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Synthesis of carbazole alkaloids

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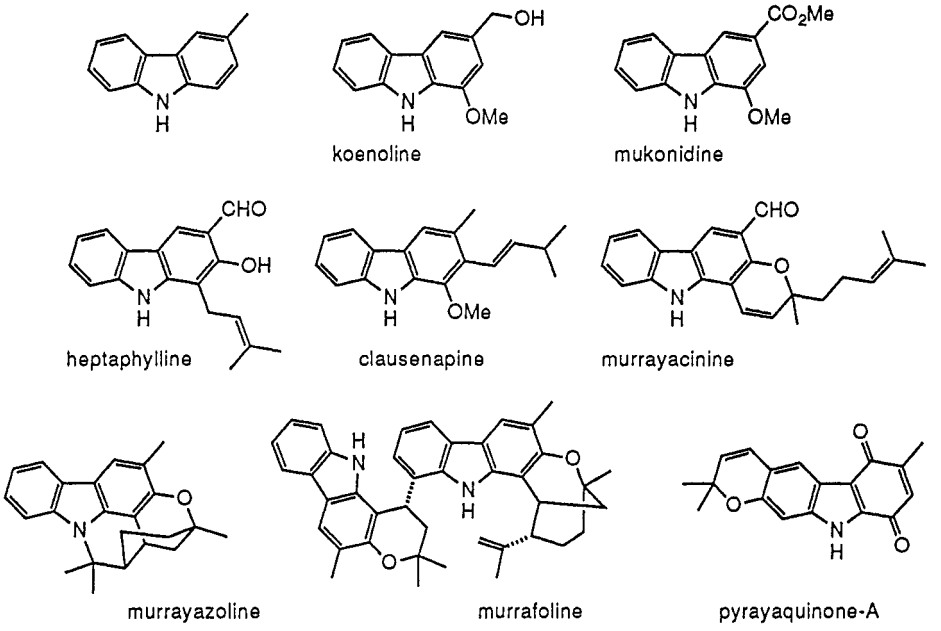
Abstract - An account of the authors work on the synthesis of carbazole alkaloids is presented. The treatise also includes relevant work from other groups as well as a review on the synthesis of hyellazoles and carbazomycins.

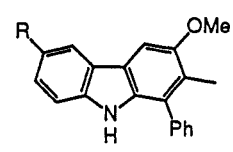
Carbazole alkaloids have received considerable attention, and various aspects of this class have been reviewed by us[1] and others.[2-10] A rough division of the carbazole alkaloids into three groups can be made. By far the largest group comprises alkaloids isolated from the *Rutaceae*-family (=the Citrus family). Selected structures are given in Figure 1. The second group contains alkaloids of the hyellazole / carbazomycin type (Figure 2), and in the third group we have placed the alkaloids that will not fall into the above categories (Figure 3). This treatise will be devoted to the synthesis of carbazoles related to the hyellazoles and carbazomycins, with the main emphasis projected to work from our laboratories. A brief discussion of relevant work concerning the synthesis of the other alkaloids will however also be included.

Figure 1.

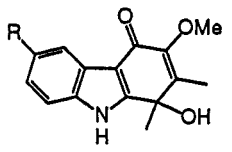


A large number of carbazole alkaloids have been isolated from the *Rutaceae* family. Most of them have a one-carbon substituent in the carbazolic 3-position and an oxygen functionality in the 1- or 2-position. The structure of these alkaloids can vary from simple substituted carbazoles to molecules with terpene appendages of various complexity and length. Dimeric and quinoid alkaloid are also known. Although plants from the *Rutaceae* family have been widely used in folk medicine, it has so far not been possible to correlate any particular physiological effects to a carbazole alkaloid. As the chemistry and synthesis of the *Rutaceae* alkaloids already have been thoroughly reviewed[1-9,11], only newer syntheses not included in these reviews, and work relevant for the discussion, will be presented here.

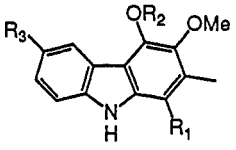
Figure 2.



R = H hyellazole
R = Cl chlorohyellazole

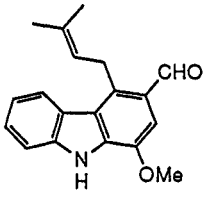


R = H carbazomycin G
R = OMe carbazomycin H

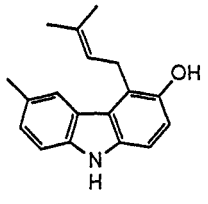


R_1	R_2	R_3		
Me	H	H	carbazomycin	A
Me	Me	H		B
Me	H	OMe		C
Me	Me	OMe		D
CHO	H	H		E
CHO	H	OMe		F

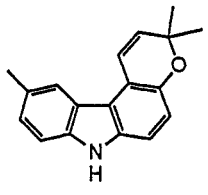
Figure 3.



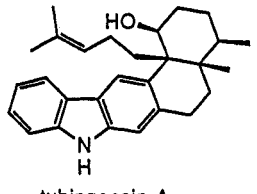
ekebergenine



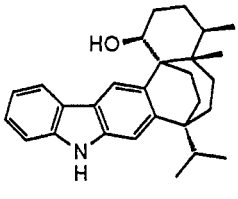
glycomaurrol



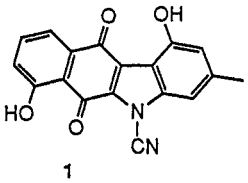
glycomaurin



tubingensin A



tubingensin B



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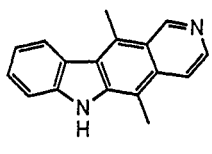
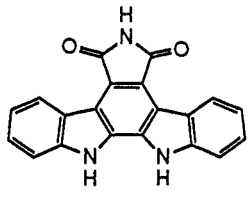


ellipticine



arcyriaflavin A

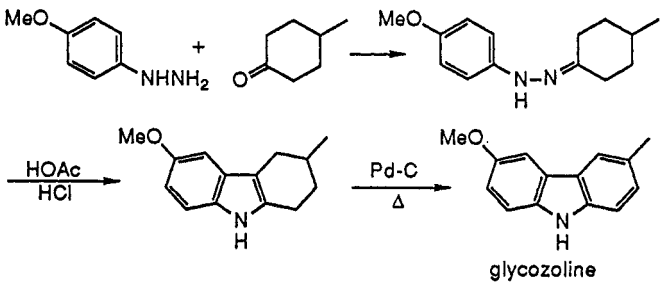
Recently two *Rutaceae* alkaloids, glycomaurrol and glycomaurin having an unusual substitution pattern have been isolated (Scheme 3).[15] The latter represents a ring system not previously found in nature. Ekebergenine, having a structure resembling the *Rutaceae* alkaloids have been isolated from the *Meliaceae* family.[16] The sclerotia of *Aspergillus tubingensis* contains two carbazoles with completely different structures, the antiviral tubingensin A and the cytotoxic tubingensin B (Scheme 3).[17-8] The quinoid carbazole **1**, have been claimed to be a possible biogenetic precursor to the kinamycins.[19] The very interesting chemistry and biological activity of the pyridocarbazole and the indolocarbazole alkaloids, represented in Figure 3 by ellipticine and arcyriaflavin A, will not be included in this treatise.[20]

The majority of the syntheses of the *Rutaceae* alkaloids, in particular the older ones, are based on well known synthetic strategies, such as the Fischer indole synthesis (Scheme 1)[27], or coupling of two substituted benzene rings, followed by cyclization (Scheme 2 and 3).[28-9] The flexibility of these methods is however severely limited by their inherent lack of regioselectivity and that it often is difficult to obtain appropriately substituted cyclohexanones or benzenes. The same is of course also true for the synthesis of the hyellazoles and carbazomycins. These problems can in many cases be circumvented by choosing a synthetic strategy utilizing an indole as starting material.

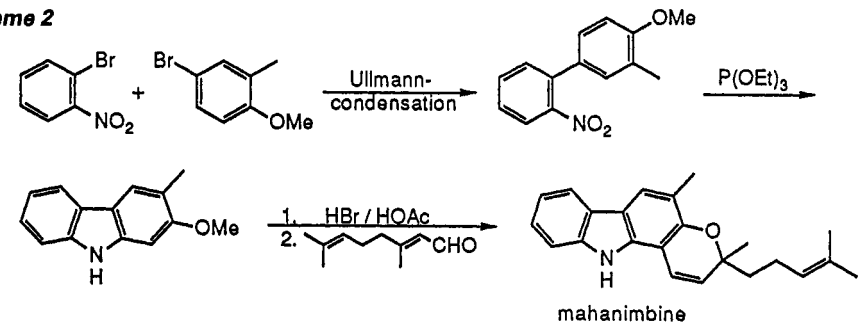
An example where an indole is used as the starting material for a *Rutaceae* carbazole alkaloid has been provided by Oikawa and Yonemitsu (Scheme 4).[30] Thus, indole is allowed to react with methacrylic acid to, after esterification, afford **2**. The ester is then converted in two steps into the ketosulfoxide **3**, which after an acid catalyzed ring closure, followed by protection of the nitrogen, dehydrogenation, and finally, deprotection, yields girinimbine (**5**). Oxidation of girinimbine, promoted by DDQ, gave murrayacine(**6**).

A shorter synthesis of girinimbine (**5**), which in addition does not involve a protection / deprotection sequence, have been developed in our laboratories (Scheme 5).[31] Condensation of 2-methylindole with α-formylpropionate gives the 2:1 adduct **7**, which on thermolysis eliminates 2-methylindole to give **8**. This vinylindole will then undergo a

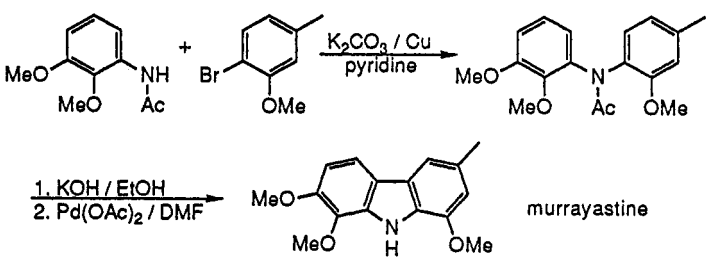
Scheme 1



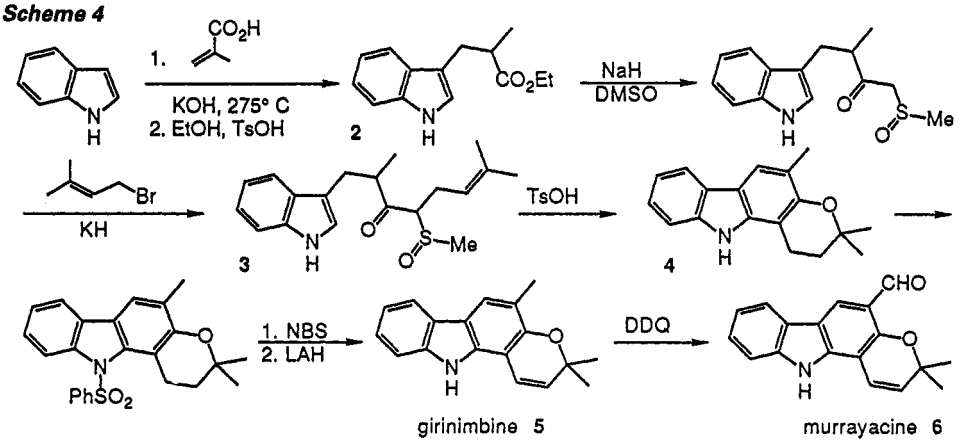
Scheme 2



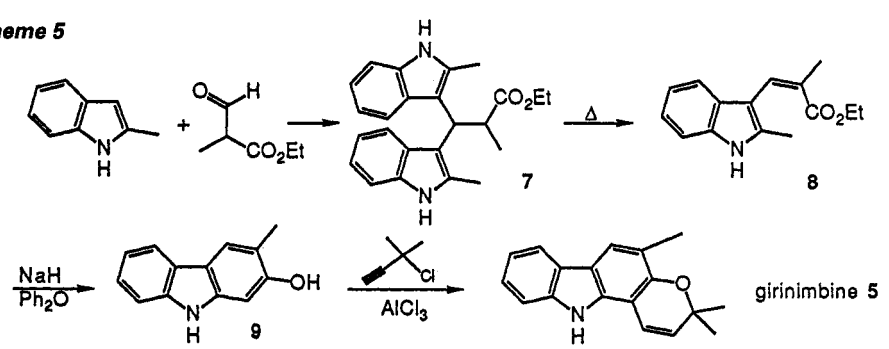
Scheme 3



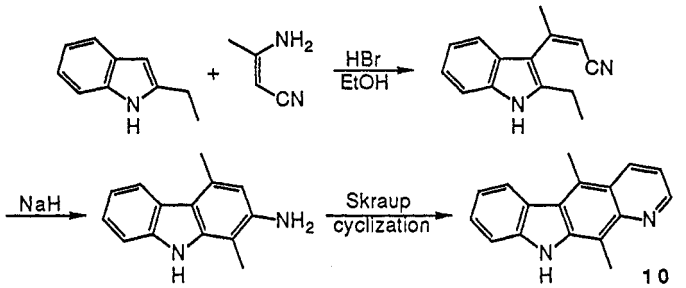
Scheme 4



Scheme 5



Scheme 6

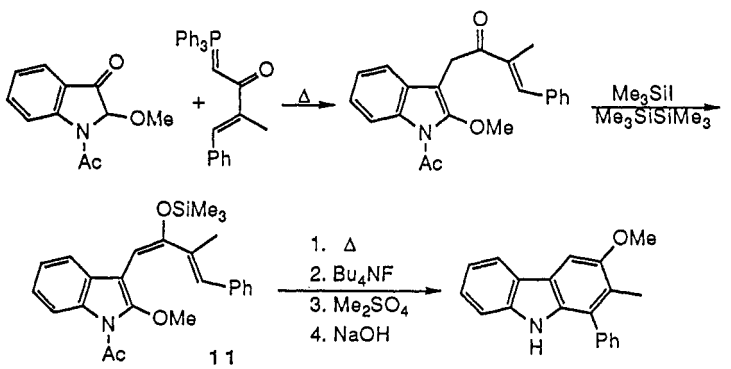


base induced cyclization to afford 2-hydroxy-3-methylcarbazole **9**, which gives girinimbine (**5**) on reaction with 3–chloro-3-methyl-1-butyne in the presence of $AlCl_3$. Moreover, compound **9** has not only been used as an intermediate in a synthesis of mahanimbine (Scheme 3)[29], but is also a natural product in its one respect, [32] and is also most likely the biogenetic precursor to both mahanimbine (Scheme 2) and 2-methoxy-3-methylindole as they have been isolated from the same plant species.[32-3] The base induced cyclization of **9** seems to be of general nature and we have utilized this protocol in a synthesis of the ellipticine analogue **10** (Scheme 6).[34]

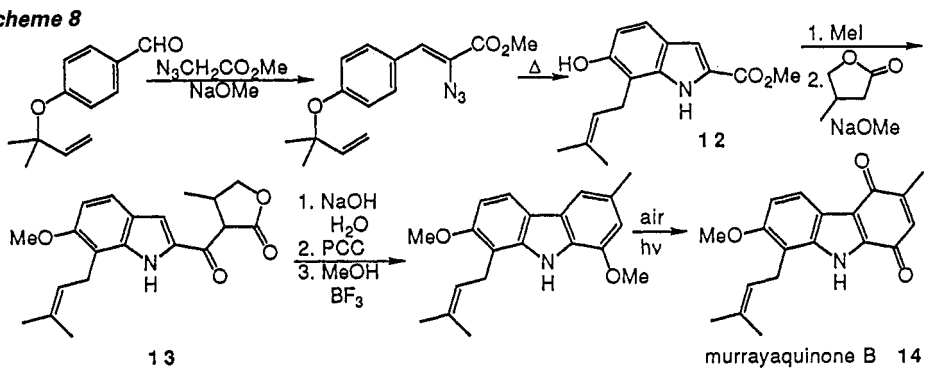
1-Acetyl-2-methoxyindolin-3-one is the starting material in a synthesis of hyellazole described by Sakamoto (Scheme 7).[35] A Wittig reaction followed by silylation afforded the 3-buta-1,3-dienylindole **11**, which cyclized on heating. Desilylation, methylation and deprotection finally gave the target alkaloid.

Moody and coworkers have synthesized several quinoid *Rutaceae* alkaloids employing indole-2-carboxylates as intermediates.[36-9] One example is given in Scheme 8. The indole-2-carboxylate **12** was prepared by condensation of an appropriately substituted benzaldehyde with methyl azidoacetate, followed by a thermolytically induced cyclization / Claisen rearrangement. After methylation, the product was condensed with 4-methylbutyrolactone to give **13**, which in a number of steps is converted to murrayaquinone B (**14**).

Scheme 7



Scheme 8

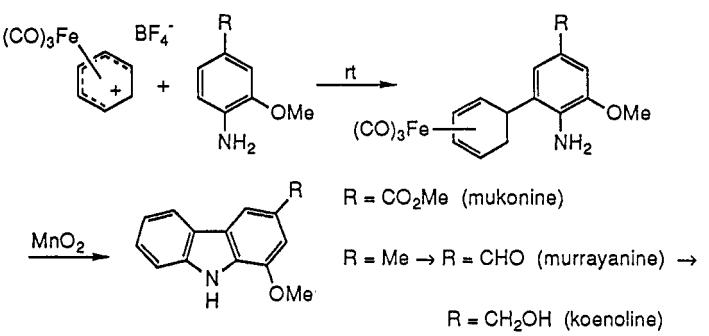


Knölker and coworkers have devised a synthesis of koenoline, mukonine and murrayanine using an electrophilic aromatic substitution of an aniline with a cyclohexadienyltricarbonyliron cation as the key step (Scheme 9).[40] Although this approach offers the advantage of few synthetic steps and mild reaction conditions, its applicability may be thwarted by the lack of regioselectivity and the requirement of properly substituted anilines and cyclohexadienyls. The same approach has also been used in a synthesis of carbazomycins (*vide infra*).

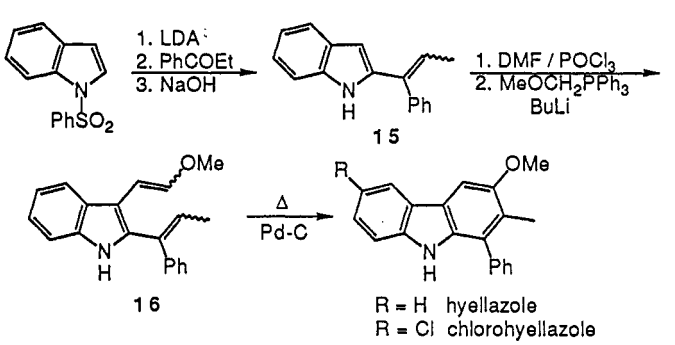
Despite their structural resemblance, the hyellazoles and the carbazomycins (Figure 2) have been isolated from two completely non-related biological systems, a blue green alga (*Hyella caespitosa*)[41] and an actinomycete (*Streptoverticillium ehimense*),[42-4] respectively. These alkaloids have an interesting substitution pattern that has proven to be a synthetic challenge to several research groups. In addition, there has been antibiotic activity reported for carbazomycin B. The presently six known synthetic approaches to these alkaloids will be compiled below.

The first synthesis was reported by Kano *et al.* (Scheme 10).[45-6] Here the vinylindole **15**, prepared by a procedure involving the well known regioselective lithiation of 1-benzenesulphonylindole, is converted in two steps to **16**. This 1,3,5-hexadienic system undergoes an electrocyclic ring closure with concomitant dehydrogenation, when heated in the presence of Pd-C, to give hyellazole. Chlorohyellazole was similarly prepared.

Scheme 9

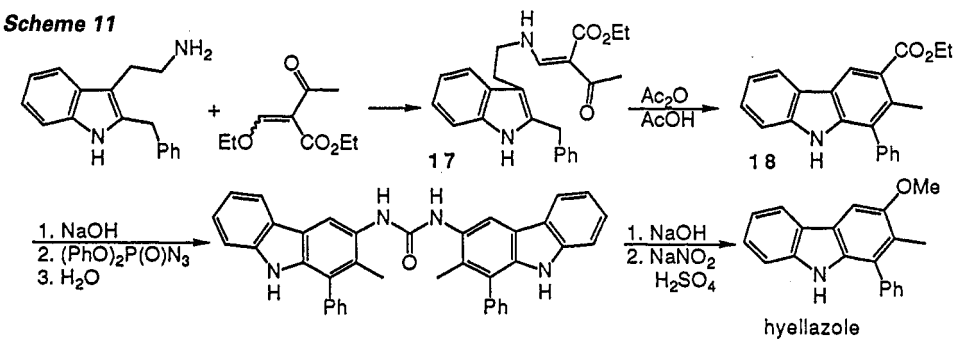


Scheme 10



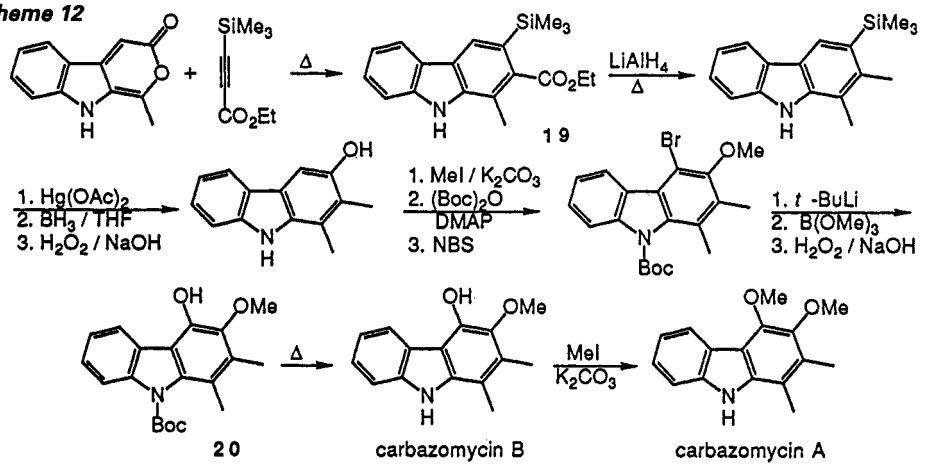
Another interesting approach to hyellazole, reported by Takano and coworkers, starts with 2-benzyltryptamine and ethoxymethyleneacetoacetate (Scheme 11).[47] Although the enamine **17** was readily converted into the ester **18**, the final transformation of the ester group to a methoxy group was cumbersome, and only resulted in a low yield of hyellazole.

Scheme 11

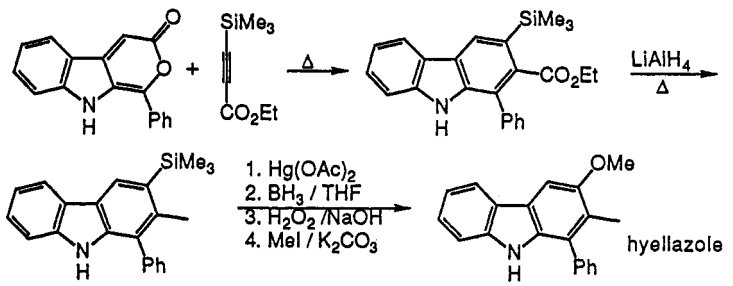


Carbazomycin A and B have both been synthesized by Moody and Shah by an approach in which the pivotal reaction is the regioselective cycloaddition of an acetylenic ester with a pyranoindolone (Scheme 12).[48] The ester group in the cycloadduct **19** was reduced to a methyl group with $LiAlH_4$ in refluxing dioxane, followed by transformation of the trimethylsilyl group to a hydroxy group using a mercurodesilylation / hydroboration procedure. To introduce the remaining oxygen functionality in the 4-position of hyellazole it was found necessary to protect the nitrogen. Bromination, bromine-lithium exchange and treatment with trimethylborate, followed by alkaline hydrogen peroxide work-up, gave the hydroxycarbazole **20**. The protecting group was then finally removed to give carbazomycin B which could be methylated to carbazomycin A. The same strategy was also used for the synthesis of hyellazole (Scheme 13).[48]

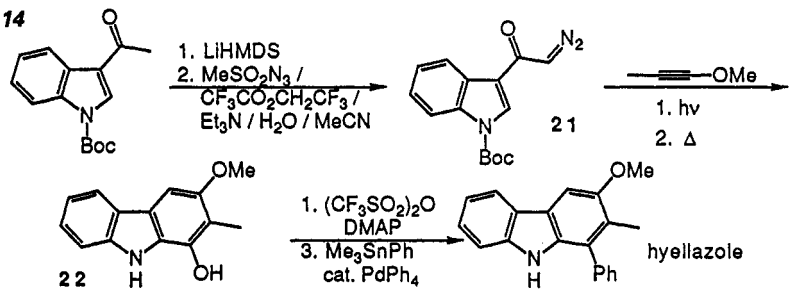
Scheme 12



Scheme 13



Scheme 14

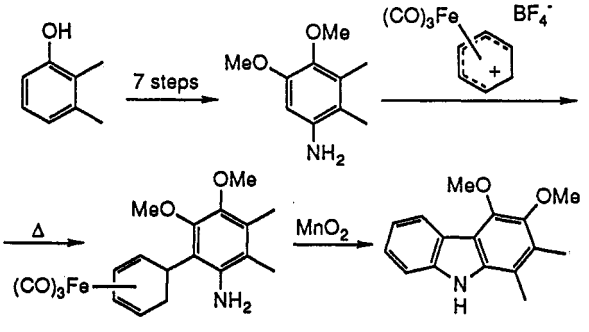


A synthesis of hyellazole has also been reported by Danheisers group.[49] A photoinduced cycloaddition of 1-methoxypropyne to the diazoketone **21** gives the hydroxycarbazole **22** in which the hydroxy group is converted to the phenyl group in hyellazole by a palladium catalyzed coupling of the corresponding triflate ester with phenyltrimethylstannane (Scheme 14). The Boc protecting group was lost during the process.

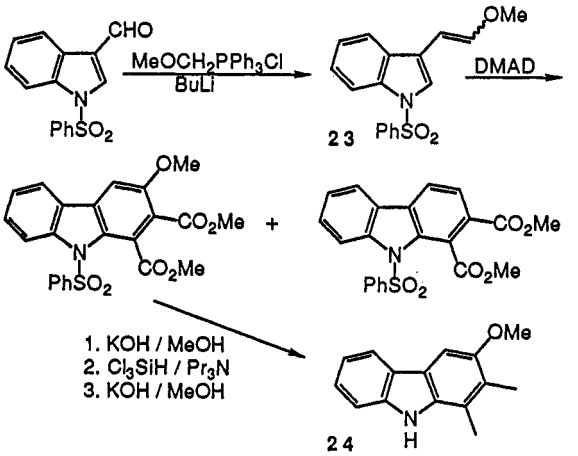
As already mentioned, Knölker and coworkers have also used their cyclohexadienyltricarbonyliron cation / aniline approach to the synthesis of carbazomycins (Scheme 15).[50-1]

An attempt to synthesize carbazomycins have also been reported by Pindur and Pfeuffer (Scheme 16).[52] The 3-vinylindole **23**, prepared by a Wittig reaction of a protected indolecarboxaldehyde, was allowed to react with DMAD to give a mixture of Diels-Alder adducts. After separation, the carbomethoxy groups was converted in a three step procedure to the methyl groups in the carbazomycin analogue **24**.

Scheme 15



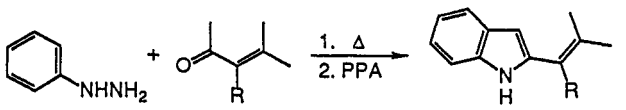
Scheme 16



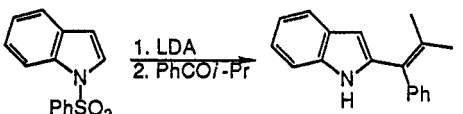
Our own efforts in the syntheses of hyellazole and the carbazomycins began with model studies towards a general synthesis of 1,2–disubstituted carbazoles, which hopefully also would allow for the introduction of substituents in the 3- and 4-position, either by choosing a properly substituted starting material, or by manipulation in a later stage of the synthesis.

To test one of our approaches we needed a ready access to various N-unsubstituted 2-vinylic indoles. One of the best way to synthesize indoles is the Fischer indole synthesis, but this method have, with one exception[53], not been used in the synthesis of 2-vinylic indoles. We however found that compounds such as **25** were readily obtained when the appropriate ketones were heated with phenylhydrazine, followed by treatment of the crude reaction mixture with PPA (Scheme 17).[54-5] In this manner we were able to produce multigram quantities of **25a** or **25b** in a few hours. However, the modest yields made this reaction less satisfactory when the required ketones were not easily available. The vinylindole **25c** was instead prepared in high yield when lithiated 1-benzenesulphonylindole was allowed to react with isobutyrophenone (Scheme 18).[55] It has to be pointed out that the protective group is lost during the process, in contrast to the reaction with the same lithiated indole with propiophenone (Scheme 10), in which dehydration and removal of the protective group had to be performed in a separate step.[45-6]

Scheme 17

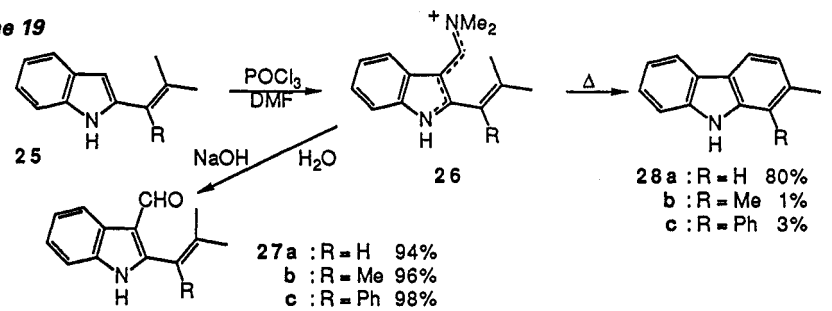


Scheme 18



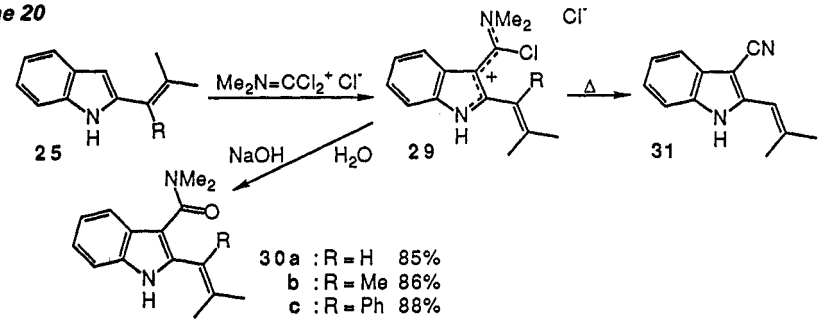
When **25a-c** was allowed to react with $POCl_3$ in DMF (the Vilsmeier reagent) at room temperature, followed by hydrolysis of the intermediate immonium salts **26a-c**, the aldehydes **27a-c** were obtained in excellent yields. If **26a** instead was heated, a good yield of 2-methylcarbazole **28a** was obtained (Scheme 19).[54-5] Unfortunately, when the same reaction was applied to **25b** and **25c**, only very low yields of the desired carbazoles could be isolated.[55-6]

Scheme 19



Along the same lines we wanted to investigate if a one-carbon electrophile with a higher oxidation state than the Vilsmeier reagent could be used to synthesize carbazoles with a heteroatom, preferentially an oxygen, in the 4-position. Electrophilic substitution of **25a-c** with Viehe's reagent (*i.e.* dichlorodimethyl immonium chloride or phosgene immonium chloride), which is a commercially available hygroscopic salt, afforded high yields of the

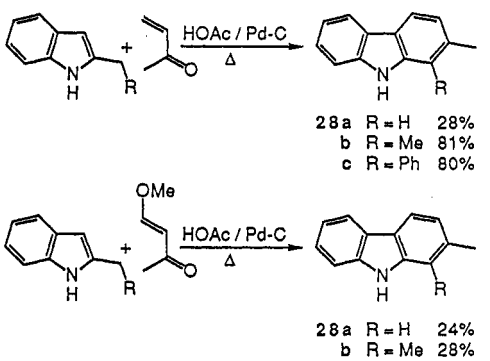
Scheme 20



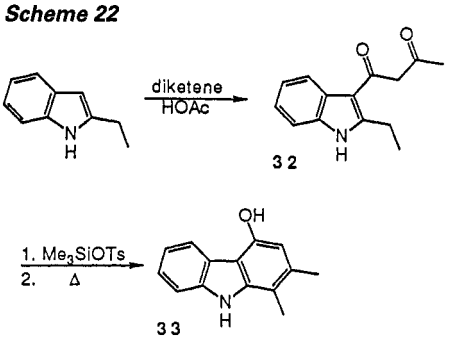
corresponding amides **30a-c**, after hydrolysis of the intermediates **29a-c** (Scheme 20).[55-6] However, when the intermediate **29a** (which was stable and could be isolated) was heated under a variety of reaction conditions, we were not able to isolate any carbazoles. Instead two equivalents of chloromethane was lost (the von Braun reaction) and, as best, a modest yield of the nitrile **31** could be obtained.[55-6]

Under suitable conditions, 2-methylindoles is known to give carbazoles on reaction with 2,3-unsaturated ketones.[57-9] After a reinvestigation of this reaction we found that it was well suited to the synthesis of a variety of 1,2-disubstituted carbazoles (Scheme 21).[55-6] So far, attempts to use this strategy in the synthesis of 4-methoxy substituted carbazoles have failed. The reaction of 2-substituted indoles with 4-methoxy-3-buten-2-one only gave carbazoles in which the methoxy group had been lost.[55] A similar approach, which indeed gives a 4-hydroxy-substituted carbazole, is depicted in Scheme 22. Thus, 2-ethylindole reacts with diketene[60] to yield 3-acetoacetyl-2-ethylindole (**32**), which upon silylation and thermolysis cyclizes to give the desired 4-hydroxycarbazole (**33**).

Scheme 21

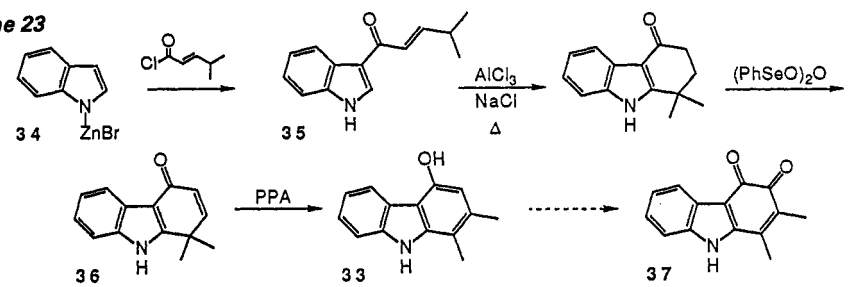


Scheme 22



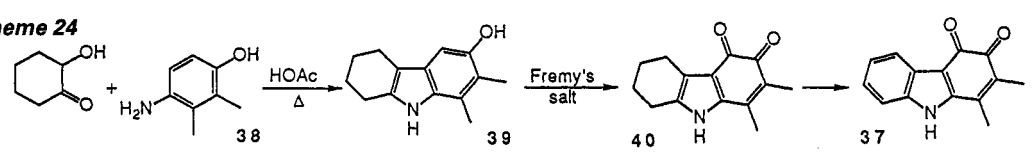
Another, more fruitful, approach to oxygenated carbazoles was also investigated. We found that the unsaturated ketone **35** was formed when the zinc salt **34**, prepared by transmetallation of the indole Grignard salt, was allowed to react with an appropriate acid chloride (Scheme 23).[61] Ring closure of the ketone **35** employing a mixture[62] of $AlCl_3$ and NaCl gave after introduction of a double bond compound **36**, which underwent a dienol-phenol rearrangement in the presence of PPA. However, oxidation to the *o*-quinone **37**, have so far not been successful.

Scheme 23

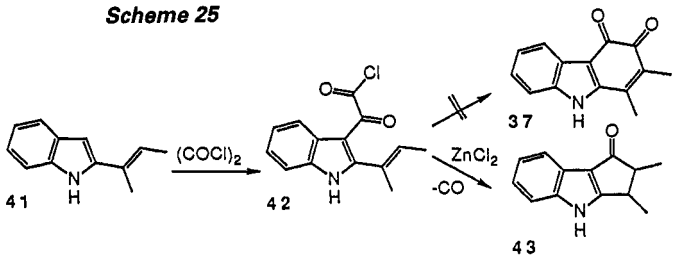


In connection with these studies we found that commercially available 2,3-dimethyl-4-hydroxyaniline (**38**) could be condensed with 2-hydroxycyclohexanone (Scheme 24). The tetrahydrocarbazole **39** formed, was then converted to the *o*-quinone **40** employing Fremy's salt, which could be oxidized to **37**.

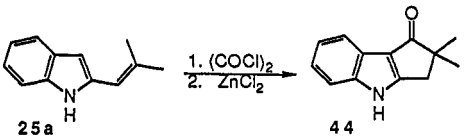
Scheme 24



Scheme 25

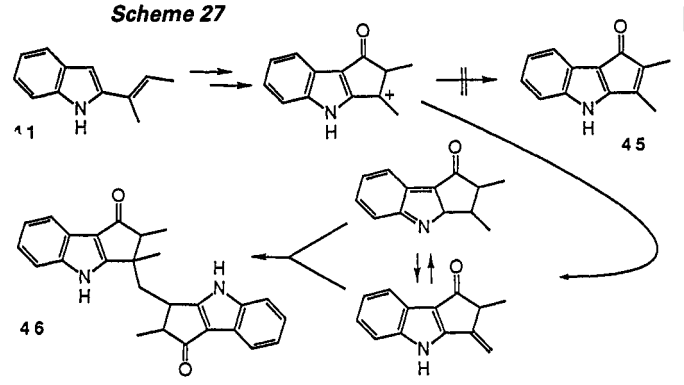


Scheme 26

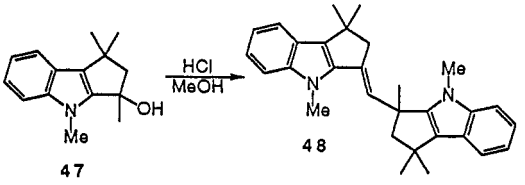


An attempt to use the 2-vinylindole **41**[63] in a shorter approach to the *o*-quinone **37** failed (Scheme 25). Instead, the intermediate **42** lost carbon monoxide and cyclized to the cyclopentanoindole **43**, apparently formed *via* some kind of a reduction process. Analogously, the cyclopentanoindole **44**, was obtained from **25a** (Scheme 26). Surprisingly, the cyclopentenoindole **45** was not obtained from **41**. However, a dimeric product (**46**), derived from non-reduced precursors, could be isolated as a minor product (Scheme 27). Interestingly, a dimer (**48**) with a striking resemblance to **46** was obtained in the acid catalyzed dimerization of **47** (Scheme 28).[64]

Scheme 27



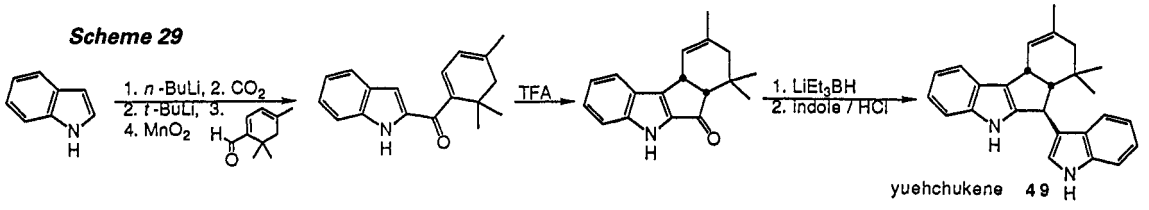
Scheme 28



Our interest in cyclopentanoindoles have of course been boasted by the recent discovery of the strong anti-implantatory action of yuehchukene (**49**), of which we also have developed a short and efficient synthesis (Scheme 29).[65]

In summary we have shown that although there has been a large amount of work devoted to the synthesis of carbazole alkaloids, there is still room for new approaches to these very interesting compounds. It is also our belief (and hope!) that more compounds will be discovered.

Scheme 29



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