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Recent Developments in the Syntheses of Carbazole Alkaloids

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Abstract. Recent developments in preparative methods for the construction of pharmacologically interesting and novel carbazole alkaloids are described. The spectrum of synthetic strategies ranges from polar (ionic) through radical to pericyclic methodologies.

1. Introduction

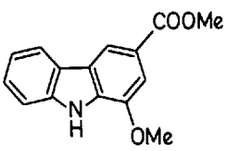
In alkaloid chemistry, interest in carbazole alkaloids has increased considerably during the past years [1–6] as a result of the expected potential of new types of pharmacologically active substances. Thus, *e.g.*, many carbazole derivatives [7], tetrahydrocarbazoles [8], oxotetrahydrocarbazoles [9], glycozoline and mukonine isomers [10] [11], carbazomycins [12], prenylcarbazoles [2–6], nitro- and aminocarbazoles [13] as well as pyrido[*b*]carbazoles (*e.g.* ellipticine derivatives and analogues) [14–19] possess anti-tumour, anti-convulsant, psychotropic, anti-inflammatory, anti-histamine, fungistatic, and antibiotic properties. Although most carbazole alkaloids are characterized by structural simplicity, selectively functionalised and/or annellated carbazoles are, in general, difficult to prepare [1–6]; hence, there is still an urgent requirement for both more selective and more efficient methods as well as for the development of novel synthetic strategies.

The present review is concerned with newer developments in the syntheses of pharmacologically attractive and, in particular, more recently isolated carbazole alkaloids. The numerous synthetic methods for the anti-tumour active pyrido[*b*]carbazole alkaloids known to date are not included in this review since wide-ranging and informative surveys [14–19] have already been published.

The strategies employed for the synthesis of carbazole alkaloid derivatives range from polar (ionic) through radical to pericyclic reaction types.

2. Members of the C_{13}-Skeletal Group: Mukonine Isomers, Glycozolidal

Mukonine (**1**), isolated from the stem bark of *Murraya koenigii* SPRENG [5], was first synthesised by a *Japp-Klingemann* carbazolisation reaction of a diazonium salt of 4-amino-3-hydroxybenzoic acid with 2-(hydroxymethylidene)cyclohexanone, followed by treatment with conc. HCl/AcOH, then *Wolff-Kishner* reduction, methylation with CH_2N_2, and dehydrogenation (Pd/C) [5].



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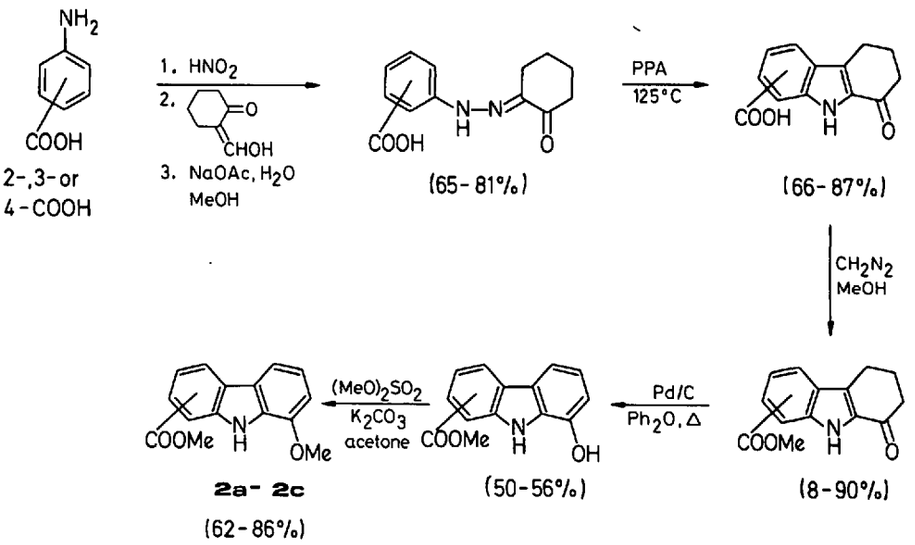
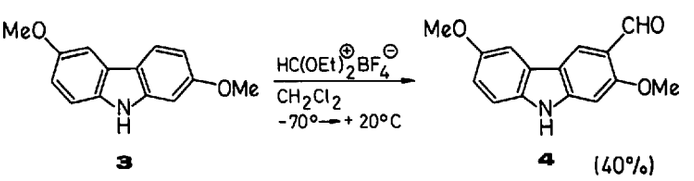
This carbazolisation modification is, in general, more flexible, more effective, and more convenient than the classical *Fischer-Borsche* method. Thus, analogous reactions of the diazonium salts of *ortho*-, *meta*-, and *para*-aminobenzoic acids with 2-(hydroxymethylidene)cyclohexanone gave rise to the three new regioisomeric analogues **2a–c** of mukonine, respectively (*Scheme 1*) [20].

Glycozolidal (**4**), recently isolated from the roots of *Glycosmis pentaphylla* [21], was prepared from **3** under very mild conditions and with high regioselectivity by

Scheme 1



Scheme 2



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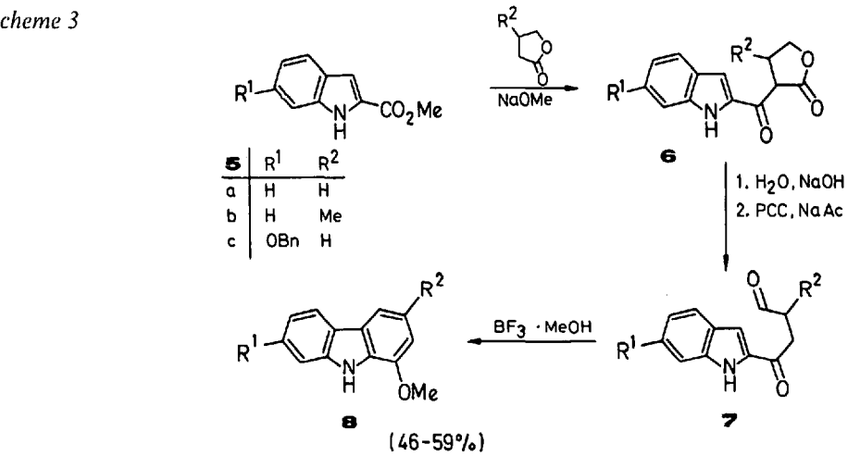
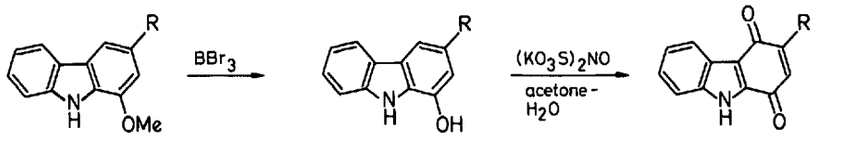
Scheme 3



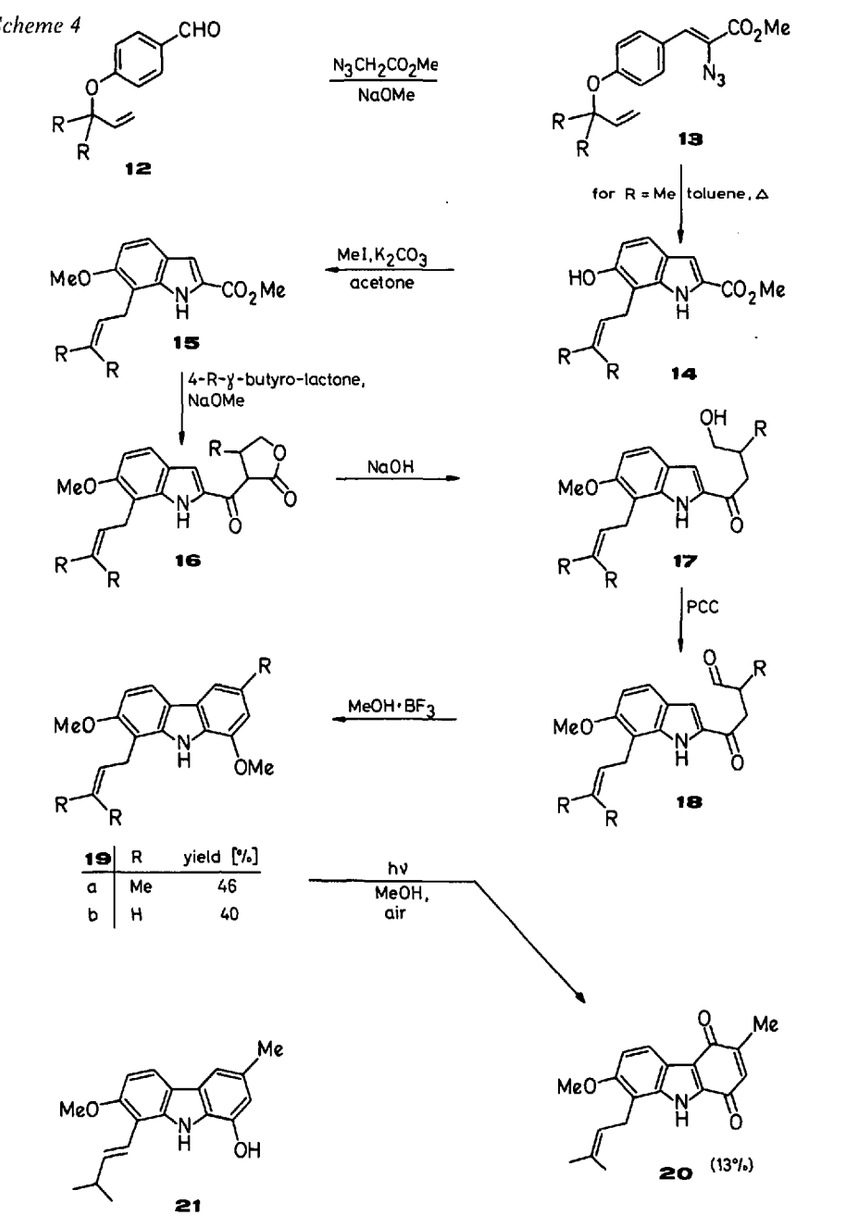
5	R^1	R^2
a	H	H
b	H	Me
c	OBn	H



9	R
a	H
b	Me

11	R	yield [%]
a	H	85
b	Me	40

Scheme 4



19	R	yield [%]
a	Me	46
b	H	40

using diethoxycarbenium tetrafluoroborate as a formylating agent (*Scheme 2*) [22].

3. 1-Oxygenated Carbazole Alkaloids, Carbazolequinones

New strategies for the syntheses of the carbazole alkaloids from the genus *Murraya* (Rutaceae) by a polar annellation route were recently developed by *Moody* and coworkers [23] [24]. Thus, selectively oxygenated carbazoles were prepared by an elegant, four-step synthesis starting from the indole-2-carboxylates **5**. A modification of the *Claisen* reaction of **5** with butyrolactones gave the lactones **6** which were hydrolysed with concomitant decarboxylation to the corresponding alcohols and then oxidised to give the aldehydes **7** (*Scheme 3*). The latter were cyclised to the 1-methoxycarbazoles **8** by treatment with BF_3/MeOH (or methanolic HCl).The thus prepared 1-methoxycarbazoles **9a** and **9b** (murrayafoline A) were transformed to the corresponding carbazolequinones **11a** and **11b** (murrayaquinone A) by demethylation and subsequent oxidation with *Fremy*'s salt *via* the hydroxycarbazoles **10a, 10b** [23].

The new carbazole alkaloid murrayaquinone B (**20**), isolated from the root bark of *Murraya euchrestifolia* HAYATA, was synthesised from **12** following an analogous methodology (*Scheme 4*) [24]. The pathway to the 1,7-dimethoxycarbazole **19** consists of a highly regioselective *Claisen* rearrangement to furnish the selectively functionalised indole **14.** Construction of the third ring of **19** was achieved by cyclisation of the aldehyde **18**, prepared in turn from **14** *via* the lactone **16.** Photooxidation of **19a** finally supplied murrayaquinone B (**20**).

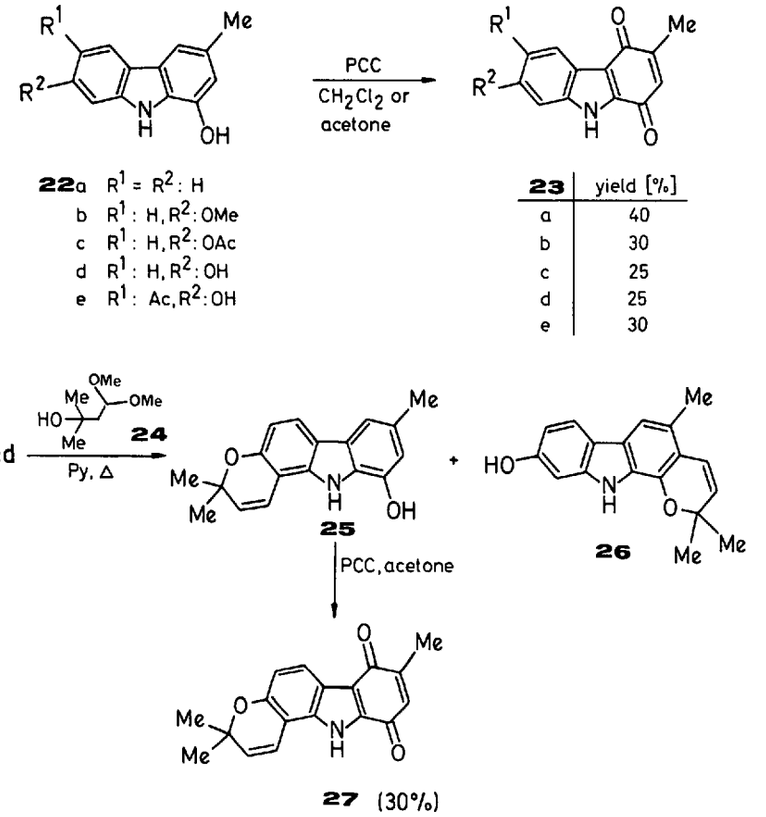
A more classical approach to murrayafoline B (**21**) and murrayaquinone B (**20**) commences with a 1-oxocarbazole precursor, consists of a four- to five-step sequence,and furnishes reasonable yields of *ca.* 80 and 30%, respectively [25].

In [25] another facile route to carbazole-1,4-quinones was also reported (*Scheme 5*). The 1-hydroxycarbazoles **22** are oxidised by pyridinium chlorochromate (PCC) in CH_2Cl_2 or acetone to the quinones **23.** Compound **22d** reacts with the acetal **24** to produce a mixture of the isomers **25** and **26.** The former is then oxidised with PCC to furnish pyrayaquinone B (**27**), a further new pyranocarbazole alkaloid isolated from Rutaceae [26] (for further pyranocarbazoles, see also *Chapt. 4*).

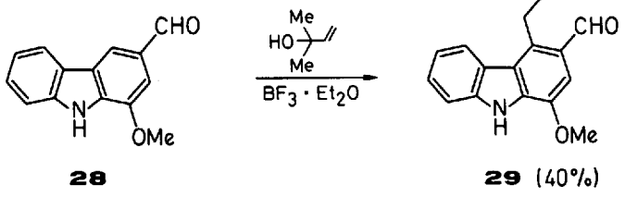
4. Members of the C_{18}-Skeletal Group: Prenylcarbazoles, Pyranocarbazoles

Alkaloids of the C_{18}-skeletal group possess either prenyl substitution or, in the cyclised form, pyranoannellation [6]. Among the more recently discovered members of the prenylcarbazole alkaloid series,

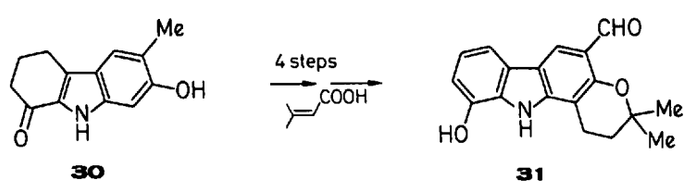
Scheme 5



Scheme 6

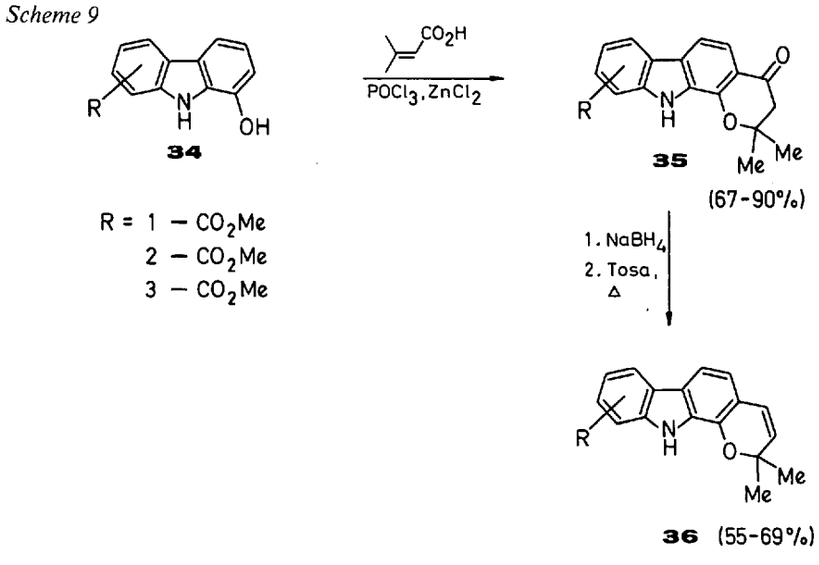


Scheme 7



Scheme 8

Scheme 9



indizoline, heptaphylline, heptazoline [6], and ekeberginine (**29**; isolated from *Ekebergia senegalensis* (Meliaceae)) [27] represent pharmacologically interesting substances for the development of fungistatically active drugs [6].

The synthesis of **29** was achieved by regioselective electrophilic substitution of **28** with 2-methylbut-3-en-2-ol in the presence of $BF_3 \cdot Et_2O$ (*Scheme 6*) [28] in analogy to a modification described previously for the preparation of 6-methoxyheptaphylline [5] [29].

In the pyrano[*a*]carbazole series, cycloheptazoline (**31**) was prepared by a classical, four-step procedure starting from 2-hydroxy-3-methyl-8-oxo-5,6,7,8-tetrahydrocarbazole (**30**) for the purpose of unambiguous elucidation of the structure of the prenylcarbazole alkaloid heptazoline (*Scheme 7*) [30].

Heptazolidine (**33**), isolated from *Clausena heptaphylla* WT. et ARN., was first prepared from the corresponding arylhydrazone and 4-methylcyclohexanone by the *Fischer-Borsche* method or by the *Japp-Klingmann* procedure to furnish the tetrahydrocarbazole **32** which was readily converted to **33** by sequential treatment with 1) 3-methylbut-2-enoyl chloride/$POCl_3$, 2) Pd/C, 3) reduction, 4) tosylation, and 5) detosylation (*Scheme 8*) [31].

The 2,2-dimethyl-2*H*-pyrano[*a*]carbazoles **36** were synthesised from the 8-hydroxycarbazoles **34** and 3-methylbut-2-enoic acid *via* **35**. Reduction of the C=O group of **35** and subsequent elimination of H_2O gave **36** (*Scheme 9*) [32a].

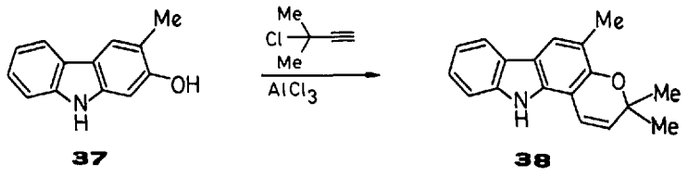
New synthetic routes to girinimbine (**38**) and norgirinimbine (**41**) were elaborated recently: the 2-hydroxy-3-methylcarbazole **37** was allowed to react with 3-chloro-3-methylbut-1-yne in a one-pot procedure yielding **38** directly (*Scheme 10*) [32b].

Decarboxylation of 2-hydroxycarbazole-3-carboxylic acid (**39**) using $SbCl_3$ as the decarboxylating agent followed by a multi-step sequence led to the linear pyranocarbazole ring system **40**, norgirinimbine (**41**; R = H), and the alkaloid girinimbine (**38**; R = Me) by means of a new polar cyclisation key step (*Scheme 11*) [33].

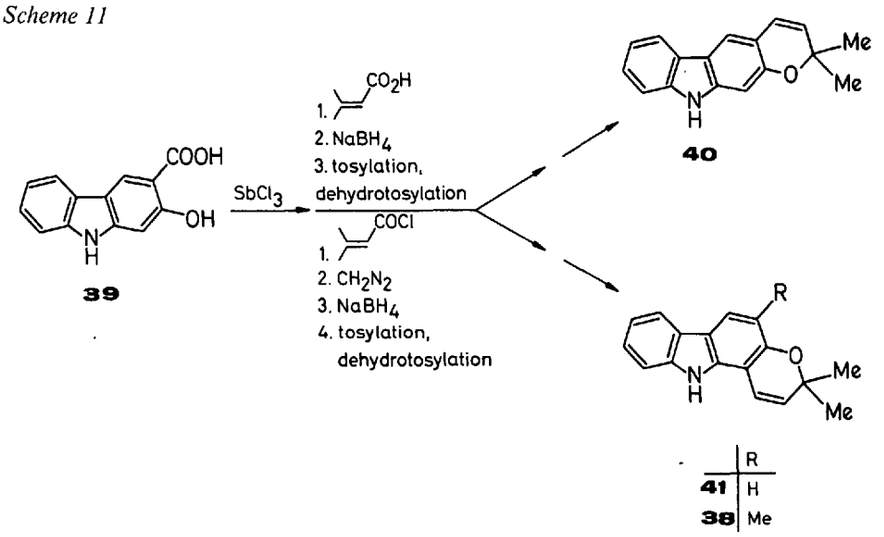
5. Oxygenated Carbazole Alkaloids from Lower Plants

In the last few years, applications of pericyclic methodologies with, *e.g.*, the *Diels-*

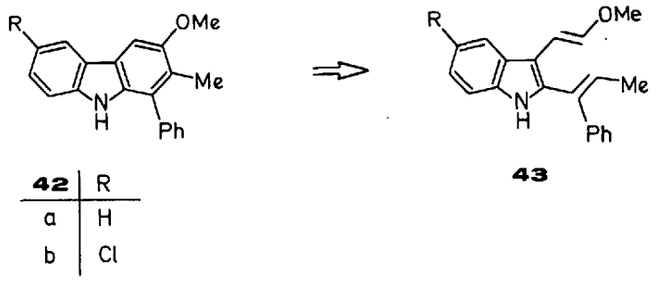
Scheme 10



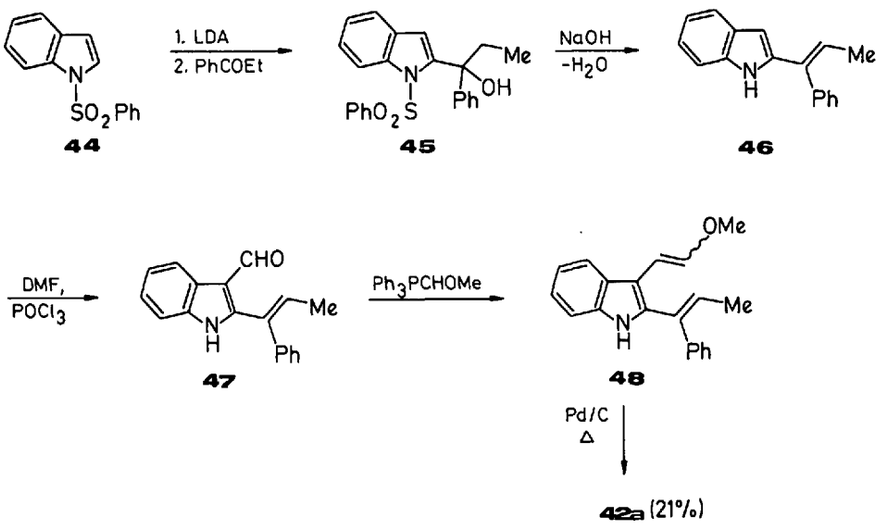
Scheme 11



Scheme 12



Scheme 13



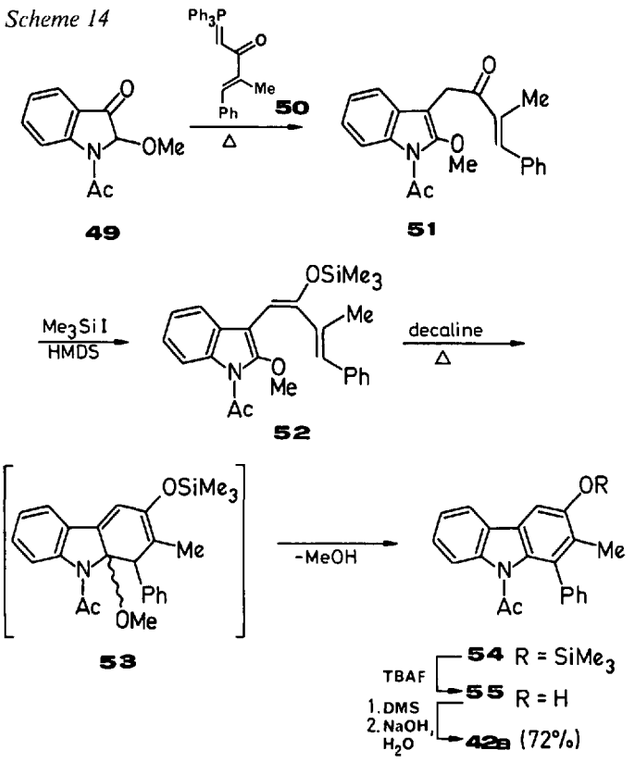
Alder and electrocyclic reactions as the key steps, for the construction of selectively functionalised carbazoles and/or [*b*]annellated indoles have increased considerably [34–37]. In this connection, the poly-substituted methoxycarbazoles such as the marine alkaloids hyellazole (**42a**) and 6-chlorohyellazole (**42b**) (isolated from the blue-green alga *Hyella caespitosa* [38]) and carbazomycins A and B (isolated from *Streptoverticillium ehimence*) [39–41] represent synthetically interesting target compounds. In particular, the carbazomycins belong to the first carbazole alkaloids exhibiting antibiotic activities.

The synthesis of hyellazole (**42a**) and its 6-chloro derivative **42b** was first achieved by an elegant 6π-electrocyclic key step involving the 2,3-divinylindoles **43** (*Scheme 12*) [42]. The preparation of **42a**, *e.g.*, starts from *N*-(benzenesulphonyl)indole (**44**) *via* regiospecific lithiation and reaction with propiophenone to furnish the alcohol **45**. Subsequent treatment with NaOH affords 2-(1-phenylprop-1-enyl)-indole (**46**) which was converted to the aldehyde **47** by means of the *Vilsmeier* reaction. A *Wittig* reaction of **47** gave the key compound **48** which, on heating with 5% Pd/C in xylene or decaline at higher temperatures, underwent cyclisation to produce hyellazole (**42a**) in 21% yield (*Scheme 13*). 6-Chlorohyellazole (**42b**) was prepared by an analogous reaction sequence in 47% yield.

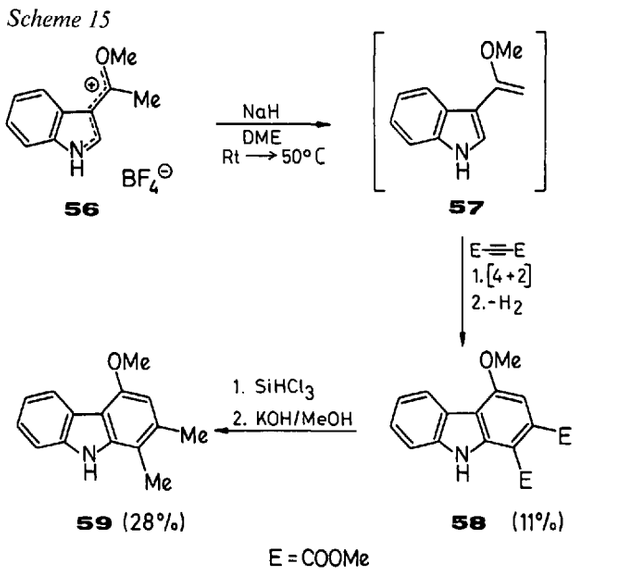
Recently, a further new and more efficient access to **42a** based on a novel variation of the benzannellation of indoles was described [43]. In this case, also a 6π-electrocyclic ring closure represents the key step (*Scheme 14*). Starting material for this procedure is the readily available 2-methoxy-3-oxo-2,3-dihydroindole (**49**) and the reaction sequence comprises a *Wittig* reaction of **49** with the ylide **50** to give the 3-(2-oxobut-3-enyl)indole **51** (74% yield), and treatment of **51** with Me_3SiI in the presence of hexamethyldisilazane (HMDS) to produce the desired 3-(buta-1,3-dienyl)indole **52** in 80% yield. Heating of **52** induces an electrocyclic ring closure to form the intermediate **53** which undergoes spontaneous elimination of MeOH to furnish the 3-hydroxycarbazole **55** and its trimethylsilyl derivative **54** in 13 and 53% yield, respectively. When the silyl derivative **54** is treated with Bu_4NF (TBAF) it is converted to **55** in 81% yield. Methylation of **55** with dimethyl sulphate (DMS) followed by a standard deacetylation reaction finally gives rise to **42a** in 72% yield.

Carbazomycins and their demethoxy derivatives have also been synthesised previously. In continuation of our investigations in the field of *Diels-Alder* reactions of 2- and 3-vinylindoles [34–36], we have succeeded in preparing the two regioisomeric deoxycarbazomycins. Thus, 3-deoxycarbazomycin (**59**) is readily accessible by an *in situ* 3-vinylindole *Diels-Alder* step (*Scheme 15*). The thermally sufficiently stable indolyl(methoxy)methylcarbenium

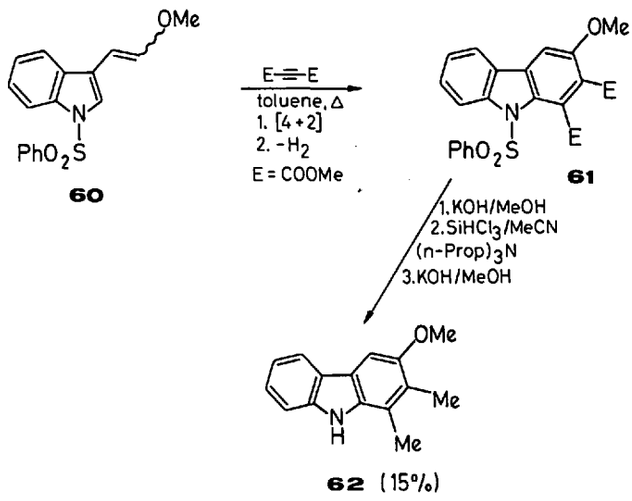
Scheme 14



Scheme 15



Scheme 16

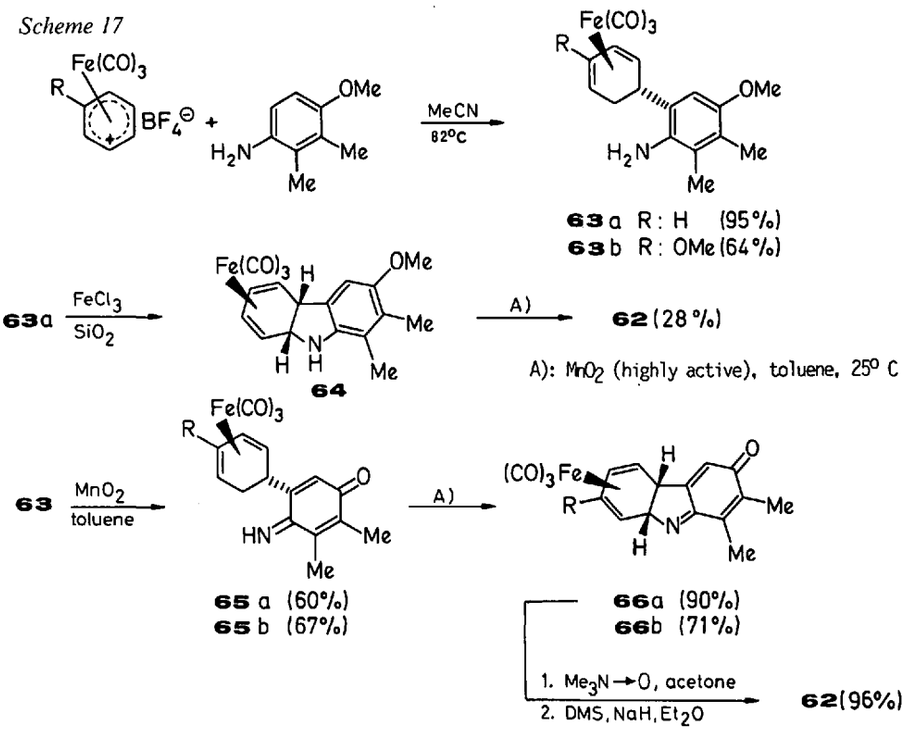


tetrafluoroborate **56** was deprotonated *in situ* to form the highly reactive 3-vinylindole **57** as an intermediate. A [4+2]-trapping reaction of **57** with dimethyl acetylenedicarboxylate and subsequent dehydrogenation gave the carbazole **58** in a one-pot procedure; finally, **58** was reduced to **59** in 28% yield [44].

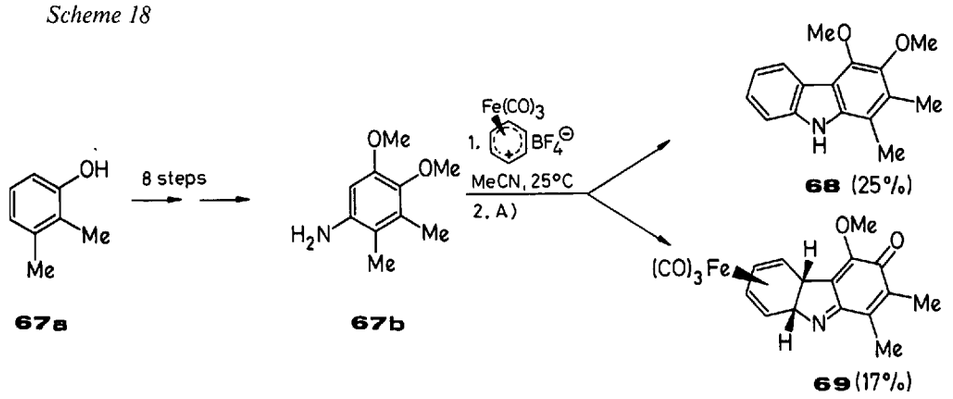
The synthesis of 4-deoxycarbazomycin (**62**) was achieved by a related *Diels-Alder* methodology in which the stable (*E*/*Z*)-2′-methoxy-substituted 3-vinylindole **60** was employed as a starting 4π-compound. The indole **60** was readily converted to the carbazole **61** by reaction with dimethyl acetylenedicarboxylate as a C,C-dienophile. The resultant product **61** was then transformed to the target molecule **62** by the same method as described above for the synthesis of **59** (*Scheme 16*) [45].

Another very selective route to **62** and the first total synthesis of carbazomycin A (**68**) was recently reported by *Knölker* and coworkers [46]. This highly effective, Fe-induced C,C- and C,N-coupling method permits a general synthesis involving only a few steps of naturally occurring carbazole derivatives that are oxygenated at C(3) or at C(2) and C(6) (*Scheme 17*). Hence, cyclisation of the preparatively easily accessible Fe complex under reaction conditions *A*) leads directly to **62**. The transformation involves the intermediate Fe complex **64** which can even be isolated when **63a** is treated with $FeCl_3$/silica gel. Selective oxidation of compounds **63** with commercial MnO_2 produces the iminoquinones **65** which undergo cyclisation when subjected to reaction conditions *A*) to furnish **66a** and **66b**. Demetallation of **66a** followed by methylation of the resul-

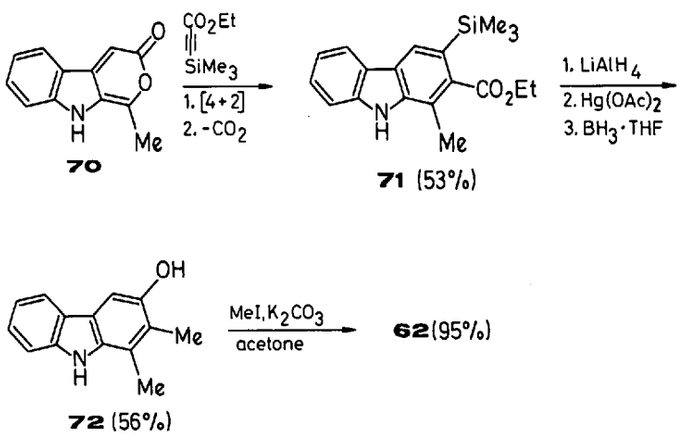
Scheme 17



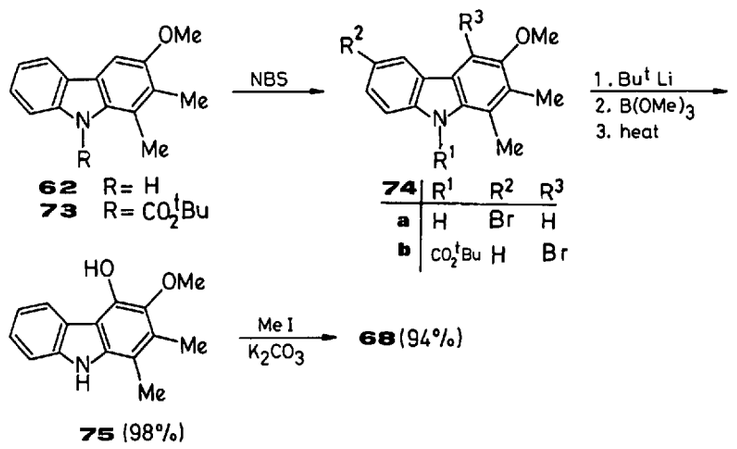
Scheme 18



Scheme 19



Scheme 20



tant alcohol affords **62** in 48% overall yield from **63a**, thus, demonstrating the advantages of the route to aromatic carbazoles *via* iminoquinone cyclisations. The utility of the above methodology was further illustrated by the total synthesis of carbazomycin A (**68**) (*Scheme 18*). In addition, the by-product **69** was isolated [46].

Recently, a further new strategy for the total syntheses of carbazomycins A and B as well as the marine alkaloid hyellazole (**42a**) was described by *Moody* and coworkers [47]. This methodology is based on the [4+2]-cycloaddition of pyrano-[3, 4-*b*]indol-3-ones; this same *Diels-Alder* process has since found a wide application in the synthesis of selectively functionalised carbazoles both by *Moody*'s group and by ourselves (see also [37]).

Thus, 4-deoxycarbazomycin (**62**) was prepared as follows: the readily – and meanwhile commercially – available 1-methylpyrano[3,4-*b*]indol-3-one (**70**) underwent a highly regioselective *Diels-Alder* reaction with ethyl 3-(trimethylsilyl)propynoate and loss of CO_2 to furnish the carbazole ester **71**. It was then reduced to the 2-methylcarbazole by treatment with $LiAlH_4$ in refluxing dioxane. Subsequent mercuriodesilylation of the resultant, 1,2-dimethyl-3-(trimethylsilyl)carbazole furnished the arylmercury derivative which, upon hydroboration and oxidation, gave the required hydroxycarbazole **72**. Finally, the latter was easily converted to **62** (*Scheme 19*).

In a further procedure, compound **62** was converted to carbazomycin A (**68**) or B (**75**) by selective introduction of an OH or MeO group, respectively, at C(4) of the carbazole nucleus of **73** (*Scheme 20*) [47].

Here, bromination of the carbazole **62** with *N*-bromosuccinimide (NBS) gave the corresponding 6-bromo compound **74a**, whereas bromination of the *N*-(*tert*-butoxycarbonyl) derivative **73** under the same conditions gave the desired 4-bromo derivative **74b**. Treatment of **74b** with *t*-BuLi in THF at −78°, followed by reaction of the resultant carbazolyllithium derivative with trimethyl borate, and alkaline H_2O_2 workup gave a 4-hydroxycarbazole from which removal of the *N*-protecting group to give **75** was simply achieved by heating. Methylation of **75** then yielded **68**.

Hyellazole (**42a**; 92% yield in the last step) was obtained from 1-phenylpyrano[3,4-*b*]indol-3-one using an analogous procedure [47]. For a further new but polar approach to selectively methylated carbazoles, see [48].

6. Conclusions

In addition to the more classical methods and the meanwhile well established methodologies for the synthesis of carbazole derivatives and carbazole alkaloids such as the *Fischer-Borsche* cyclisation, the *Japp-Klingemann* procedure, the *Graebe-Ullmann* method, the Pd-promoted cyclisation of diphenylamines, the cyclisation of indolyl-substituted β-keto sulphides, the free radical cyclisation of diphenylamines, and the *Nenitzescu* method, alternative pericyclic strategies such as, *e.g.*, the *Diels-Alder* reactions of vinylindoles or pyrano-[3,4-*b*]indoles as well as the 6π-electrocyclisation of selectively functionalised indole derivatives have been developed during the last few years. Complementary to these synthetic strategies, the novel, consecutive, Fe-induced C,C- and C,N-coupling method is also highly attractive for the synthesis of carbazoles. It is to be hoped – and this represents a major challenge for preparative chemistry – that, in consideration of the generally very high selectivity of pericyclic reactions, the future will bring about the syntheses of more complicated carbazole alkaloids (*e.g.* members of the C_{23}-skeletal group) with more than one stereocentre. A first prerequisite for this is the achievement of an intelligent combination of polar and pericyclic reaction sequences.

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Matrix-Assisted Laser Desorption and Ionization Mass Spectrometry and Its Applications in Chemistry

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Abstract. The present paper gives a summary of the potentialities of matrix-assisted laser desorption and ionization mass spectrometry (LDI-MS). Mass spectrometric information on different chemical and biochemical species are obtained with LDI-MS. Sulfonic acids, polysaccharides, oligonucleotides, and peptides were measured as negatively or positively charged ions in a time-of-flight mass spectrometer (TOF-MS). The amount of sample for a measurement lies between 50 pmol and 100 fmol and is, thus, comparable with other analytical and mass spectrometric methods. The large mass range from 0.6 kDa up to 200 kDa is accessible with LDI-MS. Molecular-weight determination can be done with an accuracy of less than 0.2%. Comparison with RP HPLC reveals the power of LDI-MS as an analytical tool.

1. Introduction

Since its development in 1988 by *Karas* and *Hillenkamp* [1] matrix-assisted laser desorption mass spectrometry (LDI-MS) has received an immensely growing interest. With the fast development of peptide synthesis and genetic engineering in particular, the need for a method which allows to determine the molecular weight of proteins and polypeptides with high accuracy and sensitivity has increased simultaneously. The LDI-MS has the potential to fulfill these needs. The LDI-MS can be used as well to solve analytical and mass-spectrometric problems for other interesting chemical species besides proteins due to its high sensitivity and its low selectivity. The method allows to desorb and ionize large molecules up to 200 kDa and to determine the molecular weight with as little as 100 fmol sample. Thus, the sensitivity of LDI is comparable with other analytical methods like RP HPLC. The method has a dynamic range of at least 1:100 which al-

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