine,[33] by photocyclization.[34] In addition, the alkaloid, arcyriaflavin A,[26] has been accessed via an unusual sequence featuring an initial *n*-$Bu_3P$-mediated reaction of 3,4-dibromomaleimide with a [1,2,7,8]tetrathia macrocycle featuring four indole units[35] derived from 2,2′-biindolyl (**24**) (which was, at that time, believed to be a closely related [1,2]dithiin),[36] followed by extrusion of sulfur from a presumed intermediate 1,4-dithiocine.[37]




Scheme 6.

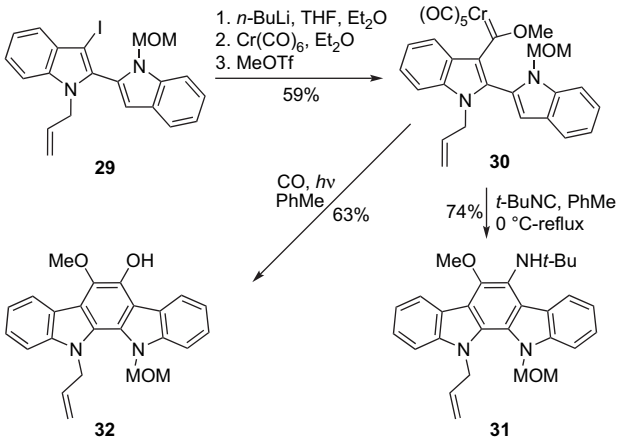
As a part of a study of the preparation of annulated carbazoles from 2-arylindoles and propargyl ethers, it was demonstrated that exposure of *N*,*N*′-dimethyl-2,2′-biindolyl (**27**) to methyl propargyl ether in the presence of the strong Lewis acid, $In(C_4F_9SO_3)_3$, as the catalyst afforded the indolocarbazole **28** in moderate yield (Scheme 7).[38]

A variety of unsymmetrically substituted indolo[2,3-*a*]carbazoles bearing combinations of methyl-, allyl-, MOM-, or Boc-substituent at the nitrogen atoms have been obtained by the reactions of chromium carbene complexes derived from suitable 3-iodo-2,2′-biindolyls, which were in turn available by Suzuki coupling of 2-iodoindole with indole-2-boronates, followed by selective iodination at one of the 3-positions. As an example, the 2,2′-biindolyl




**Scheme 7.**

**29** underwent conversion into the chromium carbene complex **30**, which could be subsequently treated with *tert*-butyl isocyanide, giving the indolo[2,3-*a*]carbazole **31**, or irradiated in the presence of carbon monoxide, affording the oxygenated product **32** (Scheme 8).[39] Admittedly, these procedures require some inconvenient operations, but they do allow the syntheses of interesting indolo[2,3-*a*]carbazoles suitable for further elaboration.

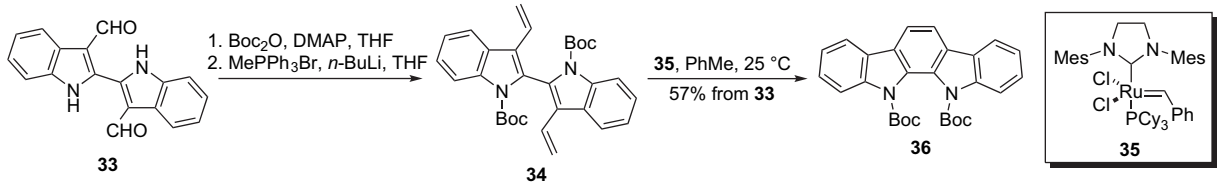



**Scheme 8.**

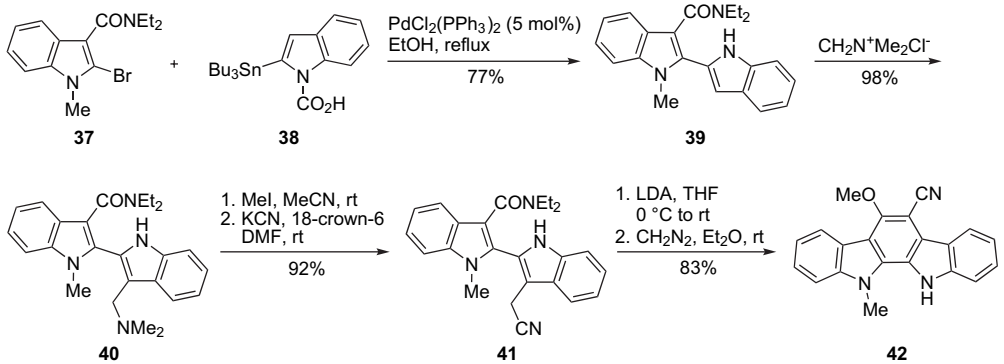
The previously known dialdehyde **33**[31] has served as a starting point for an indolocarbazole synthesis based on a ring-closing metathesis as the key transformation. Accordingly, protection and Wittig olefination of **33** gave the required precursor **34**, which was subjected to treatment with Grubbs' second-generation catalyst (**35**), rendering the simple protected indolo[2,3-*a*]carbazole **36** (Scheme 9).[40] A more straightforward route has been suggested, involving the construction of 2,2′-biindolyl-3,3′-dicarboxaldehydes by homocoupling of readily available indole-3-carboxaldehydes with the single-electron-transfer reagent, $SmI_2$, followed by annulation of the resulting products with hydrazine in refluxing THF, leading to the symmetrically substituted indolo[2,3-*a*]carbazoles via a final extrusion of nitrogen.[41]

Stille cross-coupling of the two indolic fragments **37** and **38** gave the 2,2′-biindolyl **39**, which was treated with Eschenmoser's salt, giving the gramine derivative **40** (Scheme 10). Quaternization of the amine functionality, followed by nucleophilic displacement using cyanide, yielded the molecule **41**, which could finally be annulated and *O*-methylated, thus completing a new total synthesis of the indolo[2,3-*a*]carbazole alkaloid **42**.[42]

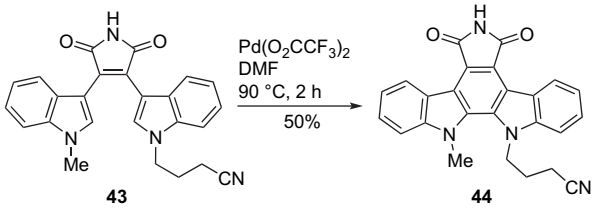
Numerous approaches to indolo[2,3-*a*]carbazoles involve creation of the direct link between the vacant C-2 sites of the indole units in bis(indol-3-yl)maleimides as the crucial step. As the required bis(indol-3-yl)maleimides are readily available compounds, e.g., by base-induced condensation of (indol-3-yl)acetamides with (indol-3-yl)glyoxylates,[43] this is a rather popular strategy. As an example, the bis(indol-3-yl)maleimide **43** was subjected to annulation induced by palladium(II) trifluoroacetate, giving the product **44** (Scheme 11), a keto derivative equipped with a longer alkyl chain of the substance, Gö6976,[44] which displays promising effects for the treatment and prevention of cancer.[45] A similar cyclization of an analogue of **43** bearing a cyanomethyl group gave the corresponding indolocarbazole in very low yield (8%).[44] In contrast, the presence of a cyanoethyl group did not lead to a significant difference in yield.[46] Higher yields (80–94%) were observed for palladium(II) trifluoroacetate-mediated annulations of bis(indol-3-yl)maleimides with masked aminopropyl chains at one of the indole nitrogen atoms.[47] However, all these cyclizations required a five-fold excess of the palladium reagent, whereas other attempts failed to give useful levels of conversion,[46] illustrating some of the limitations of this otherwise rather general cyclization strategy.




**Scheme 9.**

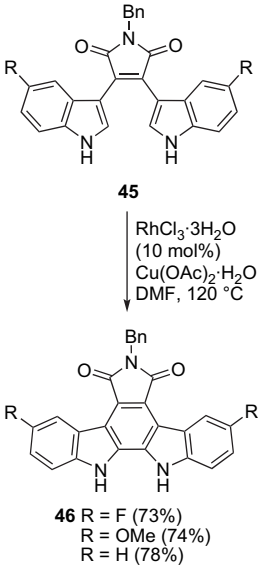



**Scheme 10.**




**Scheme 11.**

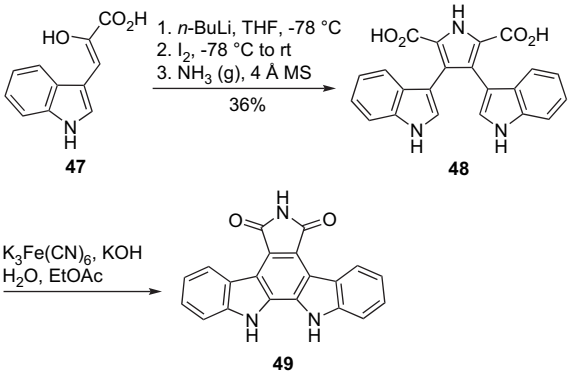
There are, however, a number of related annulations, which involve less problematic precursors, allowing the application of more cost-effective conditions. In one example, the set of bis(indol-3-yl)maleimides **45**, which was constructed by treatment of the appropriate indoles with LHMDS in toluene, followed by reaction of the resulting salts with 1-benzyl-2,3-dibromomaleimide, underwent exposure to oxidative cyclization using the catalyst, $RhCl_3 \cdot 3H_2O$ (10 mol %), in the presence of 1.1 equiv of $Cu(OAc)_2 \cdot H_2O$, leading to the target compounds **46** in good yields (Scheme 12).[48] Excellent results have also been obtained upon annulations of similar substrates with a system consisting of $Pd(OAc)_2$ (5 mol %) and $CuCl_2$ (1 equiv) in hot DMF in the presence of air,[49] as demonstrated by the successful and efficient conversion of 100 g of a specific bis(indol-3-yl)maleimide.[50] Moreover, phenyliodine(III) bis(trifluoroacetate) (PIFA) in combination with $BF_3 \cdot OEt_2$ has also been evaluated for the oxidative cyclization of bis(indol-3-yl)maleimides to indolo[2,3-*a*]pyrrolo[*c*]carbazoles, although such reactions proceeded at best in modest yields only.[51] An alternative method for the conversion of 3,3′-bisindolylmaleimides into indolo[2,3-*a*]pyrrolo[*c*]carbazoles encompassed an initial bromination at C-2 of one of the indole units, followed by annulation of the resulting product by irradiation in the presence of an amine base with simultaneous heating.[52]




**Scheme 12.**

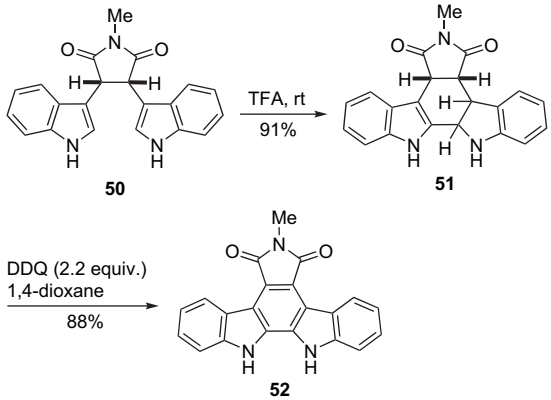
Apart from the various conditions outlined above, transformation of bis(indol-3-yl)maleimides to indolo[2,3-*a*]pyrrolo[*c*]carbazoles is often accomplished by some other well-established methods (or their variants), such as irradiation in the presence of iodine (and air),[53–58] heating in benzene in the presence of DDQ and *p*-toluenesulfonic acid,[53–55,58,59] or employing DDQ in boiling TFA.[60]

An interesting example of an oxidative annulation has been reported in connection with studies on the oxidative condensation of pyruvic acids with ammonia, which gives 3,4-diarylpyrrole-2,5-dicarboxylic acids. Consequently, sequential treatment of (indol-3-yl)pyruvic acid (**47**) (enol tautomer shown) with *n*-butyllithium, followed by iodine and ammonia, gave the diacid **48**, which was subsequently exposed to $K_3Fe(CN)_6$ in basic solution, completing an elegant and convenient biomimetic synthesis of the alkaloid, arcyriaflavin A (**49**) (Scheme 13). Unfortunately, no yield was given for the final oxidative annulation.[61]



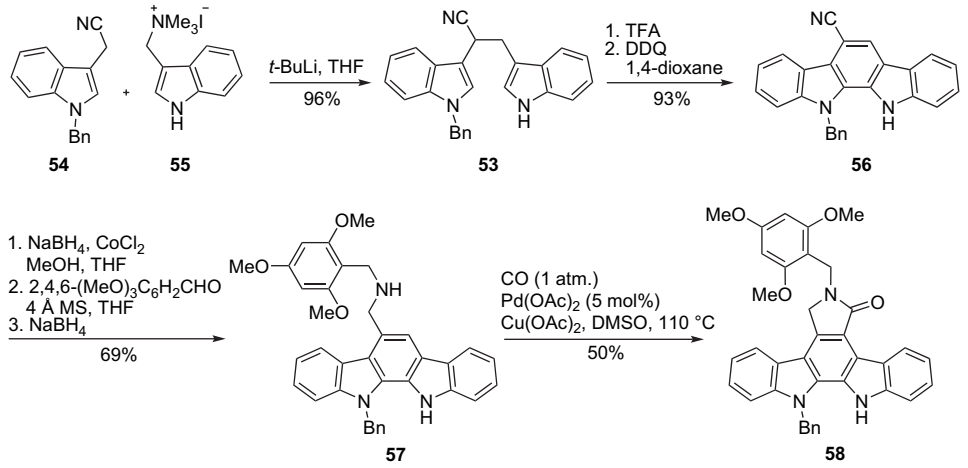

**Scheme 13.**

Acid-induced cyclization of bis(indol-3-yl)succinimides or related precursors and subsequent aromatization of the resulting intermediates constitutes yet another useful path to indolo[2,3-*a*]carbazoles.[62] The methodology may be illustrated by an initial catalytic hydrogenation of a readily available bis(indol-3-yl)maleimide to the succinimide **50**, which was thereafter treated with trifluoroacetic acid, giving the cyclized product **51**. The indolo[2,3-*a*]pyrrolo[*c*]carbazole **52** was finally obtained after treatment of **51** with DDQ in 1,4-dioxane (Scheme 14).[63] It should also be pointed out that compounds related to **51** are valuable synthetic intermediates, as the indoline part may undergo selective glycosylation[62] or selective N-oxidation using the system $H_2O_2/Na_2WO_4 \cdot 2H_2O$ (cat.) in methanol/water, which occurs with concomitant dehydrogenation, providing access to *N*-methoxyindolo[2,3-*a*]carbazole derivatives after a final methylation step.[64]




**Scheme 14.**

Following the annulation strategy discussed above, a new route to unsymmetric indolo[2,3-*a*]carbazoles has become available. After the initial construction of the precursor **53** from the acetonitrile **54** and gramine methiodide (**55**), subsequent acid-induced cyclization and ensuing dehydrogenation gave the product **56** (Scheme 15), which upon reduction and condensation with the appropriate aldehyde, followed by a second reduction, produced the amine **57**, which could eventually be converted into the indolo[2,3-



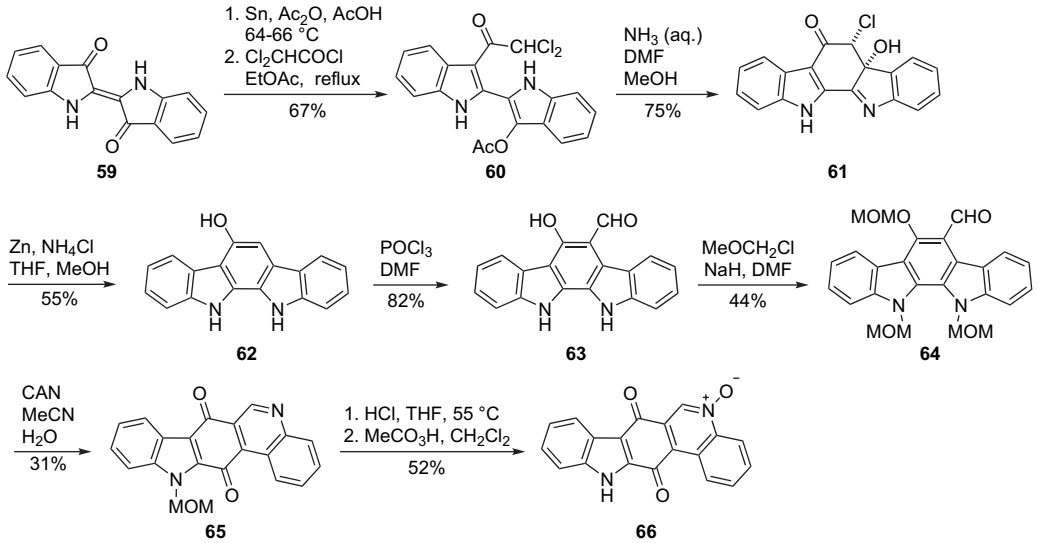

**Scheme 15.**

*a*]pyrrolo[*c*]carbazole **58** by palladium-catalyzed carbonylation. This material could finally be transformed into the aglycone of staurosporine [or K-252a (**6**)] in excellent yield.[65] Even though there are several more convenient methods for the construction of such derivatives, this approach could prove to be useful for accessing certain types of indolo[2,3-*a*]carbazoles, which are otherwise difficult to prepare, as illustrated by the amine derivative **57**.

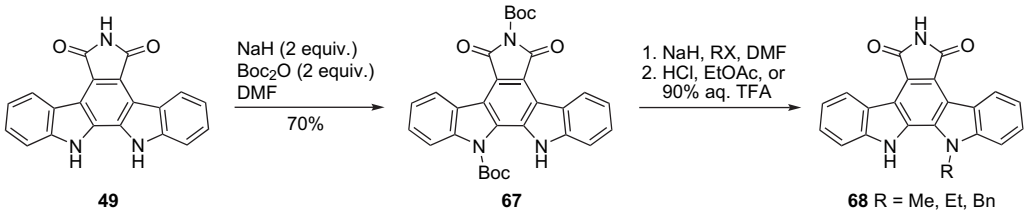
In connection with studies on a biomimetic route to the pentacyclic indole alkaloids, calothrixins, a CAN-induced rearrangement of suitable indolo[2,3-*a*]carbazoles was used in order to access the desired indolo[3,2-*j*]phenanthridine ring system.[66,67] The approach commenced with a sequential reduction and acylation of indigo (**59**), giving the 2,2′-biindolyl **60**, which was in turn cyclized to the indolo[2,3-*a*]carbazole derivative **61** and further reduced to 5-hydroxyindolo[2,3-*a*]carbazole (**62**), as described previously (Scheme 16).[68–70] The latter material was subjected to a Vilsmeier formylation, producing **63**, which was thereafter converted into the MOM-protected derivative **64**, as attempts to effect the intended rearrangement of **63** failed. However, exposure of **64** to CAN in aqueous acetonitrile afforded the system **65**, which could be finally deprotected and oxidized to the target natural product, calothrixin A (**66**).[67]

Numerous useful synthetic procedures involving modifications of the indolo[2,3-*a*]carbazole skeleton have emerged during the reporting period of this account. As an example, in the course of the development of a synthetic approach to *N*-alkylated indolo[2,3-*a*]pyrrolo[*c*]carbazoles as inhibitors of human cytomegalovirus replication, it was concluded that exposure of arcyriaflavin A (**49**) to 2 equiv each of sodium hydride and di(*tert*-butyl)dicarbonate in DMF gave the protected system **67** in good yield. Subsequent alkylation of the remaining available nitrogen atom, followed by deprotection, afforded the products **68** (Scheme 17). However, alkylations involving less reactive alkyl halides gave complex mixtures, probably owing to the instability of the protecting groups under the reaction conditions.[58] Monoalkylation of indolo[2,3-*a*]pyrrolo[*c*]carbazoles has also been performed using 3-bromopropylamine hydrobromide, giving intermediates en route to systems having amino acid units[71] or indolo[2,3-*a*]pyrrolo[*c*]carbazole–oligonucleotide conjugates.[72] Treatment of **49** with alkyl iodides in the presence of KOH as the base in acetone resulted in alkylation of all three acidic sites.[59]

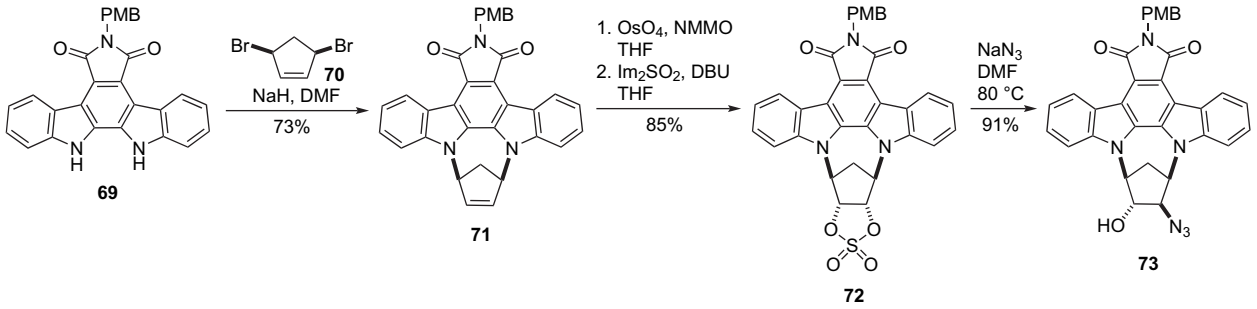
Alkylation of the partially protected indolo[2,3-*a*]pyrrolo[*c*]-carbazole **69** with the dibromide **70** proceeded in good yields, rendering the product **71** (Scheme 18). In contrast, when the parent indolo[2,3-*a*]pyrrolo[*c*]carbazole system **49** was subjected to such conditions, only a low yield of the corresponding product bearing a cyclopentene ring was obtained. The PMB-protected molecule **71** served as an excellent substrate for further manipulations, giving




**Scheme 16.**



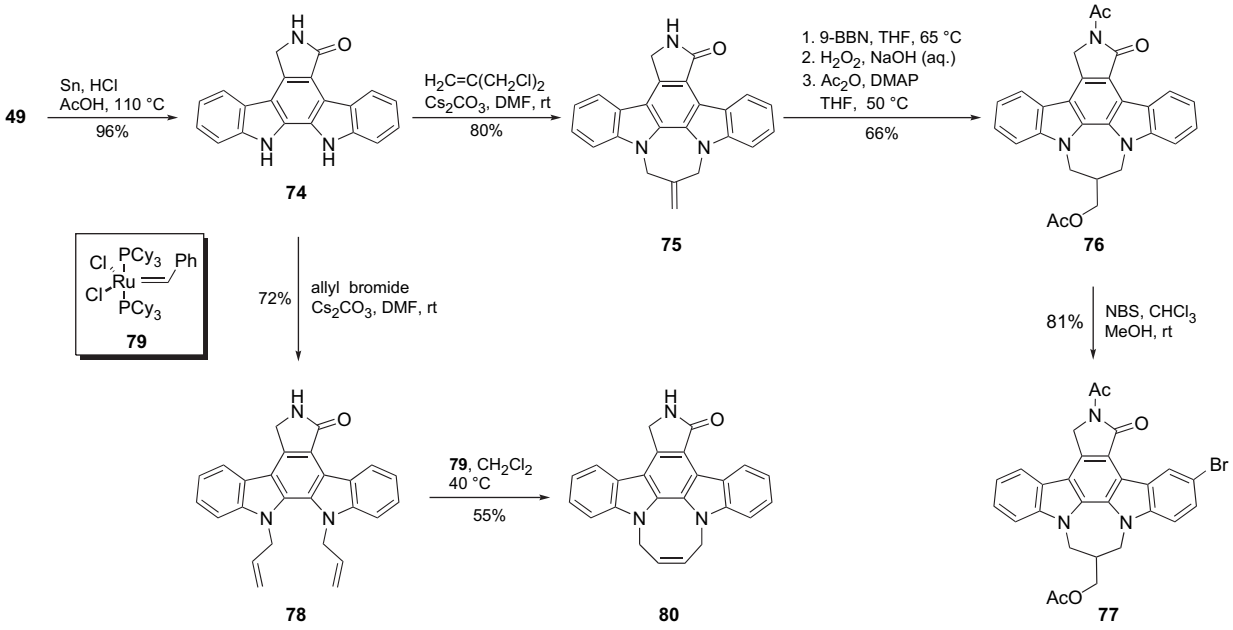

**Scheme 17.**




**Scheme 18.**

rise to kinase-inhibiting analogues of the alkaloid K-252a incorporating a cyclopentane instead of a furanose unit. As an example, dihydroxylation of **71** with $OsO_4$, followed by treatment of the resulting diol with sulfuryl diimidazole ($Im_2SO_2$), gave the sulfate **72**, which could be further converted into the azide **73** or a series of related amino derivatives.[73,74] Compound **71** has also served as a key intermediate for the development of a series of related derivatives bearing an amino group at the cyclopentane unit for application as protein kinase inhibitors.[52] New K-252a analogues and related molecules have also been prepared by a new variant of a cyclofuranosylation reaction involving the displacement of two methoxy units by the indole nitrogen atoms in a set of highly functionalized carbohydrate derivatives using CSA as the catalyst.[75]

Selective reduction of arcyriaflavin A (**49**) with tin metal gave staurosporine aglycone (**74**),[76,77] which was, for instance, further treated with 3-chloro-2-chloromethyl-1-propene, affording the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole derivative **75**. This material was used as an intermediate en route to an extensive series of new derivatives (Scheme 19). In one example, hydroboration and subsequent acetylation of **75** gave the acetate **76**, which was brominated using NBS, giving the synthetically useful product **77**.[76] On the other hand, alkylation of **74** with allyl bromide produced **78**, which was subjected to a ring-closing metathesis catalyzed by the ruthenium complex **79**, giving the heptacyclic system **80**. Related chemistry was also employed for creating targets incorporating even larger rings.[77] These developments set the stage for the elaboration of additional related indolo[2,3-*a*]carbazoles with protein kinase-inhibitory effects.[78] Stepwise reduction of one of the carbonyl functionalities in the methyl derivative of **49**, namely compound **52** (cf. Scheme 14), has been achieved by an initial




**Scheme 19.**

reduction with $LiAlH_4$ in THF and subsequent exposure of the intermediate alcohol to $Et_3SiH$ in the presence of TFA in 50% overall yield.[79] In this context, it is also noteworthy that a series of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles having an additional ring fused via the nitrogen atom and C-7 in one of the indole units has been prepared and evaluated as cyclin-dependent kinase (CDK) inhibitors[80] for cancer treatment.[81]

### 2.2. Indolo[2,3-*a*]carbazole natural products and biosynthetic aspects

The biosynthetic gene cluster, which produces the heterocyclic core of the indolocarbazole antibiotics, such as the aglycones of staurosporine[33] and rebeccamycin[82,83] (**81**), has been studied intensely, and the current understanding of the genes responsible for these transformations has been recently discussed in detail.[15,84] Consequently, only a brief summary is included in this section in order to provide a general orientation. As an example, the biochemical route to rebeccamycin (**81**) involves an initial chlorination of tryptophan at C-7, giving the building block **82** (Scheme 20).[85] Dehydrogenation of the amino acid unit in **82** by RebO, an FAD-dependent L-amino acid oxidase, forms the imine of 7-chlorotryptophan (**83**), which is in equilibrium with the corresponding (7-chloroindol-3-yl)pyruvic acid.[86,87] An ensuing oxidative coupling of two units of **83**, mediated by the enzyme RebD, produces the chromopyrrolic acid **84**,[86,88] which thereafter undergoes oxidative decarboxylation and cyclization, giving rise to the rebeccamycin aglycone (**85**).[89–91] The aglycone formation has recently been suggested to involve several nonenzymatic oxidative steps, where the enzymes participate only in the creation of the C2–C2′ bond between the indole units.[92] Eventually, two additional enzymatic transformations ensure the glycosylation and O-methylation,[93–95] necessary for completion of the biosynthesis of rebeccamycin (**81**). It should also be mentioned in this context that a biomimetic synthesis of the alkaloid, arcyriaflavin A, based on this biosynthetic pathway has been reported recently.[61]

The identification of the genes involved in the biosynthesis of staurosporine and rebeccamycin (**81**) has allowed the construction of libraries of engineered indolo[2,3-*a*]carbazole derivatives.[17,90,94] Such approaches provide new possibilities for the construction of further indolocarbazole antibiotics with increased potency and selectivity.

Several simple indolo[2,3-*a*]carbazole natural products have been found recently. As an example, the previously described alkaloid, tjipanazole D[20] (**86**) (Fig. 3), has been isolated from the terrestrial cyanobacterium *Fischerella ambigua*.[96] A study of the extracts of field-collected fruiting bodies of the myxomycete *Lycogala epidendrum* led to the identification of the new natural products, 6-hydroxystaurosporinone (**87**) and 5,6-dihydroxyarcyriaflavin A (**88**),[97] along with the known molecule, arcyriaflavin B (**89**), which has also been recently found in *Tubifera casparyi*.[98] Furthermore, the cytotoxic activity of **89** has been demonstrated in an assay involving various human cancer cell cultures.[99]

### 2.3. Special applications

The first report that structurally simple indolo[2,3-*a*]carbazoles may be used in anion sensing, by forming complexes detectable by fluorescence spectroscopy,[28] has been rapidly followed by further efforts in this direction. In one example, the macrocyclic molecule **90** (Fig. 4), which is available from the indolo[2,3-*a*]carbazole **16** (Section 2.1) via two consecutive Sonogashira reactions, has been demonstrated to bind various anions, such as halides. The association constants for a set of anionic complexes involving **90** have been determined and the possibility to distinguish between different anions by inspection of the $^1H$ NMR chemical shifts of the complexes was also inferred.[100] Moreover, the system **90** has been shown to coordinate an azide ion by hydrogen bonding between all four NH groups and one of the terminal nitrogen atoms of the anion, whereas the larger macrocycle **91** displayed a distinctly

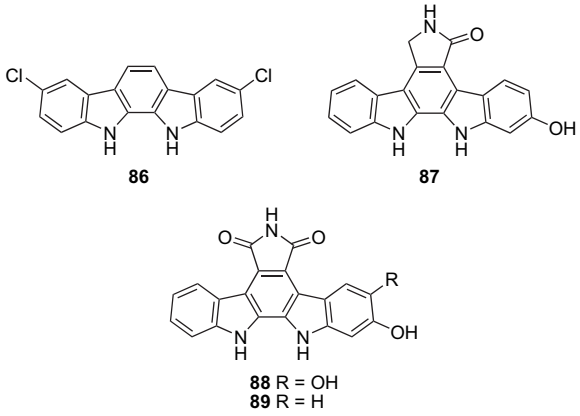
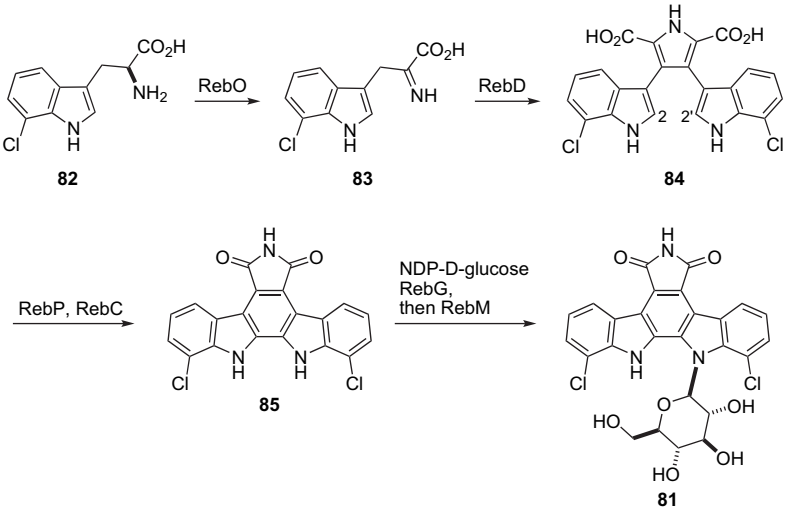



**Figure 3.**




**Scheme 20.**

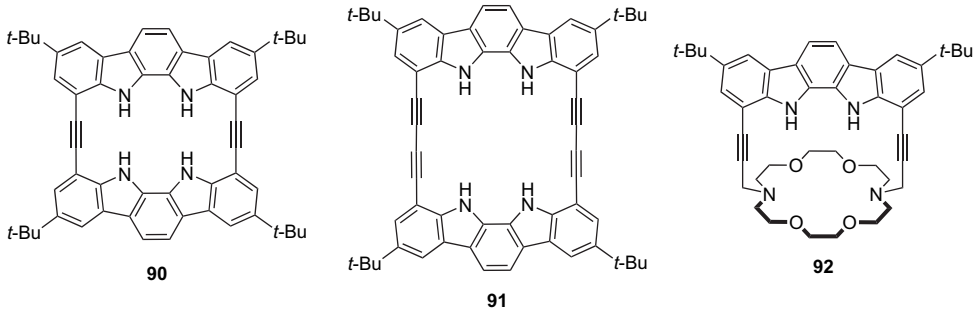



**Figure 4.**

different binding mode, forming a more stable complex, where both the terminal nitrogen atoms of the azide participate in hydrogen bonding with two NH units each.[101] The indolo[2,3-*a*]carbazole framework has been complemented with a diazacrown unit, resulting in the ion pair receptor **92**, which possessed an enhanced anion-binding capability in the presence of alkali-metal ions.[102] An additional related open indolo[2,3-*a*]carbazole derivative bearing two arylamide functionalities with the ability to coordinate anions by hydrogen bonding has also been devised.[23] Finally, two indolo[2,3-*a*]carbazole systems incorporating a fused quinoxaline unit have been prepared by annulation of 2,3-di(1*H*-indol-3-yl)quinoxaline or 2,3-di(1*H*-indol-3-yl)-6-nitroquinoxaline, respectively, and were shown to be useful for sensing fluoride and acetate ions.[60]

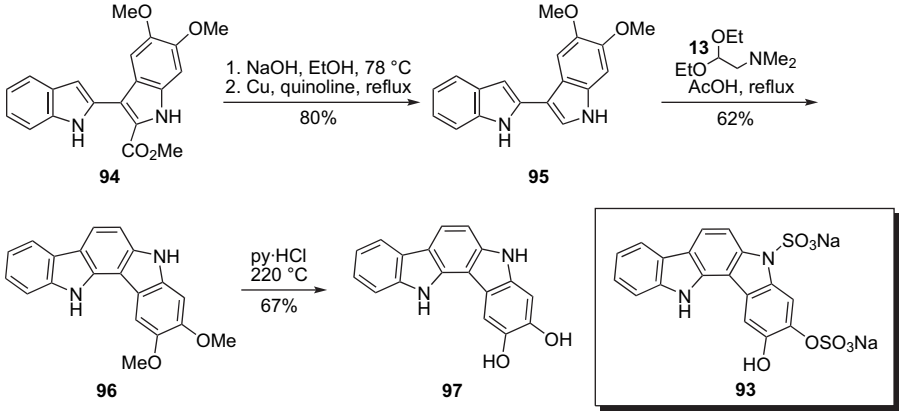
## 3. Indolo[3,2-*a*]carbazoles

The indolo[3,2-*a*]carbazole ring system has been scarcely studied and has only recently been discovered in nature. Studies of the aqueous extract of the sponge *Ancorina* sp. resulted in the isolation of the sulfated indolocarbazole alkaloid, ancorinazole (**93**).[103] A synthetic approach towards the indolocarbazole skeleton of this natural product has also emerged, involving a previously reported protocol for the construction of indolo[3,2-*a*]carbazoles from suitable 2,3′-biindolyl precursors.[22] The necessary 2,3′-biindolyl **94** was prepared in 68% yield by exposure of oxindole to trifluoromethanesulfonic anhydride followed by introduction of methyl 5,6-dimethoxyindole-2-carboxylate. Saponification of **94** and subsequent decarboxylation provided the desired precursor **95**, which was thereafter annulated to the indolo[3,2-*a*]carbazole **96** (Scheme 21). Subsequent Prey demethylation of **96** gave eventually the system **97**, which displays the same oxygenation pattern as ancorinazole.[104] Indolo[3,2-*a*]carbazole derivatives have also been encountered as minor products resulting from the reaction of indoles with maleimides in refluxing acetic acid,[105,106] as might be expected based on previous findings.[107] Additionally, it has been demonstrated recently that the heating of aromatic 1,2-diones (benzil derivatives) and indoles in refluxing toluene with the catalyst *p*-toluenesulfonic acid gives rise to indolo[3,2-*a*]carbazoles bearing two aryl groups at the central ring. Although this approach was fairly general when applied to benzils, the reaction between butane-2,3-dione and indole gave only a low yield of the expected product, 6,7-dimethylindolo[3,2-*a*]carbazole.[108]

## 4. Indolo[3,2-*b*]carbazoles

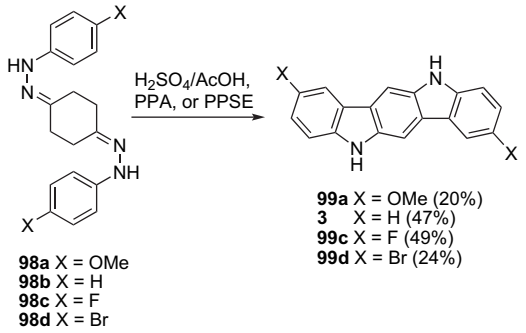
### 4.1. Synthesis and reactions

Numerous approaches for the construction of the indolo[3,2-*b*]carbazole system have been reported over the years.[7] One of the first syntheses of such compounds was developed by Robinson,[109] who used a double Fischer cyclization reaction of a bis-phenylhydrazone to access the parent indolo[3,2-*b*]carbazole **3**. This is still the method of choice for the preparation of symmetric indolo[3,2-*b*]carbazoles bearing relatively robust functional groups (e.g., halogens), as it involves readily available and inexpensive starting materials, and gives useful yields in only two steps. Following this principle, several *p*-substituted phenylhydrazones (**98a**–**d**) have recently been subjected to acid-induced cyclization (Scheme 22).[110] The electron-rich *p*-methoxyphenylhydrazone **98a** was unstable, but could nevertheless be cyclized using polyphosphoric acid trimethylsilyl ester (PPSE) to give 2,8-dimethoxyindolo[3,2-*b*]carbazole (**99a**), along with the angular 2,11-dimethoxyindolo[2,3-*c*]carbazole and a dihydro derivative thereof as a mixture that was separated into its components after exhaustive Boc-protection. The Boc groups of the purified products could then be removed thermally in quantitative yield. Polyphosphoric acid (PPA) or sulfuric acid in acetic acid was used as the medium for further cyclizations



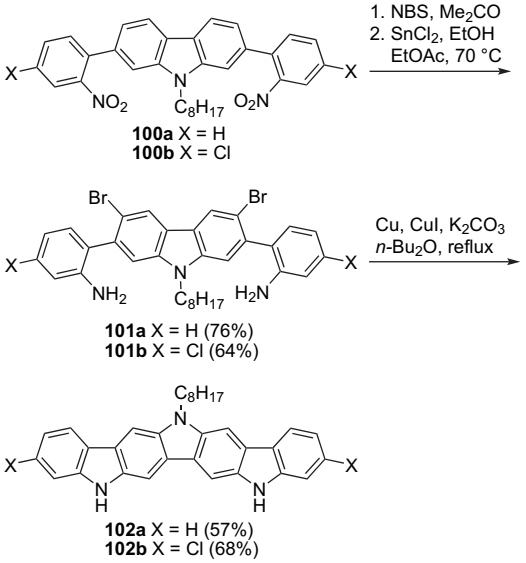

**Scheme 21.**

involving substrates **98b–d**, leading to the systems **3**, **99a**, and **99c**,**d**.[110] Compound **99d** is a useful substrate in transition metal-catalyzed coupling reactions for the construction of indolo[3,2-*b*]carbazole-based materials (see Section 4.3). The Fischer indole synthesis has also been used for the preparation of 3,9-dibromo-indolo[3,2-*b*]carbazole, as well as the 3,9-dichloro and 2,8-dichloro derivatives.[111]



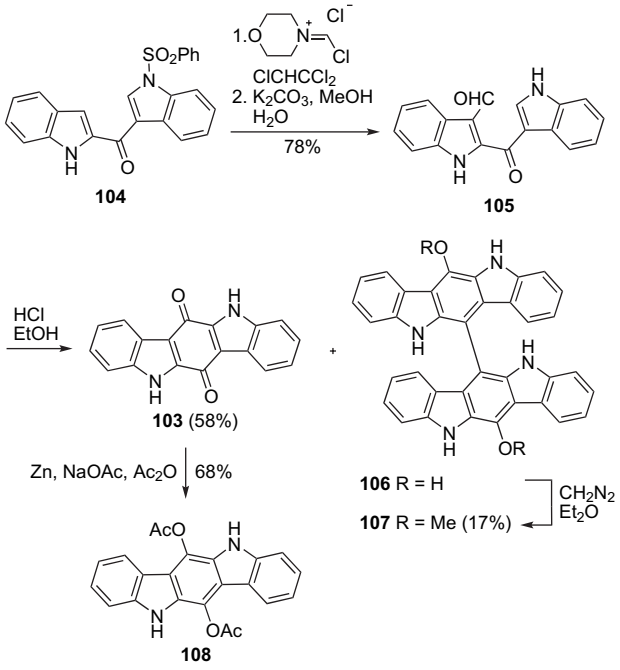

**Scheme 22.**

The Ullmann reaction has been used as the key step for the construction of extended indolo[3,2-*b*]carbazole systems. Suzuki coupling of a carbazole bis-boronate with suitable 2-bromonitrobenzenes gave the carbazole derivatives **100a**,**b**, which were thereafter brominated and reduced to the intermediates **101a**,**b** (Scheme 23). Annulation of **101a**,**b** using the system Cu/CuI/$K_2CO_3$ finally produced the heptacyclic molecules **102a**,**b** in acceptable overall yields.[112] Precursors related to **100a**,**b** have also been subjected to reductive annulation in refluxing $P(OEt)_3$ (Cadogan conditions), giving similar products, albeit in lower yield or with low regioselectivity, leading to mixtures of isomers, which are difficult to purify.[113] Nonetheless, the solubility of heptacyclic systems such as **102a**,**b** can be improved considerably by alkylation of the two remaining available nitrogen atoms.[112]




**Scheme 23.**

Several different synthetic routes to indolo[3,2-*b*]carbazole-6,12-dione (**103**) have been examined, including oxidation of the parent indolo[3,2-*b*]carbazole or employing novel ring-closing strategies. In a direct approach, oxidation of indolo[3,2-*b*]carbazole (**3**) with chromium(VI) oxide in aqueous acetic acid produced the dione **103** in 34% yield. The quinone **103** could also be constructed from indole as one of the building blocks using two sequences. The first strategy was based on the precursor **104**, which was prepared in three steps from indole and *N*-benzenesulfonylindole-3-carbaldehyde. Subsequent formylation of **104** with chloromethylene-morpholinium chloride in trichloroethylene, followed by deprotection under basic conditions, produced the aldehyde **105** in good overall yield (Scheme 24). Finally, heating of **105** in refluxing ethanol containing hydrochloric acid effected ring closure and concomitant dehydrogenation induced by air affording **103**, along with the structurally rare dimeric side product **106**, which was isolated in the form of its dimethyl ether **107** after treatment of the crude material with an ethereal diazomethane solution. However, attempted reduction of **103** to the corresponding dihydroquinone failed. Only when conducted using zinc dust in the presence of sodium acetate and acetic anhydride did the reduction take place giving the stabilized *O*,*O*′-diacetyl compound **108**. All attempts to remove the acetyl groups produced complex mixtures.[114]

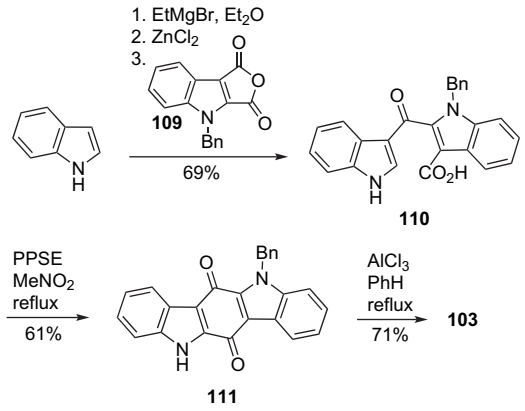



**Scheme 24.**

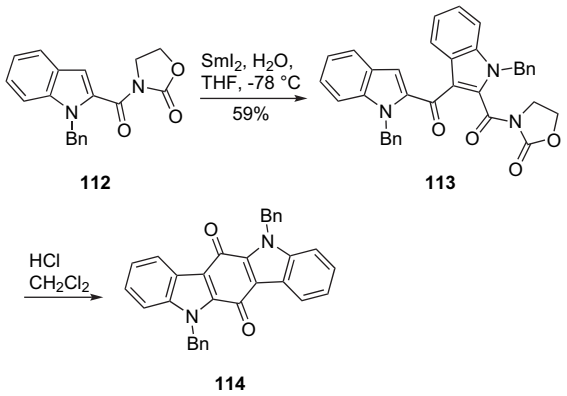
In a complementary approach, indole was treated with ethylmagnesium bromide followed by transmetallation with zinc chloride.[115] Subsequent reaction of the resulting organometallic reagent with the anhydride **109**[116] gave the keto-acid **110** in good yield (Scheme 25). Ring closure of **110** was accomplished by heating in refluxing nitromethane with PPSE to give *N*-benzylindolo[3,2-*b*]carbazole-6,12-dione (**111**), which could be finally debenzylated by $AlCl_3$ in benzene into the target compound **103**.[114]

It has recently been demonstrated that samarium diiodide-promoted reaction of the indole derivative **112** leads to the formation of the molecule **113**. Ring closure of the intermediate **113** took place upon exposure to hydrochloric acid in dichloromethane to give the dione **114** (Scheme 26). The structure of this product was confirmed by X-ray crystallography. Unfortunately, no yield was reported for this interesting transformation.[117]

Acid-induced cyclization of 2,3′-diindolylmethanes (readily available by the acylation of indoles with indole-2-carbonyl chlorides followed by reduction of the resulting ketones with $LiAlH_4$)[118] with a one-carbon synthon is an efficient procedure for the

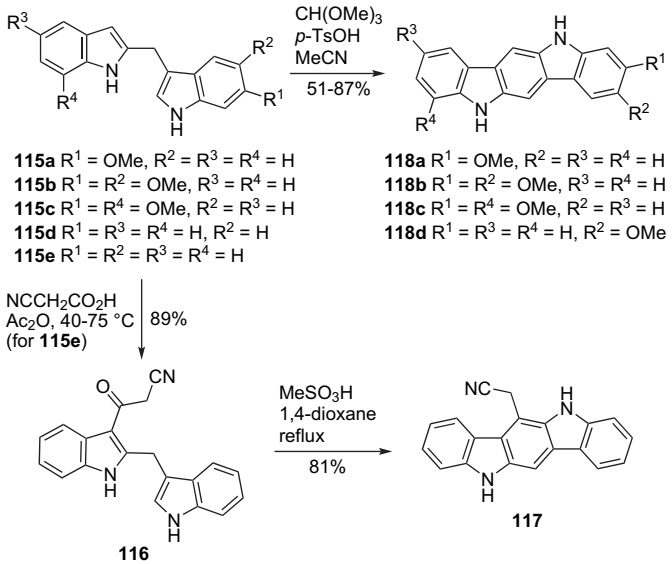



**Scheme 25.**




**Scheme 26.**

construction of unsymmetrically substituted indolo[3,2-*b*]carbazoles. In a variant relying on an intramolecular cyclization, cyanoacetylation of 2,3′-diindolylmethane **115e** with cyanoacetic acid in acetic anhydride produced the intermediate bisindole **116**, which could thereafter be annulated with methanesulfonic acid in dioxane to give the indolo[3,2-*b*]carbazole **117** in good yield (Scheme 27).[119] Prior to this study, a series of different methoxy-substituted indolo[3,2-*b*]carbazoles **118a**–**d** have been obtained upon




**Scheme 27.**

treatment of the diindolylmethanes **115a**–**d** with triethyl orthoformate in acetonitrile with *p*-TsOH as the catalyst.[118]

Reactions of 2,3′-diindolylmethanes have also been exploited in a total synthesis of the mono- or dihydroxylated 6-formylindolo[3,2-*b*]carbazole metabolites **119**–**123** (see Section 4.2). The sequence commenced with exposure of the 2,3′-diindolylmethanes **124**[118] to ethyl oxalyl chloride and pyridine in THF to give the intermediates **125**, which were subjected to annulation with methanesulfonic acid in 1,4-dioxane, affording the indolocarbazoles **126** (Scheme 28). In a one-pot procedure comprising two synthetic steps, the esters **126** were initially reduced to the corresponding alcohols, which were in turn dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to give the aldehydes **127** in 78–93% overall yield. In order to simplify the purification process (these compounds have rather poor solubility in common organic solvents), the aldehydes **127** were first demethylated using boron tribromide in methylene chloride, and all the liberated hydroxyl groups were converted into TBS ethers by treatment of the crude products with TBSCl and imidazole in DMF, providing the indolo[3,2-*b*]carbazole derivatives **128** in 41–72% yield over two steps. Finally, cleavage of the TBS groups with tetrabutylammonium fluoride in THF produced the desired metabolites **119**–**123**.[120]

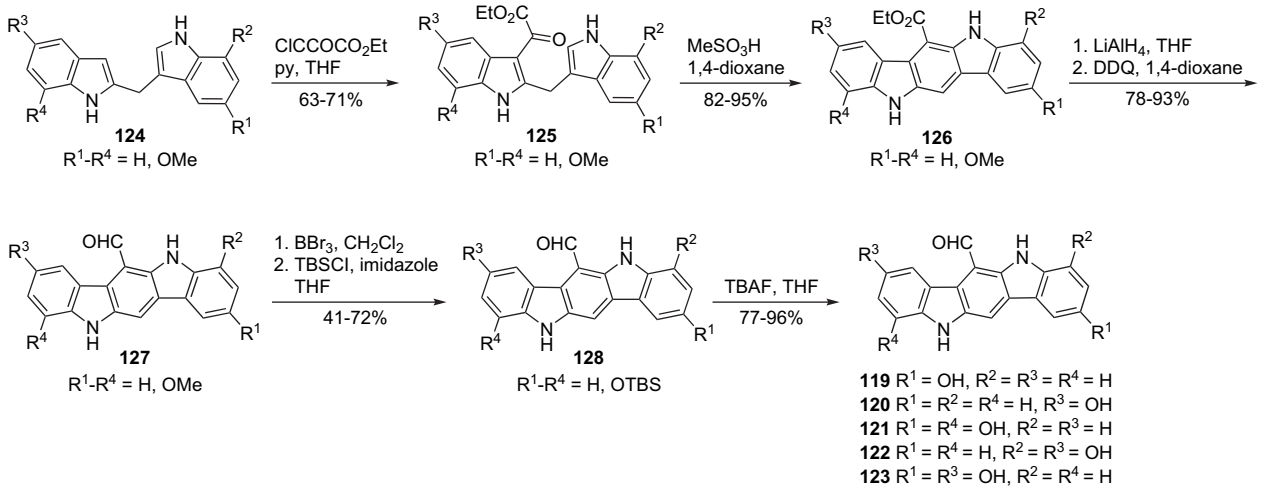
A series of 6-substituted indolo[3,2-*b*]carbazoles were prepared via 2,3′-diindolylmethanes in a robust one-pot procedure.[121] Exposure of indoles to aldehydes in the presence of iodine in acetonitrile gave the required series of intermediate 2,3′-diindolylmethanes **129** (Scheme 29). Sequential addition of triethyl orthoesters and methanesulfonic acid or sulfuric acid as the catalyst to the crude products **129** gave the indolo[3,2-*b*]carbazoles **130**, possessing either one or two substituents. During the preparation of the precursors, it was observed that the optimal reaction time was 14 h in order to achieve the most useful level of isomerization from the initially formed 3,3′-diindolylmethanes to the corresponding 2,3′-diindolylmethanes.[122] It has also been suggested recently that heating of 3,3′-diindolylmethanes with iodine in acetonitrile gives 6,12-disubstituted indolo[3,2-*b*]carbazoles in good yields with the concomitant formation of indole.[123] However, a reinvestigation of this work has been performed by Dehaen and co-workers, who concluded that the major products of such transformations are in fact 6,12-dihydroindolo[3,2-*b*]carbazoles.[124]

A double palladium-catalyzed N-arylation reaction between aniline and the terphenyl derivatives **131a**,**b** in the presence of the phosphine ligand **132** has resulted in the formation of the new unsymmetric indolo[3,2-*b*]carbazoles **133a**,**b** in moderate yield (Scheme 30).[125] Despite this successful application, this route has one additional obvious drawback, apart from the long reaction time, as the assembly of the necessary starting materials is time consuming, requiring multiple synthetic steps.

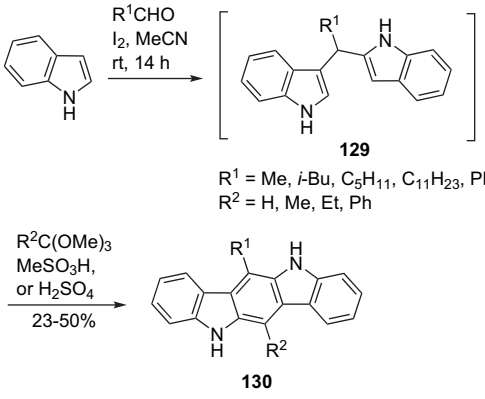
It should also be noted that, during studies on the conversion of benzoins in basic media, it was observed that thermolysis of compound **134** gives the indolo[3,2-*b*]carbazole **135** (Scheme 31). This transformation is, however, of little synthetic value, due to the harsh conditions, which produce only very low yields of useful material.[126,127]

Some of the ring-forming syntheses outlined above provide the starting materials suitable for further modification to more complex indolo[3,2-*b*]carbazole derivatives. As an example, alkylation of the indolo[3,2-*b*]carbazole **136** using sodium hydride and bromoethane in DMF gave the *N*,*N*′-dialkylated product **137** (Scheme 32). Furthermore, reaction of **136** with aryl or heteroaryl iodides under Ullmann coupling conditions in the presence of copper bronze provided access to several new *N*,*N*-diarylated products **138**.[122] Double N-alkylation of indolo[3,2-*b*]carbazoles may also be accomplished efficiently under phase-transfer conditions.[128,129]

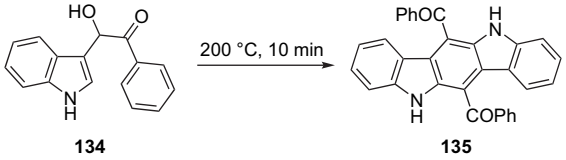
In contrast to the alkylation reaction described above, tosylation of **136** with *p*-toluenesulfonyl chloride under similar conditions




**Scheme 28.**




**Scheme 29.**

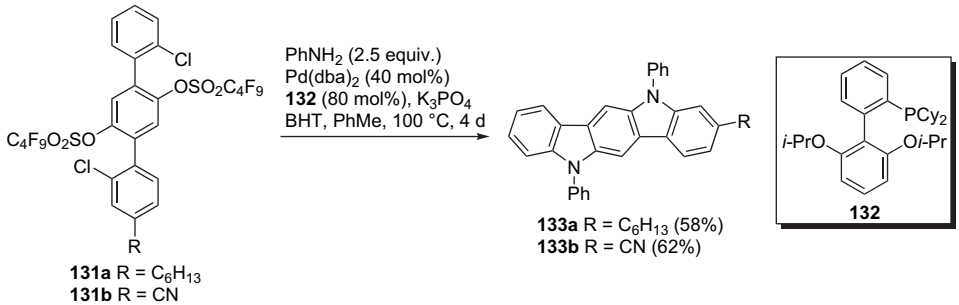



**Scheme 31.**

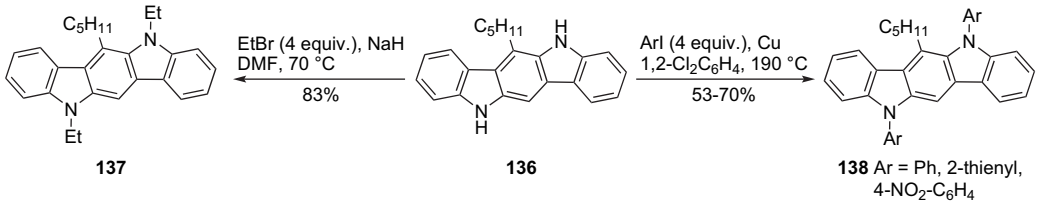
gave selective mono-substitution, providing **139** in 60% yield. The indolo[3,2-*b*]carbazole **139** also proved to be a useful synthetic intermediate, as it could be further elaborated under Ullmann conditions, giving an arylated product in good yield, which upon removal of the tosyl group with potassium hydroxide in methanol/THF rendered the system **140**, bearing a phenyl group at one of the nitrogen atoms (Scheme 33).[122] Double N-arylation of the parent indolo[3,2-*b*]carbazole (**3**) has also been performed using, for instance aryl iodides in the presence of the reagent combination, L-proline/CuI/$K_2CO_3$, in warm DMSO[130]or Cu/12-crown-6 in refluxing 1,2-dichlorobenzene.[131]

The indolo[3,2-*b*]carbazole **136** has also been used as a starting material for some additional new chemistry of this series. Azo-couplings with **136** have been achieved using arenediazonium tetrafluoroborates in THF in the presence of pyridine as the base to give the 6,12-disubstituted derivatives **141** in modest yields (Scheme 34). Formylation of **136** with an excess of the Vilsmeier reagent obtained from $POCl_3$/DMF furnished mixtures of *N*- and *C*-formylated products. However, by using 1.2 equiv of the Vilsmeier reagent in refluxing 1,2-dichloroethane, a useful route to **142** was found. The formylated indolocarbazole **142** was next converted into the benzimidazole derivatives **143** by treatment with three different *o*-phenylenediamines in DMF at 120–150 °C.[122] An interesting recent contribution involved Friedel–Crafts alkylation of the indolo[3,2-*b*]carbazole **136** with *tert*-butyl chloride using $ZnCl_2$ as the catalyst, leading to the corresponding 2,4,8,10-tetra-*tert*-butyl derivative in good yield.[132]

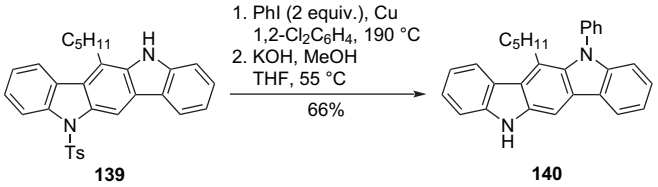
Further applications involving the indolo[3,2-*b*]carbazole **136** were realized by homocoupling across the 12,12′-positions with $FeCl_3 \cdot 6H_2O$ in chloroform, thereby producing the dimer **144** (Scheme 35).[133] Later studies showed that the same transformation could be performed with anhydrous $FeBr_3$ in chloroform.[122] Chlorination at C-12 of **136** has been accomplished with anhydrous $FeCl_3$ in chloroform, giving **145** with the co-formation of minor amounts of the dimeric side product **144**,[133] whereas bromination proceeded in excellent yield, using $FeBr_3$ in a 5:2 mixture of THF/



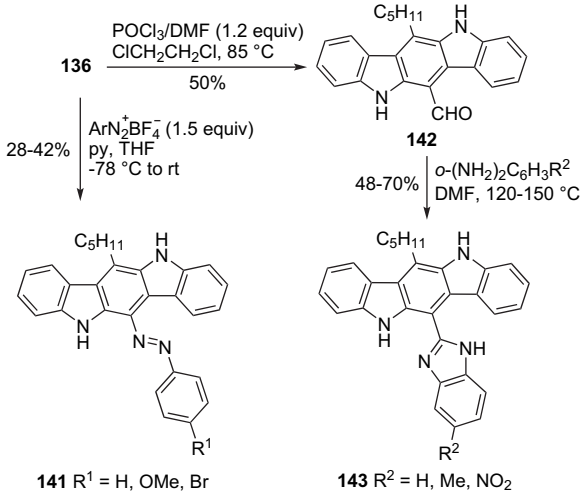

**Scheme 30.**




**Scheme 32.**




**Scheme 33.**




**Scheme 34.**

water, affording **146**.[122] The parent indolo[3,2-*b*]carbazole **3** undergoes bromination at both C-6 and C-12 upon exposure to NBS in *N*-methylpyrrolidone (NMP) at 30 °C, thereby providing 6,12-dibromoindolo[3,2-*b*]carbazole in 42% yield, a useful starting material for the construction of electroluminescent polymers.[134]

By contrast, coupling of two molecules of **136** with a slight excess of $Pd(OAc)_2$ in refluxing acetic acid resulted in the formation of the dimer **147** in modest yield (Scheme 36). In addition to the formation of one N–C bond, an acetoxy group was incorporated in the structure, which was confirmed by X-ray crystallographic analysis. The propensity of **136** to undergo dimerization reactions was further demonstrated by the preparation of a second N–C dimer lacking the acetoxy group, namely **148**, which was formed upon treatment of **136** with an excess of NaH in THF under a nitrogen atmosphere, followed by exposure to air.[133]

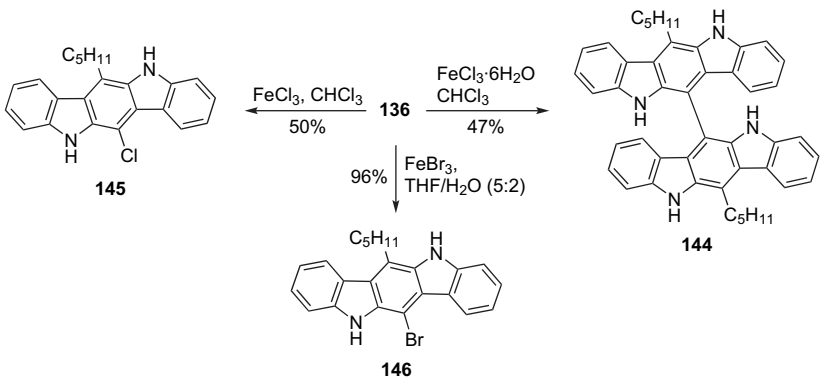
The brominated indolo[3,2-*b*]carbazole **146** served as an excellent substrate in standard Suzuki couplings using 0.5 mol% $Pd[PPh_3]_4$ as the catalyst and $K_2CO_3$ as the base in dioxane/water (4:1), producing, for instance, the extended system **149**, as well as some additional 6-aryl-12-pentylindolo[3,2-*b*]carbazole derivatives in good yields (Scheme 37).[122]

## 4.2. Naturally occurring and biologically active indolo-[3,2-*b*]carbazoles

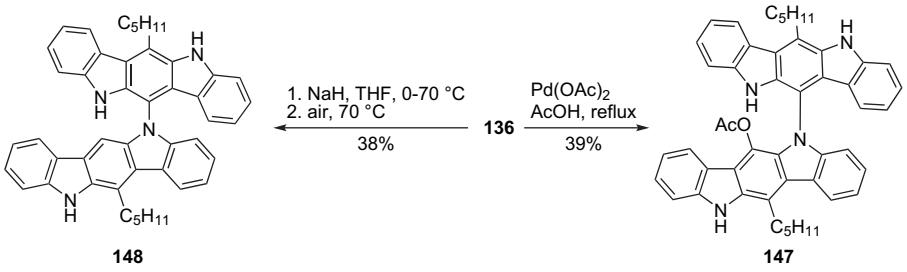
The strong on-going interest in the isolation, synthesis, and biochemical studies of indolo[3,2-*b*]carbazoles is mainly powered by the many interesting biological properties that these compounds exert in vitro and in vivo. Much knowledge of the role and action of indolo[3,2-*b*]carbazoles in organisms has been accumulated over the years, but many important questions still remain to be answered.

The lipophilic yeast *Malassezia furfur*, which is part of the residential flora of human skin, is responsible for skin disorders such as pityriasis versicolor, which is manifested by flaky lesions with variable coloration and fluorescence. When cultivated with L-tryptophan as the single nitrogen source, *M. furfur* gives rise to a variety of products, including the indolo[3,2-*b*]carbazoles **150**–**152**, malasseziazoles A–C (Fig. 5). The biogenesis of malasseziazole B (**151**) has been suggested to involve the oxidative dimerization of two units of (indol-3-yl)pyruvic acid, followed by decarboxylation and annulation.[135]

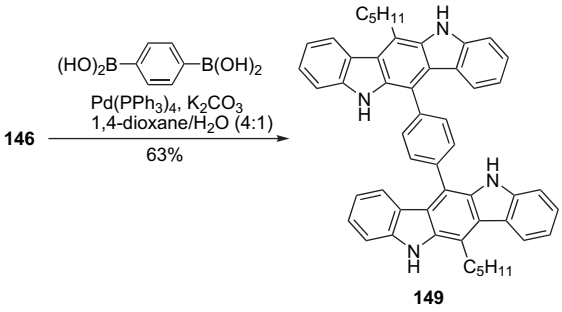
A tyrosinase guided fractionation of the ethyl acetate extract of *M. furfur* resulted in the isolation of the alkaloid malassezin (**153**), which was also demonstrated to be an agonist of the AhR, an activity, which could possibly be associated with its easy conversion



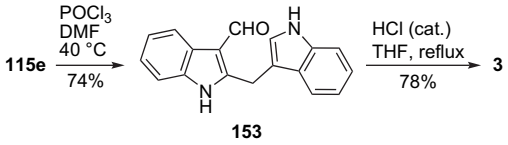

**Scheme 35.**




**Scheme 36.**




**Scheme 37.**



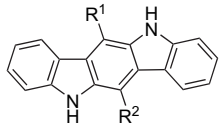

**Scheme 38.**

into indolo[3,2-*b*]carbazole (**3**) in the cell. The structure of malassezin (**153**) was verified by Vilsmeier formylation of the known 2,3′-diindolylmethane **115e**, which gave the expected product **3** (Scheme 38), as well as by X-ray crystallographic analysis. Furthermore, it was also shown that treatment of **153** with hydrochloric acid in THF leads to the expected parent indolocarbazole **3** in good yield.[136] A study has demonstrated that compound **153** induces apoptosis in primary human melanocytes, and could thus contribute to the marked depigmentation observed in individuals suffering from pityriasis versicolor.[137] It has also been proposed that several indole derivatives with phenol oxidase-inhibitory properties, which are produced by *M. furfur*, e.g., the system **150**, can be used in the treatment of hyperpigmentation, and for the inhibition of melanocytes.[138]

Consumption of vegetables belonging to the genus *Brassica*, such as cabbage, cauliflower, kohlrabi, and brussels sprouts, which all produce the secondary plant metabolite indole-3-carbinol (I3C), gives rise to the formation of indolo[3,2-*b*]carbazole (**3**), along with other products, in the gastrointestinal tract. This has been demonstrated a long time ago by experiments involving oral intubation of rats with I3C.[139] The first validated high-performance liquid chromatography (HPLC) method has been reported for the simultaneous determination of plasma levels of I3C and some of its condensation products, including indolo[3,2-*b*]carbazole (**3**), which are formed on contact of orally administered I3C with the stomach juice.[140] By measuring the tissue levels of the condensation products after oral administration of I3C in mice, it was concluded for the first time that I3C and its acid condensation products, e.g., indolo[3,2-*b*]carbazole (**3**), are absorbed from the gut and distributed systemically to blood, liver, kidney, lung, heart and brain, enabling biological interactions of these compounds in vivo.[141]

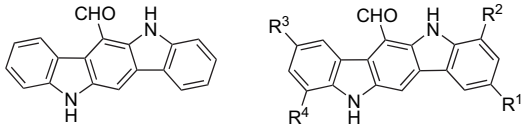
Interestingly, it has been suggested that combinations of dietary indoles, including **3**, may act as colon cancer protective agents by stimulating apoptosis and enhancing the cell defenses against DNA damage.[142] However, the comparable binding affinity of indolo[3,2-*b*]carbazole (**3**) and the persistent environmental pollutant, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), to the AhR,[139] combined with the fact that the exposure to **3** is relatively high, owing to dietary intake of its precursors through consumption of cruciferous vegetables, has raised some concern regarding its toxicity. It has been shown that indolo[3,2-*b*]carbazole (**3**) has tumor-promoting activity, which could in part be explained by activation of the AhR.[143] Meanwhile, a contemporary study could not find any evidence that exposure to indolo[3,2-*b*]carbazole (**3**) via the diet would present AhR-mediated health hazards to humans.[144] Recent results emerging from studies based on Caco-2 human colon cells indicate, e.g., that both **3** and the xenobiotic AhR agonist TCDD have inhibiting effects on benzo[*a*]pyrene (BaP)–DNA adduct formation at a BaP-concentration of 0.1 μM,[145] and that the expression of a number of genes, which were up- or down-regulated by TCDD, was modulated in a similar manner by BaP, compound **3**, as well as other natural AhR agonists present in citrus fruit extracts.[146] It is clear that much more work in this field is still required, before convincing conclusions can be drawn concerning the implications of the wide range of biological effects of **3** and its derivatives.

Simple indolo[3,2-*b*]carbazoles have recently been shown to display a variety of additional different biological effects. The tryptophan photoproduct, 6-formylindolo[3,2-*b*]carbazole (**7**) (Fig. 6), which was originally identified as a high-affinity AhR ligand formed by UV photolysis,[8] has also been recognized as one of the multiple products formed from tryptophan solutions upon window



**150** $R^1$ = $COCO_2H$, $R^2$ = H
**151** $R^1$ = $COCO_2H$, $R^2$ = CHO
**152** $R^1$ = $CO_2H$, $R^2$ = CHO

**Figure 5.**



**7**

**119** $R^1$ = OH, $R^2$ = $R^3$ = $R^4$ = H
**120** $R^1$ = $R^2$ = $R^4$ = H, $R^3$ = OH
**121** $R^1$ = $R^4$ = OH, $R^2$ = $R^3$ = H
**122** $R^1$ = $R^4$ = H, $R^2$ = $R^3$ = OH
**123** $R^1$ = $R^3$ = OH, $R^2$ = $R^4$ = H

**Figure 6.**

sunlight exposure indoors, capable of eliciting CYP1A induction in primary chick embryo hepatocytes and in vivo.[147] Furthermore, **7** has also been found in a cell culture medium, contributing to the background activity of the cytochrome P450 1A1 (CYP1A1) in cultured cells.[148] Recent data have provided evidence for an intracellular generation of 6-formylindolo[3,2-*b*]carbazole (**7**) as an important AhR-dependent initiator of the UVB stress response.[149] Photo-oxidized tryptophan derivatives such as **7** have also been suggested to play a role in the neuro-endocrine signaling of light, thus acting as light hormones,[150] whereas a recent study demonstrated the potential for photo products like **7** to modulate light-dependent regulation of the circadian rhythm through activation of the AhR signaling pathway.[151] Both indolo[3,2-*b*]carbazole (**3**) and 6-formylindolo[3,2-*b*]carbazole (**7**) have also been shown to have an inhibitory effect on the estrogen $\alpha$ receptor through binding and triggering of the AhR in fish liver.[152] In addition, it has been suggested that 6-formylindolo[3,2-*b*]carbazole (**7**) has an influence on the autoregulation of CYP1A1 transcription.[153]

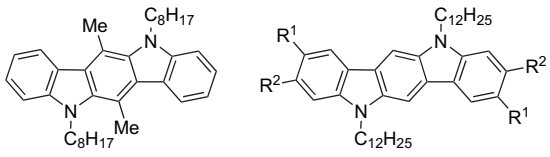
The reversed-phase HPLC elution profile from the metabolite mixture of **7** showed three distinct fractions.[153] In a later study, the three fractions were analyzed by NMR spectroscopy and it was deduced that the first fraction contained **123** as a single compound, whereas the metabolites **121** and **122** co-eluted in the second fraction. The third fraction contained a mixture of compounds **119** and **120** (Fig. 6).[154] It was later established that **119** and **120** serve as precursors for further metabolism into **121**–**123** by CYP1A1/CYP1A2-mediated hydroxylation. The hydroxylated metabolites are subjected to further metabolism, especially sulfo conjugation.[155] The structures of all these metabolites have also been confirmed by total synthesis[120] (Section 4.1).

Different computational screening models have been tested and verified to give good correlation and good prediction for flat aromatics like the dibenzo-*p*-dioxins, dibenzofurans, and indolo[3,2-*b*]carbazoles, i.e., compounds, which are known to have a strong affinity for the AhR,[156] providing theoretical support for earlier experimental studies, which have been summarized in our previous review,[7] and for a recent contribution which outlines the current status of the quest for endogenous AhR activators.[157] Since the physiological function of the AhR is still not yet fully understood, more studies on this subject will surely be conducted.

### 4.3. Technical applications, structural aspects, and other related studies

The planar aromatic structure, which allows extensive conjugation, in conjunction with the stability, and the relatively easy availability of indolo[3,2-*b*]carbazoles make them potentially suitable for the design of various electronic components, as evidenced by the many recent contributions targeting such applications. Even rather simple indolo[3,2-*b*]carbazoles can exhibit promising properties in this context, which have been demonstrated by the construction of an organic field effect transistor (OFET) incorporating an active layer consisting of the material **154** (Fig. 7).[128] Likewise, organic thin-film transistors have been based on the *N*-alkylated indolo[3,2-*b*]carbazoles **155a**–**c**. In particular, the derivative **155b** proved to be valuable, giving devices with high mobility.[111] The structural, optical, and photophysical properties of these types of indolo[3,2-*b*]carbazoles have been discussed in detail from both the experimental and the theoretical viewpoints, providing an additional theoretical basis for further rational design of new electronic devices.[130,158–161] A specialized account detailing some aspects of the preparation and properties of indolo[3,2-*b*]carbazole materials, including some extended systems, is also available.[162]

Thin-film transistors fabricated from the system **156** also exhibited some interesting characteristics, e.g., good environmental stability, which is in part due to the relatively low-lying HOMOs of

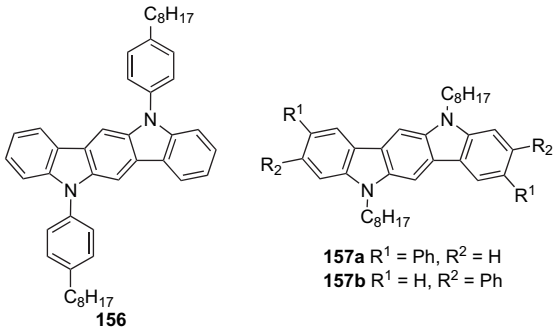



**154**

**155a** $R^1 = R^2 = H$
**155b** $R^1 = Cl$, $R^2 = H$
**155c** $R^1 = H$, $R^2 = Cl$

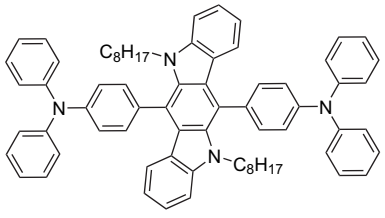
**Figure 7.**

**156** (Fig. 8).[131] Suzuki coupling of 2,8- and 3,9-dibromo-5,11-dioctylindolo[3,2-*b*]carbazole with phenylboronic acid provided the materials **157a** and **157b**, respectively, suitable for the fabrication of field-effect transistors (FETs) with high hole mobility and stability, which proved to be particularly fruitful in the case of **157b**. Two closely related indolo[3,2-*b*]carbazoles substituted with two thien-2-yl units were also prepared for similar applications using Stille coupling.[163] In addition, it has been demonstrated that the condensation of indole with 4-(diphenylamino)-benzaldehyde in the presence of sulfuric acid following a known procedure[164] gave, after subsequent phase-transfer alkylation, the system **158**, a potential hole-transporting material for organic light-emitting diodes.[129] Materials incorporating two indolo[3,2-*b*]carbazole moieties interlinked by alkenes, alkynes, or various aromatics have also been designed using palladium-catalyzed coupling reactions,[165] and used for the construction of electronic devices.[166] A comparison between three 5,11-di-*n*-octylindolo[3,2-*b*]carbazole derivatives bearing two 4-diphenylaminophenyl, 9,9′-di-*n*-butylfluoren-2-yl, or 1-*n*-butylcarbazol-3-yl substituents, respectively, at C-2 and C-8, revealed that the presence of phenyl- and fluorenyl-based moieties is crucial during the design of materials with sufficient hole-transporting properties for the fabrication of electroluminescent devices.[167] The value of indolo[3,2-*b*]carbazoles as active materials

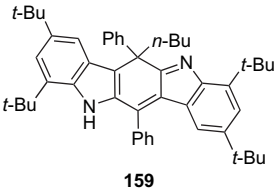



**156**

**157a** $R^1 = Ph$, $R^2 = H$
**157b** $R^1 = H$, $R^2 = Ph$

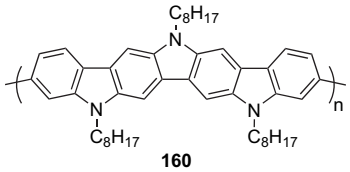



**158**

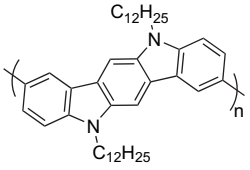



**159**

**Figure 8.**




**160**




**161**

**Figure 9.**

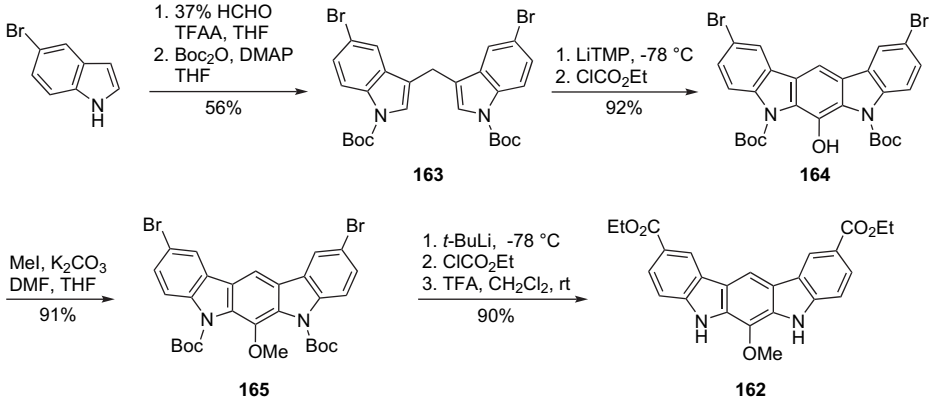
for various electronic devices is also evident from the numerous additional recent patent applications.[168–176] Additionally, the 5,12-dihydroindolo[3,2-*b*]carbazole **159** obtained by initial Friedel–Crafts *tert*-butylation of 6,12-diphenylindolo[3,2-*b*]carbazole, and subsequent introduction of a butyl group using *n*-butyllithium, has been identified as a new sensor for fluoride ions or Brönsted acids.[132]

The availability of halogenated indolo[3,2-*b*]carbazoles has provided new opportunities for the construction of polymeric materials based on this skeleton. Polymerization of a fully alkylated derivative of the extended indolo[3,2-*b*]carbazole system **102b**[112] (Section 4.1), using the reagent combination, $Ni(COD)_2$/COD/2,2′-bipyridyl, in a mixture of DMF/THF (1:3), gave the polymer **160** in good yield (Fig. 9). Similar polymerization of some related chlorinated indolo[3,2-*b*]carbazoles gave additional indolo[3,2-*b*]carbazole polymers.[177] These types of polymers have been subjected to detailed studies probing their optical, electrical, and conducting properties.[177,178] The monomer, 5,11-bis(dodecyl)indolo[3,2-*b*]carbazole, can be polymerized regioselectively with $FeCl_3$ in chlorobenzene at 50 °C, giving the polymeric material **161**, which formed the basis for solution-processed FETs with good air and light stabilities.[179] Moreover, several examples of co-polymers having alternating indolo[3,2-*b*]carbazole and 2,2′-bithiophene units,[178,180] or 9,9-dialkylfluorene blocks[134] have been prepared and characterized. The latter type of co-polymers may be used for the fabrication of luminescent devices.[134] It has been demonstrated in a recent study that the characteristics of indolocarbazole–fluorene co-polymers differ markedly between materials derived by Suzuki coupling of 9,9-dihexylfluorene-2,7-bis(trimethyleneborate) with 3,9-dibromo-di(2′-ethylhexyl)-indolo[3,2-*b*]carbazole or 2,8-dibromo-di(2′-ethylhexyl)-indolo[3,2-*b*]carbazole. The latter material displayed, for example, better FET performance, but a lower emission maximum than its isomer. Meanwhile, the FET hole mobilities of both co-polymers were better that that of polyfluorene.[181]

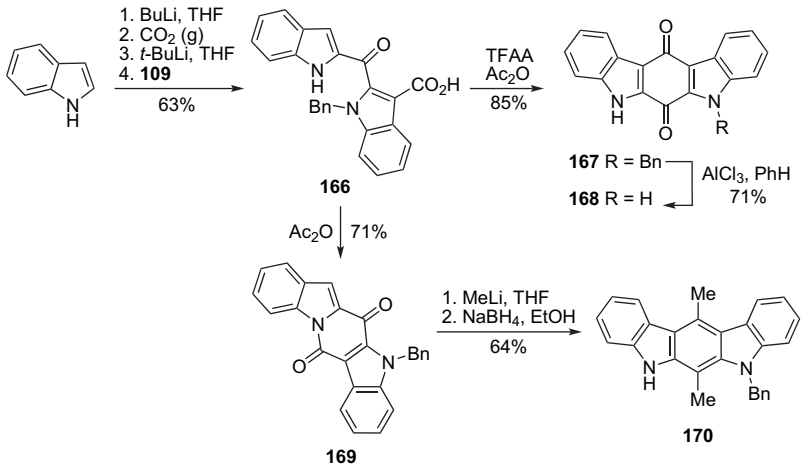
## 5. Indolo[2,3-*b*]carbazoles

Until very recently, there have been only a few studies focusing on indolo[2,3-*b*]carbazoles. This may soon change, however, as the indolo[2,3-*b*]carbazole-2,10-dicarboxylate SR13668 (**162**) has been identified as a potent anticancer agent. The route to **162** involved an initial conversion of 5-bromoindole into the corresponding 3,3′-diindolylmethane (by reaction with formaldehyde in TFA), which was thereafter protected, giving the intermediate **163**, prior to annulation to the indolo[2,3-*b*]carbazole **164** (Scheme 39). The target molecule **162** could then be created by O-alkylation, giving **165**, which underwent a double halogen–metal exchange, followed by quenching with ethyl chloroformate, and a final removal of the protecting groups.[182] As a potential cancer chemopreventive agent, **162** was included in an investigation assessing its genotoxic activity, where it showed a negative response in all the used assays.[183] The suggested new therapeutic applications of this class of indolocarbazoles range from the prevention of cancer,[184] ailments associated with respiratory syncytial virus (RSV) infections,[185] or oral mucosal disorders[186] to the treatment of diseases caused by human cytomegalovirus (HCMV)[187] or papillomavirus.[188] It should also be mentioned that a study of the methylation and allylation of 6-(indol-3-yl)-indolo[2,3-*b*]carbazole has been performed, leading to the isolation and characterization of its trimethyl, as well as its mono-, di-, and triallyl derivatives.[189] There is also a report available concerning the preparation of some partially unsaturated indolo[2,3-*b*]carbazoles by treatment of 2-hydroxymethylene-1,2,3,4-tetrahydrocarbazol-1-ones with a diazonium salt derived from *p*-toluidine under Japp–Klingemann conditions followed by annulation of the resulting intermediates in an acidic medium.[190] A later contribution based on similar chemistry involved the use of methyl 2-(1-oxo-1,2,3,4-tetrahydrocarbazol-2-yl)oxoacetate derivatives as the starting materials.[191]

A concise synthesis of indolo[2,3-*b*]carbazole-6,12-diones has been reported, using indole as the starting material (Scheme 40).[114] Hence, indole was treated, following the Katritzky protocol[192] for sequential N-protection and lithiation at the 2-position, and the resulting 2-lithioindole was quenched with the anhydride **109**[116] to give the keto-acid **166**, along with minor amounts of a side product containing three indole units. Cyclization of **166** in trifluoroacetic anhydride (TFAA)–acetic anhydride (1:5) produced the mono-*N*-benzylated quinone **167**, which was subjected to treatment with $AlCl_3$ in benzene, affording **168** in good yield. On the other hand, annulation of **166** in refluxing acetic anhydride took a different path, giving **169** (Scheme 40). Nonetheless, the pentacyclic molecule **169** could eventually be converted into the indolo[2,3-




**Scheme 39.**




**Scheme 40.**

*b*]carbazole **170** by treatment with an excess of methyllithium, followed by reductive aromatization induced by sodium borohydride in ethanol.[114]

It has also been claimed by Bhuyan that the reaction of indoles with aldehydes in the presence of iodine in refluxing acetonitrile may give indolo[2,3-*b*]carbazoles via 3,3′-diindolylmethanes as intermediates.[193] With a similar synthesis in retrospect, wherein the initially formed 3,3′-diindolylmethanes were allowed to isomerize to their 2,3′-coupled counterparts, eventually leading to a series of indolo[3,2-*b*]carbazoles (see Section 4.1),[122] it appeared likely that Bhuyan's approach[193] might in fact have resulted in the formation of indolo[3,2-*b*]carbazole derivatives. Indeed, Dehaen and co-workers have repeated some of Bhuyan's experiments[193] involving indole, selected benzaldehydes, and iodine in acetonitrile, and identified the products as 6,12-diaryl-6,12-dihydroindolo[3,2-*b*]carbazoles, which were formed in rather low yields.[124] In addition, we have also repeated some of these experiments and can confirm the observations of Dehaen. The assumption that hydroiodic acid, which is quickly generated under such conditions, could act as the catalyst was also corroborated by Dehaen.[124]

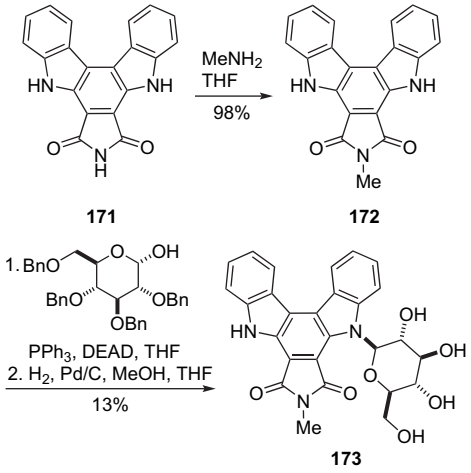
## 6. Indolo[2,3-*c*]carbazoles

This class of angular indolocarbazoles has been almost completely neglected during the reporting period of this review. Annulation of 3,3′-biindolyl with maleimide in hot acetic acid according to a previously reported procedure[194] gave the hexacyclic system **171**, which was converted into the derivative **172** by heating with dimethylamine in a sealed tube (Scheme 41). Subsequent glycosylation under Mitsunobu conditions, followed by exhaustive removal of the benzyl groups, gave the fused indolo[2,3-*c*]carbazole derivative **173**, along with a related compound bearing two glucopyranose units (not shown). Biological evaluation of **173** revealed that compounds of this type lack topoisomerase I-inhibitory activity.[195] Indolo[2,3-*c*]carbazoles may also be encountered in low yield as side products during the conversion of certain bisphenylhydrazones derived from cyclohexane-1,4-dione into indolo[3,2-*b*]carbazoles.[110]

## 7. Miscellaneous indolocarbazole structures

### 7.1. Fused indole trimers

Angular indolocarbazoles featuring an additional indole unit fused to the central benzenoid ring (fused indole trimers) have been known for some time, and are encountered, for example,

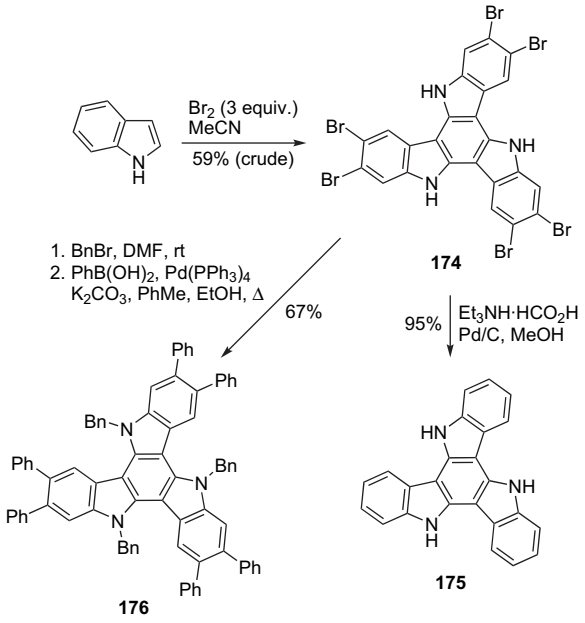



**Scheme 41.**

during the exposure of indoles to strongly acidic conditions or the electro-oxidation of indole.[7] The development of more practical conditions for their preparation have emerged recently, paving the way for new interesting developments.

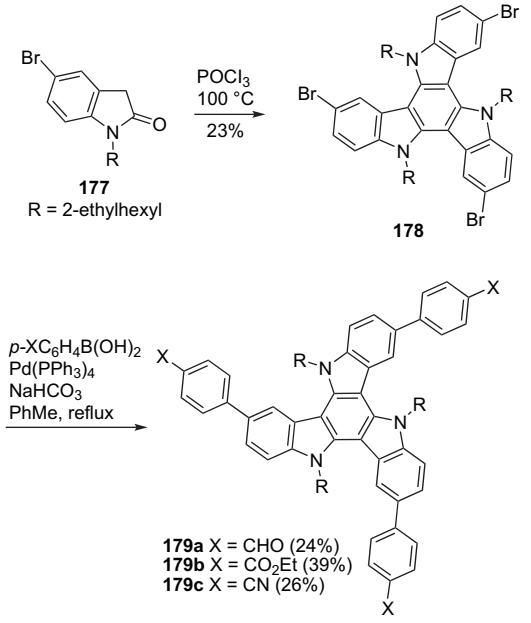
It has been established that indole undergoes a rather efficient trimerization upon treatment with 3 equiv of bromine in acetonitrile with concomitant bromination, rendering the symmetric system **174** in acceptable yield (Scheme 42).[196] The product **174** has later been subjected to dehalogenation, giving the parent molecule **175**, whereas full N-benzylation and subsequent Suzuki coupling produced the extended structure **176**.[197] Likewise, transformation of **174** into the its fully PMB-protected derivative and subsequent Sonogashira reactions with alkynes bearing one terminal phenyl or alkyl unit gave a set of new $C_3$-symmetric redox-active materials capable of forming discotic liquid crystals.[198] Additional reactions of **174** involve N-alkylation with bromohexane, providing a common intermediate for Suzuki reactions leading to pure-deep-blue light-emitting systems bearing six oligofluorene units[199] or structurally related dendrimers.[200] Fused indole trimers incorporating six carbazole moieties have also been reported,[201] whereas the parent trimer **175** has been utilized in the construction of a novel redox-active cyclophane.[202]

Access to symmetric indole trimers has also been gained by the cyclotrimerization of oxindole derivatives, as illustrated by the elaboration of the oxindole derivative **177** into the product **178**, which also proved to be a useful substrate for further synthetic manipulations, leading to the systems **179a–c** (Scheme 43). The




Scheme 42.

presence of the electron-acceptor moieties in combination with the electron-donating indole nuclei caused a rather strong fluorescence of compounds **179a**–**c**, resulting from intramolecular charge transfer.[203]




Scheme 43.

Finally, it should also be mentioned that a study of the polymerization of indole-based on density functional theory (DFT) calculations has been performed, supporting the possibility that several cyclic structures may be formed during the process, among other symmetric indole trimers.[204] An example of an unsymmetric indole trimer, compound **180** (Fig. 10), has been investigated as a cathode material for the construction of hybrid capacitors, and it displayed some promising properties.[205] There are also additional examples of asymmetric indole trimers, which have been used as electrode materials for the construction of batteries and capacitors.[206] Formation of the parent unsymmetric indole trimer, as well as linear oligomers, could be observed upon dissolution of an electro-polymerized

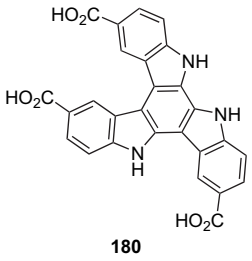
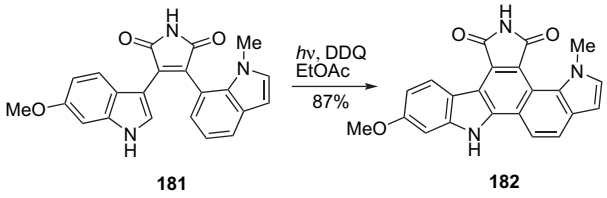



Figure 10.

polyindole film in dichloromethane by electro-reduction. Subsequent oxidation resulted in redeposition of a new polyindole film on the electrode surface, containing the same indole trimer, apart from a linear pentamer and larger insoluble oligomers.[207]

### 7.2. Other relevant systems

A novel 'non-classical' indolocarbazole framework has emerged as a new class of selective inhibitors of D1/CDK4, a protein kinase complex.[208] The required precursor, bis-3,7′-indolyl-maleimide **181**, was constructed by a base-induced reaction between methyl 6-methoxyindole-3-glyoxylate and 1-methylindole-7-acetamide in 65% yield, and was thereafter annulated to the indolo[6,7-*a*]pyrrolo[3,4-*c*]carbazole **182** by irradiation in the presence of DDQ as the oxidant (Scheme 44). These cyclization conditions were compatible with substrates featuring substituents such as bromoalkyl or hydroxyalkyl, allowing the preparation of indolo[6,7-*a*]pyrrolo[3,4-*c*]carbazoles suitable for further elaboration.[209]




Scheme 44.

## 8. Concluding remarks

With all interesting synthetic and applied studies involving indolocarbazoles in retrospect, it is quite clear why this intriguing class of heterocycles has continued to enjoy so much attention during the last decade. Therefore, their uses for diverse purposes, such as drug development, mechanistic biological studies, anion recognition, or the construction of new electronic devices, are likely to promote further innovations in these respective fields. If this is the case, the fundamental aspects concerning the synthesis and modification of indolocarbazoles will also be scrutinized in further detail, in order to provide efficient routes to new substances with new interesting properties.

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## Biographical sketch

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**Professor Jan Bergman** obtained his Ph.D. in 1971 at the Royal Institute of Technology, Stockholm, Sweden, under the direction of Professor Holger Erdtman. The title of the thesis 'Synthetic Studies of Indole Derivatives' is a good indicator of his continued interest in nitrogen heterocycles. After a spell in Canada at the University of Waterloo during the Olympic year 1976, he returned to Sweden, and since 1989 he is the Head of the Organic Chemistry unit at the Karolinska Institute, Huddinge, Sweden.