Isolation and Synthesis of Biologically Active Carbazole Alkaloids

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I. Introduction

1. General

Carbazole **1** was isolated first from coal tar in 1872 by Graebe and Glazer (Figure 1).[1] In 1965, Chakraborty et al. described the isolation and antibiotic properties of murrayanine from *Murraya koenigii* Spreng.[2−4] In India, the leaves of this small tree (known as currypatta or curry-leaf tree) are used in curry. The isolation of murrayanine was the first report of a naturally occurring carbazole alkaloid. Since then there has been a strong interest in this area by chemists and biologists due to the intriguing structural features and promising biological activities exhibited by many carbazole alkaloids. The explosive growth of carbazole chemistry is emphasized by the large number of monographs, accounts, and reviews.[5−21]

Most carbazole alkaloids have been isolated from the taxonomically related higher plants of the genus *Murraya*, *Glycosmis*, and *Clausena* from the family Rutaceae. The genus *Murraya* represents the richest source of carbazole alkaloids from terrestrial plants. The lower plants from which carbazole alkaloids have been isolated include several different *Streptomyces* species. Further natural sources for carbazole alkaloids are, for example, the blue-green algae *Hyella caespitosa*, *Aspergillus* species, *Actinomadura* species, and the ascidian *Didemnum granulatum*.

Several working hypotheses have been proposed to account for the biogenesis of carbazole alkaloids. However, there is no deep knowledge of the biogenesis of this class of compounds. A comparison of the structural features of the carbazole alkaloids isolated from higher plants suggests that 3-methylcarbazole may represent the key intermediate in their biosynthesis. On the other hand, 2-methylcarbazole appears to be the common biogenetic precursor of the conventional tricyclic carbazoles isolated from lower plants. In many cases the biogenetic precursor of the carbazole nucleus in nature is not clear.

The isolation of several 3-methylcarbazole derivatives from higher plants[9] and of carbazole **1** from *Glycosmis pentaphylla*[22] shows that the aromatic methyl group can be eliminated oxidatively from the key intermediate 3-methylcarbazole via $-CH_2OH$, $-CHO$, and $-COOH$ functionalities.[6] The isolation of 3-methylcarbazole from the genus *Clausena*,[23,24] the co-occurrence of murrayafoline A (**2**), koenoline (**3**), murrayanine (**4**), and mukoeic acid (**5**) in *M. koenigii*, as well as the subsequent isolation of mukonine (**6**) and mukonidine (**9**) and the discovery of 2-hydroxy-3-methylcarbazole (**7**) and mukonal (**8**) in *M. koenigii*[25−27] support the hypothesis of biomimetic hydroxylation of 3-methylcarbazole.[28] Congeners that differ in the oxidation state of the C-3 methyl group, i.e. $-CH_2OH$, $-CHO$, $-COOH$, and $-COOMe$, were found for various alkaloids, a fact which indicates an in vivo oxidation of carbazole alkaloids (Scheme 1).[6]

Hans-Joachim Knölker was born in Rehren, Germany, in 1958. He studied chemistry at the universities of Göttingen and Hannover, and obtained his diploma degree (Dipl.-Chem.) in 1983 and his Ph.D. (Dr. rer. nat.) in 1985 in the group Professor E. Winterfeldt at the University of Hannover. Following his postdoctoral studies in the research group of Professor K. P. C. Vollhardt at the University of California in Berkeley in 1986, he returned to the University of Hannover and finished his habilitation in 1990. He received the ADUC award for 1989 of the Gesellschaft Deutscher Chemiker (GDCh) and in 1990 the Dozentenstipendium of the Fonds der Chemischen Industrie (FCI). In 1991, his work was supported by the Gerhard-Hess award of the Deutsche Forschungsgemeinschaft (DFG). In the same year, he became Full Professor of Organic Chemistry at the University of Karlsruhe, where he was chairman of Department of Chemistry from 1995 to 1997. In 1998, he received a fellowship of the Japan Society for the Promotion of Science (JSPS). In January 2000, he was a visiting scientist in India on invitation of the Indian National Science Academy (INSA). In 2001, he moved with his research group to the Institute of Organic Chemistry at the Technical University of Dresden. His research interests include the applications of organotransition metal-π complexes to organic synthesis, Lewis acid-mediated cycloaddition reactions of allylsilanes, isocyanate chemistry, as well as the synthesis of novel fluorescent imidazole derivatives.

Kethiri Raghava Reddy was born in Garimilla Pally, Andhra Pradesh, India, in 1963. He studied chemistry at Kakatiya University in Warangal, where he received his B.Sc. in 1984 and his M.Sc. in 1987. After qualifying for the National Educational Test, he joined the group of Professor H. Ila at the North-Eastern Hill University in Shillong for a Ph.D., which he completed in 1995. He continued in the same group as research associate (CSIR) until 1996, when he moved as an Alexander von Humboldt fellow (1997–1999) to the research group of Professor H. -J. Knölker at the University of Karlsruhe, Germany. He continued as a postdoctoral fellow in the same group until 2001, when he followed the Knölker research group to the Technical University of Dresden as a staff scientist.

The occurrence of heptaphylline (**10**)[29] and murrayacine (**11**)[30] (Scheme 2) in *Clausena heptaphylla* is circumstantial evidence for the origin of the pyran ring from the prenylated congener. This explains the formation of pyranocarbazoles from 2-hydroxy-3-methylcarbazole as shown by Popli and Kapil.[31] The co-occurrence of 2-hydroxy-3-methylcarbazole (**7**),[25,26] mukonal (**8**),[27] and mukonidine (**9**)[32] provides clear evidence for the in vivo oxidation of the methyl group in 2-hydroxy-3-methylcarbazole. All these findings strongly suggest 3-methylcarbazole as the key precursor for the carbazoles isolated from higher plants.

A classical method that has been often utilized for the synthesis of aromatic carbazoles is the dehydrogenation of 1,2,3,4-tetrahydrocarbazoles prepared by Fischer−Borsche synthesis. Widely used precursors are also biphenyls with an *o*-nitrogen substituent. Many carbazole alkaloids were synthesized from a variety of indole precursors or by oxidative cyclization of diarylamines.

In this review, we summarize the occurrence and the biological activity of carbazole alkaloids obtained from diverse natural sources. Moreover, we present a detailed past-decade coverage of the classical methods (e.g., the Fischer−Borsche synthesis and the Graebe−Ullmann synthesis) and the nonclassical procedures (such as transition metal-mediated and -catalyzed processes) for the total synthesis of biologically active carbazole alkaloids. The nomenclature adopted in this review for carbazole alkaloids is that used by *Chemical Abstracts*. Conventional tricyclic ring systems are denoted by A, B, and C, and the numbering starts from ring A, as shown in Figure 1. The term carbazole used in this review refers to a 9*H*-carbazole. The classification of the carbazoles is based on the substitution pattern of ring A, although ring C may also carry various substituents.

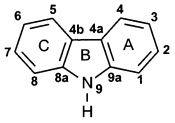

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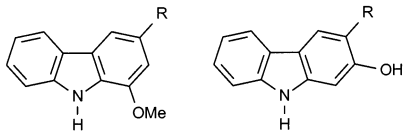
Figure 1.

Scheme 1



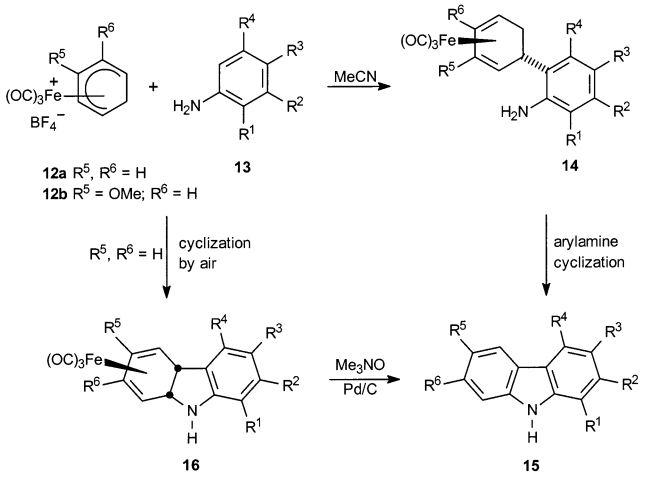
2 Murrayafoline A
R = Me
3 Koenoline
R = CH_2OH
4 Murrayanine
R = CHO
5 Mukoeic acid
R = COOH
6 Mukonine
R = COOMe

7 2-Hydroxy-3-methylcarbazole
R = Me
8 Mukonal
R = CHO
9 Mukonidine
R = COOMe

Scheme 2

10 Heptaphylline **11** Murrayacine

Scheme 3



In the following section (I.2.1−I.2.4), the procedures using transition metals (iron, molybdenum, and palladium) for the synthesis of the carbazole nucleus are described. The applications of these methods to the total synthesis of natural products will be provided in the appropriate following sections (II−XI).

2. Transition Metal-Mediated Carbazole Synthesis

2.1. Iron-Mediated Synthesis of Carbazoles

The tricarbonyliron-coordinated cyclohexadienylium ions **12** were shown to represent useful electrophiles for the electrophilic aromatic substitution of functionally diverse electron-rich arylamines **13**.[33] This reaction combined with the oxidative cyclization of the arylamine-substituted tricarbonyl(η^4-cyclohexadiene)iron complexes **14** opened up the way to highly convergent total syntheses of a broad range of biologically active carbazole alkaloids **15**.[15,20,21] The overall process of this carbazole synthesis involves a consecutive iron-induced C−C and C−N bond formation, followed by aromatization. Over the past decade we developed three different procedures for the iron-mediated oxidative coupling of arylamines with a cyclohexadiene to carbazole derivatives (Scheme 3):[20]

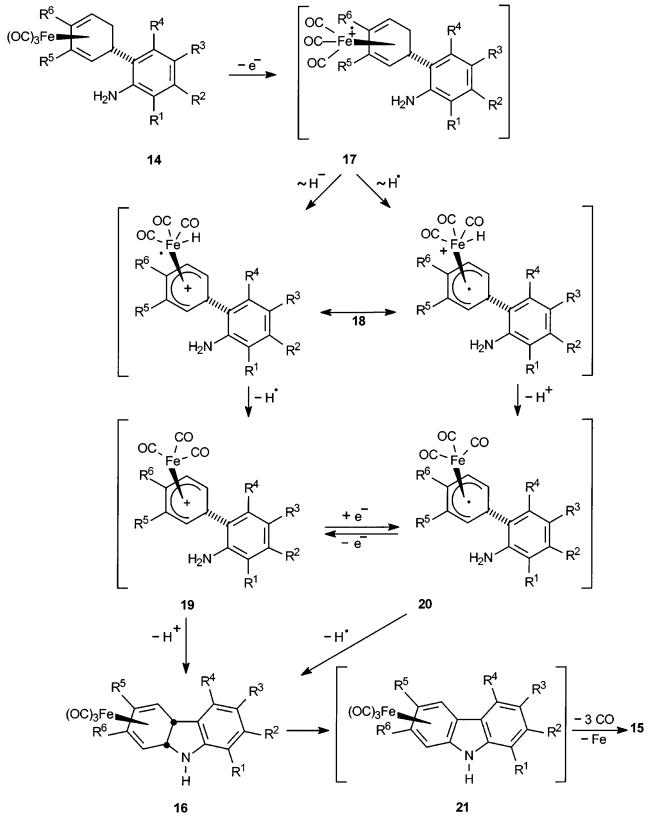
(1) the iron-mediated arylamine cyclization,

(2) the iron-mediated quinone imine cyclization, and

(3) the iron-mediated oxidative cyclization by air.

Iron-Mediated Arylamine Cyclization. The one-pot transformation of the arylamine-substituted tricarbonyl(η^4-cyclohexadiene)iron complex **14** to the 9*H*-carbazole derivative **15** proceeds via a sequence of cyclization, aromatization, and demetalation. The cyclizing dehydrogenation leads to the intermediate tricarbonyliron-complexed 4a,9a-dihydro-9*H*-carbazole **16**. On the basis of our deuterium-labeling studies,[34] this step is initiated by a single electron transfer (SET) oxidation to a 17-electron radical cation **17**. A subsequent intramolecular, syn-stereospecific hydrogen transfer affords compound **18**.[34,35] The dehydrogenation via the tricarbonyl(η^5-cyclohexadienylium)iron derivatives **19** and **20** provides the dihydrocarbazole **16**, which represents a stable

Scheme 4

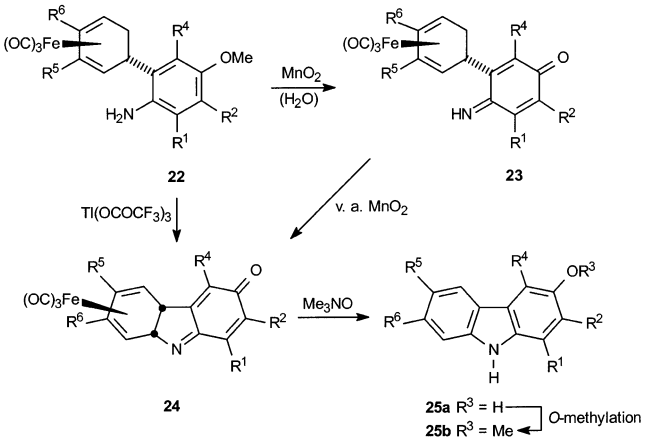


18-electron complex. Further dehydrogenation affords the tricarbonyl(η^6-arene)iron complex **21**, a 20-electron complex, which demetalates spontaneously to the carbazole derivative **15** (Scheme 4). This methodology has been widely used for the total synthesis of a broad range of 1-oxygenated, 3-oxygenated, and 3,4-dioxygenated carbazole alkaloids.[15,20]

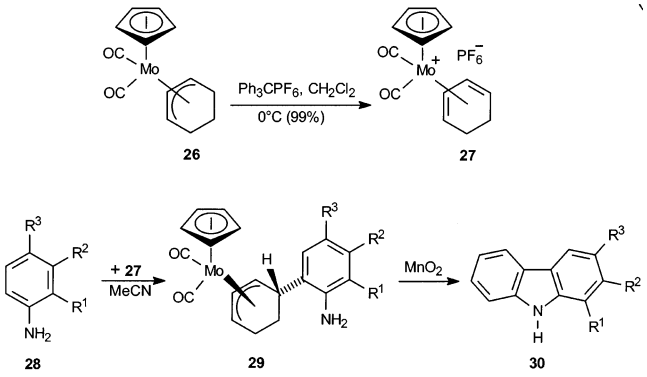
Iron-Mediated Quinone Imine Cyclization. Chemoselective oxidation of the aromatic nucleus of **22** by commercial manganese dioxide leads to the acyclic quinone imines **23**. Oxidative cyclization of the quinone imines **23** using very active manganese dioxide affords stereoselectively the cyclized quinone imines **24**, which are tricarbonyliron-complexed 4b,8a-dihydrocarbazol-3-ones.[36] Demetalation of the tricarbonyliron-complexed 4b,8a-dihydrocarbazol-3-ones **24** using trimethylamine *N*-oxide[37] provides directly the 3-hydroxycarbazoles **25a**. Finally, the 3-hydroxycarbazoles **25a** can be transformed to the 3-methoxycarbazoles **25b** by selective *O*-methylation (Scheme 5). This method provides a simple access to various 3-oxygenated and 3,4-dioxygenated carbazole alkaloids.[15,20,38]

Iron-Mediated Oxidative Cyclization by Air. By a one-pot operation in the air the tricarbonyliron-complexed cyclohexadienylium ions **12** and the arylamines **13** are selectively transformed to the tricarbonyliron-complexed 4a,9a-dihydro-9*H*-carbazole derivatives **16**. This procedure involves cyclization of the in situ generated tricarbonyliron complex **14** by molecular oxygen. Following the conditions described for the arylamine cyclization, the dihydrocarbazoles **16** are transformed to the carbazole derivatives **15** (see Scheme 3). This eco-friendly method offers an

Scheme 5



Scheme 6



excellent alternative to the previous cyclization procedures.[20,21]

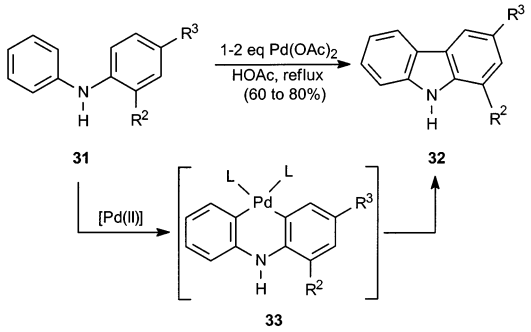
2.2. Molybdenum-Mediated Synthesis of Carbazoles

The iron-mediated synthesis of 2-oxygenated carbazole alkaloids was limited.[39] To overcome this problem, we developed a molybdenum-mediated approach as a complementary method. Following literature procedures, dicarbonyl(η^4-cyclohexa-1,3-diene)-(η^5-cyclopentadienyl)molybdenum hexafluorophosphate **27** can be prepared quantitatively from dicarbonyl-(η^3-cyclohexenyl)(η^5-cyclopentadienyl)molybdenum **26**.[40,41] The electrophilic aromatic substitution of the electron-rich arylamines **28** by the molybdenum-complexed cation **27** affords regio- and stereoselectively the molybdenum complexes **29**. Oxidative cyclization of the complexes **29** with concomitant aromatization and demetalation using activated manganese dioxide leads to the carbazole derivatives **30** (Scheme 6).

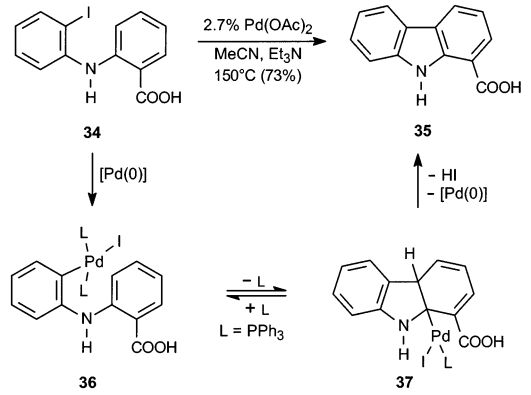
2.3. Synthesis of Carbazoles by Palladium-Mediated Cyclization of N,N-Diarylamines

Diphenylamines have been cyclized to carbazoles photochemically;[42−51] thermally in the presence of elemental iodine at 350 °C[52,53] or with platinum at 450−540 °C,[54] via free radicals with benzoyl peroxide in chloroform;[55] and chemically using activated metal catalysts such as degassed Raney nickel[56] and palladium on charcoal.[57] However, the yields are in most of the cases only low to moderate.

Scheme 7



Scheme 8

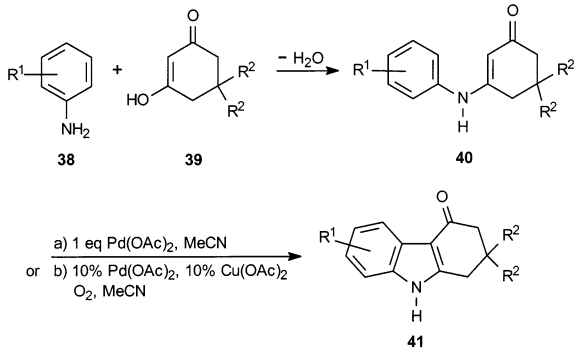


Palladium-catalyzed C−C bond formations, especially the Heck reaction (arylation or vinylation of alkenes and alkynes),[58−60] attracted considerable interest from synthetic organic chemists. Several groups demonstrated that related coupling reactions provide an efficient access to the carbazole framework.[61]

Åkermark and co-workers have shown that much better results are obtained by refluxing the corresponding diphenylamine with palladium(II) acetate in acetic acid. Many substituents are tolerated in this oxidative cyclization, which represents the best procedure for the cyclization of the diphenylamines **31** to the carbazole derivatives **32**. However, 1 equiv of palladium(II) acetate is necessary for the cyclization of diphenylamines containing electron-releasing or only moderately electron-attracting substituents. For diphenylamines with strong electron-withdrawing groups (e.g. NO_2 or COOH), 2 equiv of palladium acetate and longer reaction times (2 h) are required. Moreover, the cyclization is catalyzed by acids such as trifluoroacetic acid or methanesulfonic acid. However, both hydrochloric and sulfuric acid inhibit the cyclization. All these observations indicate an electrophilic attack of a palladium(II) species at the aromatic rings in the rate-determining step of this cyclization to give an arylpalladium intermediate **33** (Scheme 7).[62]

Ames et al. reported the preparation of the carbazole **35** by an intramolecular dehydrogenative coupling of 2-iodoarylamine **34** using catalytic amounts of palladium(II) acetate under basic conditions (Scheme 8).[63,64] The cyclization of 2-iododiphenylamine-2'-carboxylic acid **34** to carbazole-1-carboxylic acid **35** was achieved in 73% yield using 2.7 mol %

Scheme 9



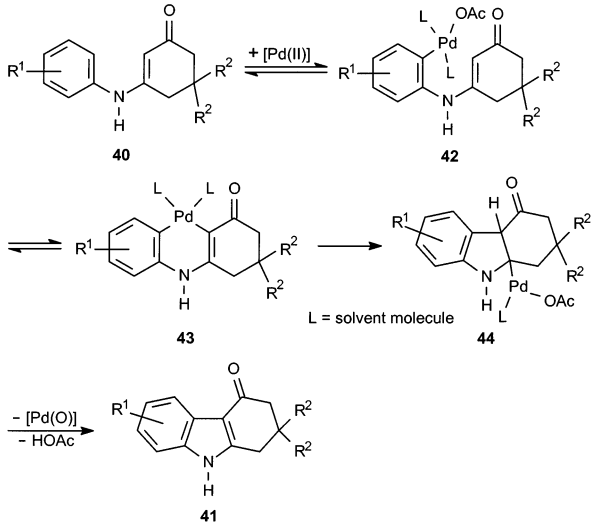
palladium(II) acetate in the presence of triethylamine at 150 °C in a stainless steal bomb. This reaction represents a palladium(0)-catalyzed cyclization. The palladium(0) is generated in situ by reduction of palladium(II). By analogy with the classical Heck reaction,[58−60] the cyclization is believed to proceed via an oxidative addition of the iodoarene to the palladium(0) species, generating a σ-aryl palladium(II) complex **36**. Subsequent insertion of a double bond of the appended aryl ring provides the σ-alkyl palladium(II) complex **37**. Elimination leads to the carbazole **35** and a palladium hydride species, which regenerates the palladium(0) species in the presence of base (Scheme 8).

Kibayashi and co-workers described the synthesis of substituted 1,2,3,4-tetrahydrocarbazol-4-(9*H*)-ones **41** by cyclization of *N*-arylenaminones **40** using either stoichiometric or catalytic amounts of palladium(II) acetate.[19] The required enaminones **40** are easily prepared by condensation of the arylamines **38** with cyclic β-ketones **39** (Scheme 9).

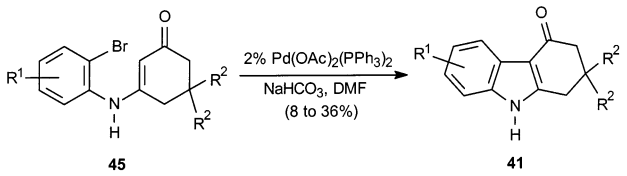
The reaction of the *N*-arylenaminones **40** with an equimolar amount of palladium(II) acetate in refluxing acetonitrile provided the corresponding carbazoles **41** in moderate yields (19−30%). This reaction represents a palladium(II)-mediated cyclization. The suggested mechanism for this reaction involves a direct electrophilic palladation of the aromatic ring to provide the σ-aryl palladium(II) complex **42**. Insertion of the enaminone double bond followed by reductive elimination generates 1 equiv of palladium(0). Thus, a catalytic reaction is possible by reoxidation of palladium(0) to palladium(II). This can be achieved under reaction conditions related to the Wacker process[65] using copper(II) acetate and oxygen as oxidizing agents. The cyclization to 6-methoxy-1,2,3,4-tetrahydrocarbazol-4(9*H*)-one (R^1 = OMe, R^2 = H) **41** was achieved in 31% yield with catalytic amounts of palladium(II) acetate and copper(II) acetate (10 mol % of each) under oxygen (Scheme 10).

Alternatively, Kibayashi and co-workers developed a catalytic cyclization by dehydrohalogenation of the 2-bromoaryl derivatives **45**. Treatment of the bromoenaminones **45** with 2 mol % bis(triphenylphosphine)palladium(II) acetate in dimethylformamide at 120−130 °C in the presence of sodium bicarbonate affords the carbazole derivatives **41** in 8−36% yield (Scheme 11).[65] This cyclization represents again a palladium(0)-catalyzed process (cf. the dehydrohalogenation of 2-iodoarylamines, Scheme 8). The probable mechanism of this reaction is related to the Heck arylation.[19,58−60]

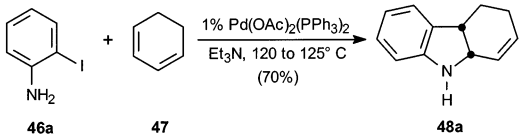
Scheme 10



Scheme 11



Scheme 12

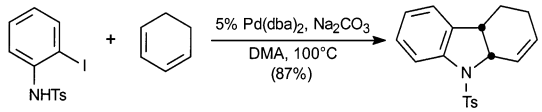


2.4. Synthesis of Tetrahydrocarbazoles by Palladium-Catalyzed Heteroannulation of 1,3-Dienes

In recent years, π-allylpalladium complexes became very valuable intermediates in organic synthesis, because they were shown to undergo reactions with a wide range of nucleophiles.[66,67] The synthesis and subsequent reactions of such palladium complexes under catalytic conditions generally take advantage of the transformation of an allylic ester, ether, or alcohol. Alternatively, π-allylpalladium complexes are available from the reaction of an initially formed σ-palladium complex with a conjugated diene.[68] The σ-palladium(II) complex is generated in situ by oxidative addition of an aryl or vinyl halide to the palladium(0) catalyst. Intramolecular nucleophilic attack by an amino group to the π-allylpalladium complex formed in this process opens up the way to the heteroannulation of 1,3-dienes. Dieck et al. applied this principle to the synthesis of 3,4,4a,9a-tetrahydro-9*H*-carbazoles **48a** through a palladium(0)-catalyzed heteroannulation of 1,3-cyclohexadiene **47** and 2-iodoaniline **46a** (Scheme 12).[69]

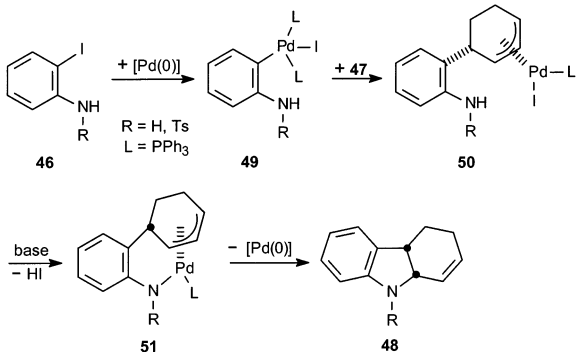
The proximity of the amino group to the π-allylic moiety is essential for the cyclization of the intermediate complex, since the attempted intermolecular

Scheme 13



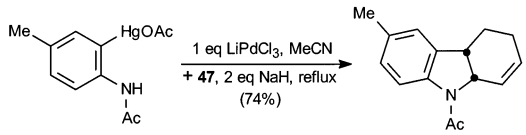
46b 47 48b

Scheme 14



46 49 50 51 48

Scheme 15



52 53

reaction of the diene with iodobenzene and aniline failed to give any product resulting from the attack of the arylamine to the π-allylpalladium complex. In the following years, Larock et al. reported the synthesis of the 3,4,4a,9a-tetrahydro-9*H*-carbazole derivative **48b** in an improved yield using *N*-tosyl-2-iodoaniline **46b** and 1,3-cyclohexadiene **47** as the substrates and palladium(0)bis(dibenzylideneacetone) [$Pd(dba)_2$] as catalyst (Scheme 13).[70]

The mechanism for this palladium-catalyzed heteroannulation is presumed to proceed via an oxidative addition of the iodoarene **46** to the (in situ generated) palladium(0) species, providing the σ-arylpalladium(II) intermediate **49**, which reacts with 1,3-cyclohexadiene **47** to afford the π-allylpalladium complex **50**. The nucleophile undergoes an intramolecular syn-directed displacement of the palladium moiety, probably through an intermediate **51**, furnishing the tetrahydrocarbazole **48** (Scheme 14).

Instead of an oxidative addition, the intermediate σ-arylpalladium(II) complex **49** may be formed by transmetalation of the arylmercury compound **52** using stoichiometric amounts of a palladium(II) salt (Scheme 15).[71] Transmetalation by addition of 1 equiv of $LiPdCl_3$ to the organomercury compound **52** in acetonitrile provides the σ-arylpalladium compound, which reacts with 1,3-cyclohexadiene **47** to generate a π-allylpalladium complex related to **50**. Addition of 2 equiv of base liberates the nucleophile, which undergoes facile intramolecular displacement of the palladium moiety to give the tetrahydrocarbazole derivative **53** (cf. Scheme 14). The cis-stereochemistry of the product arises from the intramolecular syn-attack by the amino group to the same face of the π-allyl ligand as the metal.

II. Oxygenated Tricyclic Carbazole Alkaloids

1. 1-Oxygenated Tricyclic Carbazole Alkaloids

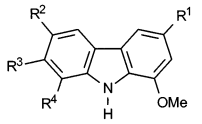
The higher plants of the genus *Murraya* (*Rutaceae* family), trees growing in southern Asia, are the major natural source of 1-oxygenated carbazole alkaloids. Extracts of leaves and bark of this tree have been used as folk medicine. Murrayafoline A (**2**) was isolated from *Murraya euchrestifolia* Hayata collected in Taiwan.[72,73] The cytotoxic carbazole alkaloid koenoline (**3**) was isolated from the roots of *M. koenigii*.[74] Chakraborty et al. reported the independent isolation of murrayanine (**4**) from two different species: *M. koenigii* [75] and *C. heptaphylla*.[76] This alkaloid shows antimicrobial properties.[3] Mukoeic acid (**5**) was isolated from the stem bark of *M. koenigii* Spreng.[77,78] It represents the first carbazole carboxylic acid from a plant source. The corresponding methyl ester, mukonine (**6**), was also isolated from the same plant.[6] The co-occurrence of murrayafoline A (**2**), koenoline (**3**), murrayanine (**4**), mukoeic acid (**5**), and mukonine (**6**) in plants of the genus *Murraya* indicates that they are biosynthesized by in vivo oxidation of murrayafoline A (see Scheme 1).

Furukawa and his group isolated murrayastine (**54**) from the stem bark of *M. euchrestifolia* Hayata.[79] Li and co-workers reported the isolation of 6-methoxymurrayanine (**55a**) from the roots of *Clausena lansium*.[80a] The roots of the Taiwanese tree *C. lansium* are used in folk medicine to treat bronchitis and malaria. In 1995, Chowdhury et al. described the isolation of the antimicrobial carbazole alkaloid clausenal (**55b**) from *C. heptaphylla*. The structure of clausenal (**55b**) was confirmed by synthesis using a Japp−Klingemann reaction and Fischer indolization.[80b] Chakraborty and co-workers isolated mukoline (**56**) and mukolidine (**57**) from the roots of *M. koenigii*.[81] Clausenapin (**58**) was isolated from the leaves of *C. heptaphylla*.[82] Prior to its isolation, it was known as a Huang−Minlon reduction product of indizoline.[6] Indizoline (**59**) was isolated from the same species *Clausena indica Oliv*.[24] Although, ekeberginine (**60**) is an alkaloid structurally closely related to indizoline (**59**), it was isolated from a different source, the stem bark of *Ekebergia senegalensis* (Meliaceae).[83] Murrayafoline B (**61**) was isolated from the root bark of *M. euchrestifolia*.[72] *O*-Demethylmurrayanine (**62**) was obtained from the root bark of *Clausena anisata* (Scheme 16).[84] The isolation of additional 1-oxygenated tricyclic carbazole alkaloids is described in section XI.5.1.

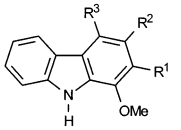
1.1. Iron-Mediated Total Synthesis of 1-Methoxycarbazole Alkaloids

The retrosynthesis of the 1-methoxycarbazole alkaloids **2**−**6** leads to cyclohexadiene **47** and the corresponding arylamines **63** as precursors for an iron-mediated synthesis (Scheme 17). The two crucial steps for the construction of the carbazole framework by the iron-mediated approach are, first, C−C bond formation by electrophilic aromatic substitution of the arylamine with the tricarbonyliron-complexed cyclohexadienyl cation and, second, C−N bond formation and aromatization by an oxidative cyclization.

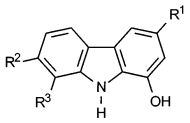
Scheme 16



54 Murrayastine
R^1 = Me; R^2 = H; R^3, R^4 = OMe
55a 6-Methoxymurrayanine
R^1 = CHO; R^2 = OMe; R^3, R^4 = H
55b Clausenal
R^1 = CHO; R^2, R^3 = H; R^4 = OMe
56 Mukoline
R^1, R^3, R^4 = H; R^2 = CH_2OH
57 Mukolidine
R^1, R^3, R^4 = H; R^2 = CHO

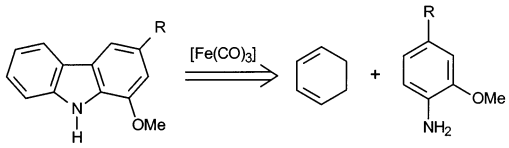


58 Clausenapin
R^1 = prenyl; R^2 = Me; R^3 = H
59 Indizoline
R^1 = prenyl; R^2 = CHO; R^3 = H
60 Ekeberginine
R^1 = H; R^2 = CHO; R^3 = prenyl



61 Murrayafoline B
R^1 = Me; R^2 = OMe; R^3 = prenyl
62 *O*-Demethylmurrayanine
R^1 = CHO; R^2, R^3 = H

Scheme 17



2 Murrayafoline A
R = Me
3 Koenoline
R = CH_2OH
4 Murrayanine
R = CHO
5 Mokoeic acid
R = COOH
6 Mukonine
R = COOMe

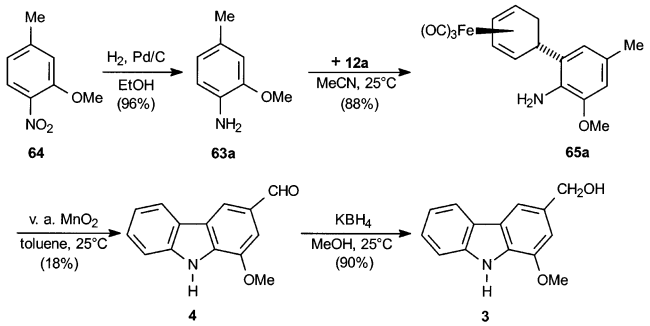
47

63a R = Me
63b R = OMe
63c R = COOMe

Application of this methodology provides murrayanine (**4**) in 15% overall yield over three steps starting from the commercial nitroaryl derivative **64**. Catalytic hydrogenation of the nitroarene **64** afforded 2-methoxy-4-methylaniline **63a**. An electrophilic substitution of the arylamine **63a** by reaction with the iron complex salt **12a** led to the tricarbonyliron complex **65a**. The one-pot conversion of complex **65a** to murrayanine (**4**) is rationalized by the following four-step sequence with very active manganese dioxide in toluene at room temperature: (1) oxidation of the methyl to the formyl group, (2) cyclizing dehydrogenation to the 4a,9a-dihydro-9*H*-carbazole, (3) aromatization to a 20-electron complex, and (4) spontaneous demetalation to murrayanine (**4**). Murrayanine (**4**) was transformed to the cytotoxic carbazole alkaloid koenoline (**3**) by borohydride reduction. The iron-mediated total synthesis provides koenoline (**3**) in four steps and 14% overall yield based on the nitroaryl derivative **64** (Scheme 18).[85,86]

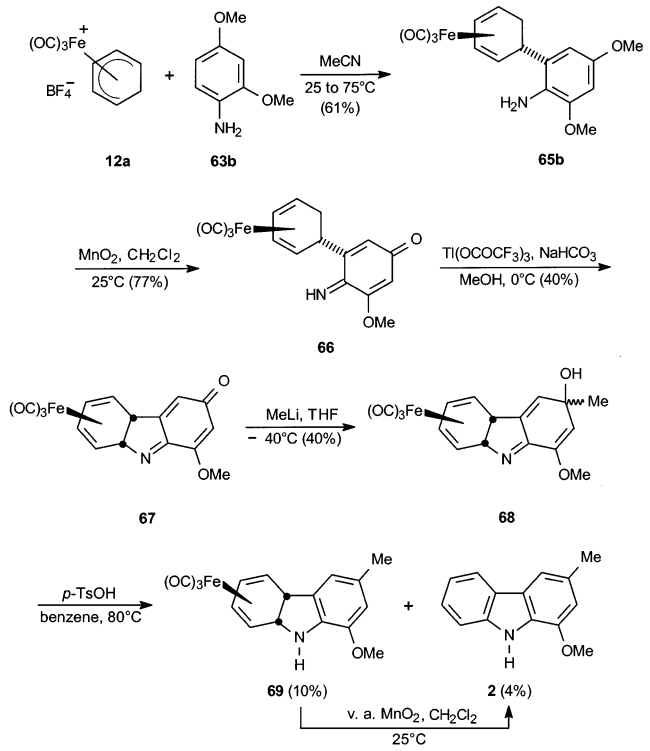
The iron-mediated quinone imine cyclization was applied to the total synthesis of murrayafoline A (**2**)

Scheme 18



64 **63a** **65a** **4** **3**

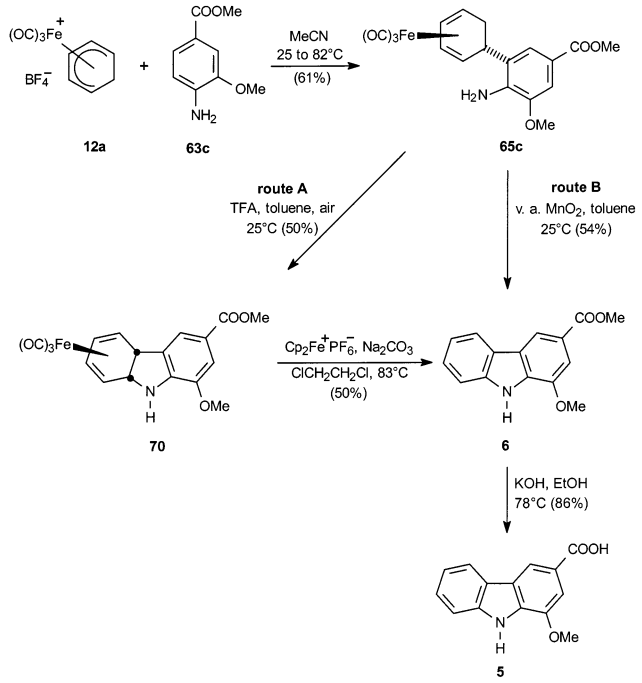
Scheme 19



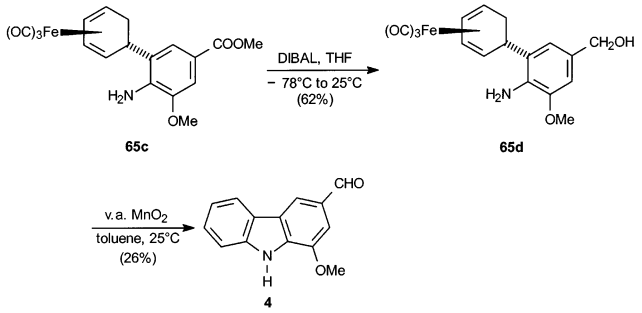
12a **63b** **65b** **66** **67** **68** **69** (10%) **2** (4%)

(Scheme 19). The methyl group of murrayafoline A (**2**) was introduced by nucleophilic addition of methyllithium to the carbonyl group of the resulting tricarbonyliron-complexed 4b,8a-dihydrocarbazol-3-one **67**. The iron complex **65b** required for the synthesis of the quinone imine complex **67** was obtained by electrophilic substitution of 2,4-dimethoxyaniline **63b** with the iron-complexed cation **12a**. A direct iron-mediated quinone imine cyclization of **65b** failed to give the desired cyclized quinone imine complex **67**. Therefore, the two-step procedure with isolation of the intermediate noncyclized quinone imine **66** was applied. The oxidation of complex **65b** using commercial manganese dioxide gave **66** in 77% yield. All attempts to cyclize the complex **66** with very active manganese dioxide led only to decomposition. However, the oxidative cyclization of **66** with thallium(III) trifluoroacetate afforded the desired cyclized quinone imine complex **67**. Addition of methyllithium to the complex **67** provided the desired tertiary carbinol **68** as a 1:1 mixture of diastereoisomers. Treatment of complex **68** with *p*-toluenesulfonic acid (*p*-TsOH) in refluxing benzene afforded directly mur-

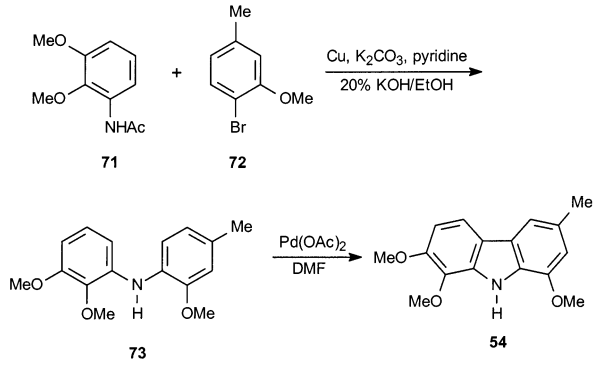
Scheme 20



Scheme 21



Scheme 22



rayafoline A (**2**) by elimination of water with concomitant aromatization and demetalation. However, the yield of murrayafoline A (**2**) was only 4% along with the corresponding tricarbonyl[η^4-4a,9a-dihydro-9*H*-carbazole]iron complex **69** in 10% yield. Complex **69** was smoothly transformed to murrayafoline A (**2**) with very active manganese dioxide (Scheme 19).[86]

The total synthesis of mukonine (**6**) and mukoeic acid (**5**) started from the arylamine **63c**.[87] An optimized procedure for the reaction of the complex salt **12a** with the arylamine **63c** by refluxing in acetonitrile gave the iron complex **65c** in 61% yield. The iron complex **65c** is subjected to smooth cyclodehydrogenation by reacting with air in trifluoroacetic acid to afford the 4a,9a-dihydro-9*H*-carbazole complex **70**. Aromatization of **70** with concomitant demetalation by using ferricenium hexafluorophosphate in the presence of sodium carbonate provided mukonine (**6**) in 50% yield (route A: three steps, 15% overall yield). Alternatively, **65c** was directly transformed to mukonine (**6**) by the iron-mediated arylamine cyclization with very active manganese dioxide in 54% yield (route B: two steps, 33% overall yield). Finally, ester cleavage of mukonine (**6**) afforded mukoeic acid (**5**) in 86% yield (Scheme 20).[86]

An alternative access for the synthesis of murrayanine (**4**) was developed starting from the mukonine precursor **65c**. The reduction of the ester group of **65c** using DIBAL afforded the benzylic alcohol **65d**. In a one-pot reaction using very active manganese dioxide, **65d** was transformed to murrayanine (**4**) (Scheme 21).[86] A similar arylamine cyclization with concomitant oxidation of the C-3 substitutent by using very active manganese dioxide was previously used for the synthesis of murrayanine (**4**) starting from the complex **65a** (cf. Scheme 18). The second synthesis provides murrayanine (**4**) in three steps and 10% overall yield based on the arylamine **63c**.

1.2. Palladium-Mediated Total Synthesis of Murrayastine

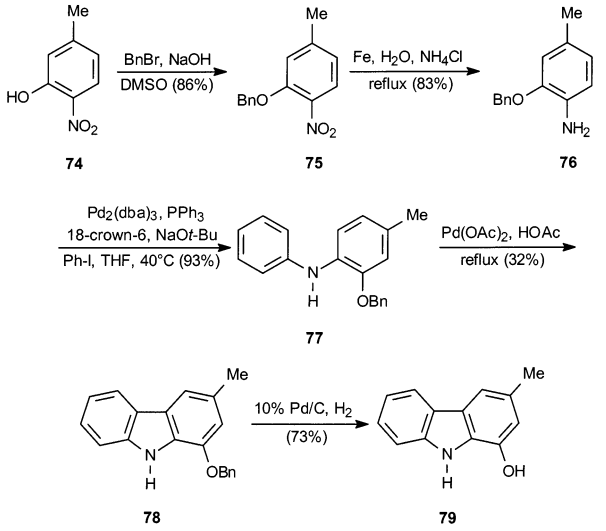
The cyclodehydrogenation of diphenylamines to carbazole derivatives has been accomplished with various activated metal catalysts. However, palladium(II) acetate is by far the best catalyst for this process. Furukawa et al. reported the synthesis of murrayastine (**54**) by cyclodehydrogenation of the diarylamine **73**. Ullmann−Goldberg coupling of *N*-acetyl-2,3-dimethoxyaniline **71** and 2-bromo-5-methylanisole **72** with Cu and K_2CO_3 in pyridine followed by hydrolysis with 20% KOH/EtOH provided the diarylamine **73**. Finally, cyclization of **73** with palladium(II) acetate in DMF afforded murrayastine (**54**) (Scheme 22).[79]

Lin et al. reported a similar reaction sequence for the synthesis of *O*-demethylmurrayafoline A (**79**) starting from 2-hydroxy-4-methylnitrobenzene **74**. After protecting the hydroxy group of **74** as a benzyl ether, the nitroarene **75** was reduced by iron to the corresponding amine **76**. The key intermediate, the diphenylamine **77**, was obtained by amination of **76** under Buchwald conditions.[88,89] Oxidative cyclization of **77** with palladium(II) acetate in acetic acid gave **78** in 32% yield. Finally, catalytic reductive debenzylation of **78** gave *O*-demethylmurrayafoline A (**79**) in 73% yield (Scheme 23).[90] The low yield of the oxidative cyclization was explained by the electron-donating effects of the methyl and the benzyloxy substituents at the benzene ring.

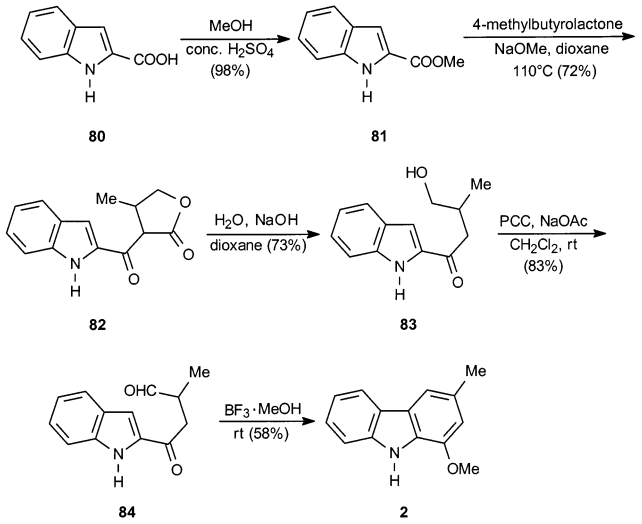
1.3. Total Synthesis of Murrayafoline A by Intramolecular Electrophilic Substitution

Moody et al. developed a new general synthetic route for 1-oxygenated carbazoles starting from indole-2-carboxylic acid **80**. This approach involves ring closure of a 2-substituted indole bearing a four-carbon

Scheme 23



Scheme 24

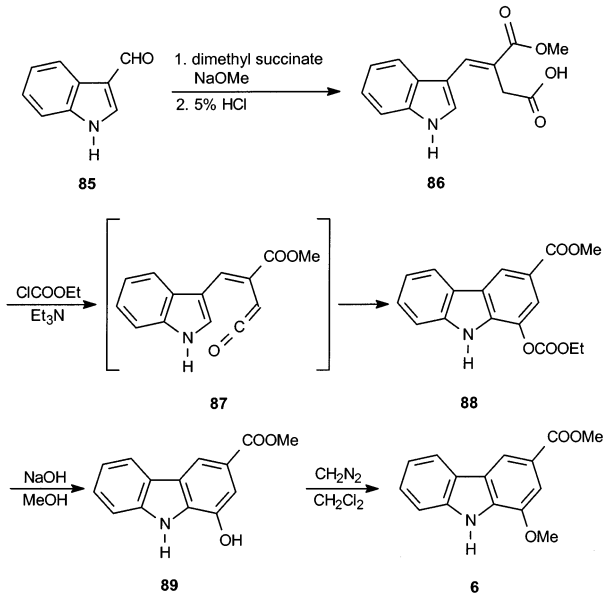


chain, in which the terminal carbon atom is electrophilic to the nucleophilic indole 3-position.[91] Using this methodology murrayafoline A (**2**) was synthesized from indole-2-carboxylic acid **80** over five steps in 25% overall yield. The key step in this synthesis is a Claisen condensation of the indole ester **81** with 4-methylbutyrolactone to give the lactone **82**. Compound **82** undergoes alkaline hydrolysis with concomitant decarboxylation to afford the alcohol **83**. After oxidation of the alcohol with pyridinium chlorochromate (PCC), the aldehyde **84** was subjected to a Lewis acid-assisted cyclization to furnish murrayafoline A (**2**) (Scheme 24).[91,92] The attempts to extend this methodology to the synthesis of the 2-prenyl-substituted carbazole alkaloids, such as clausenapin (**58**) and indizoline (**59**) (see Scheme 16), were unsuccessful due to decomposition of the corresponding aldehydes prior to the Lewis acid-assisted cyclization.

1.4. Total Synthesis of Mukonine by Electrocyclic Reaction

Brenna et al. reported the synthesis of mukonine (**6**) starting from 3-formylindole **85** via a base-promoted cyclization of the monoacid **86**. In this methodology it is assumed that the key cyclization step possibly proceeds through a 1,6-electrocyclic reaction involving a ketene intermediate **87**. The monoacid **86** required for this key-step was obtained through a Stobbe condensation[93] of 3-formylindole **85** and dimethyl succinate. In a one-pot operation, compound **86** was transformed to the aromatic derivative **88** by reacting with ethyl chloroformate in the presence of triethylamine. After deacetylation of the aromatic derivative, the corresponding hydroxy derivative **89** was methylated to give mukonine (**6**) (Scheme 25).[94] This method provides mukonine (**6**) in four steps and 32% overall yield based on 3-formylindole **85** and is formally complementary to Moody's electrophilic substitution of a 2-substituted indole. The synthesis of mukonine depicted in Scheme 25 is currently the best method, because of the easy availability of the reagents and the simplicity of the steps.

Scheme 25

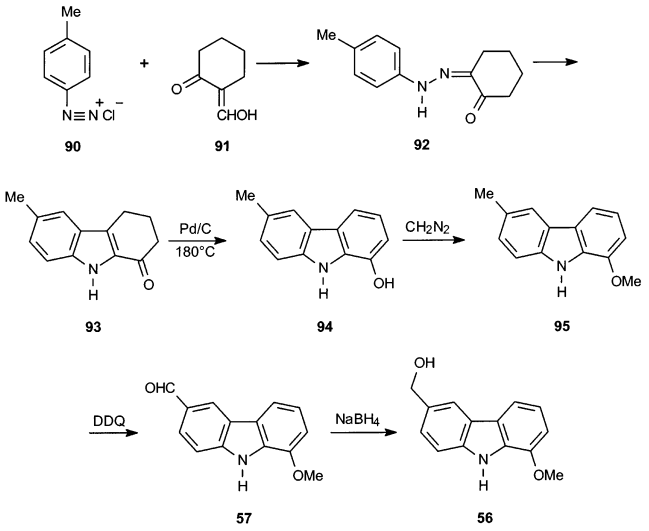


1.5. Fischer Indolization of Phenylhydrazones

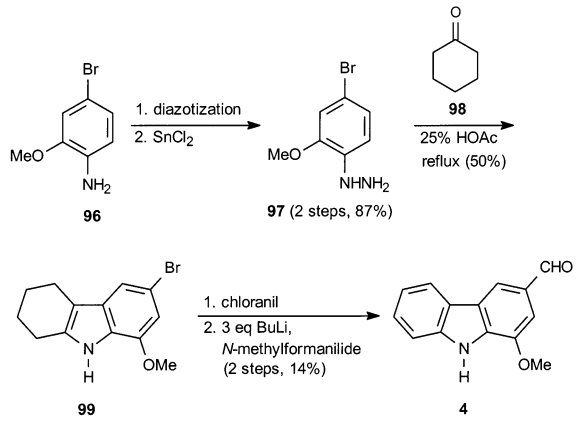
Total Synthesis of Mukolidine and Mukoline. Chakraborty et al. reported the total synthesis of mukolidine (**57**) and mukoline (**56**) using Fischer indolization of the hydrazone **92**. The required hydrazone **92** was obtained by a Japp−Klingemann reaction of toluenediazonium chloride **90** and 2-hydroxymethylenecyclohexanone **91**. The 1-oxotetrahydrocarbazole **93** was obtained by indolization of the hydrazone **92**. Dehydrogenation of **93** with Pd/C followed by methylation of the 1-hydroxycarbazole **94** afforded the corresponding *O*-methyl derivative **95**. Finally, DDQ oxidation of compound **95** furnished mukolidine (**57**). On reduction with sodium borohydride, mukolidine (**57**) was transformed to mukoline (**56**) (Scheme 26).[81]

Total Synthesis of Murrayanine, Murrayafoline A, and Koenoline. Crum and Sprague reported the total synthesis of murrayanine (**4**) starting from 4-bromo-2-methoxyaniline **96**. The methoxyaniline **96**

Scheme 26



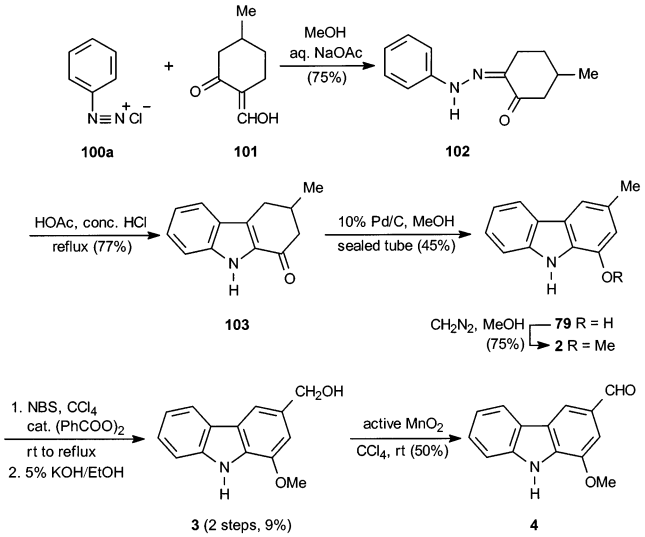
Scheme 27



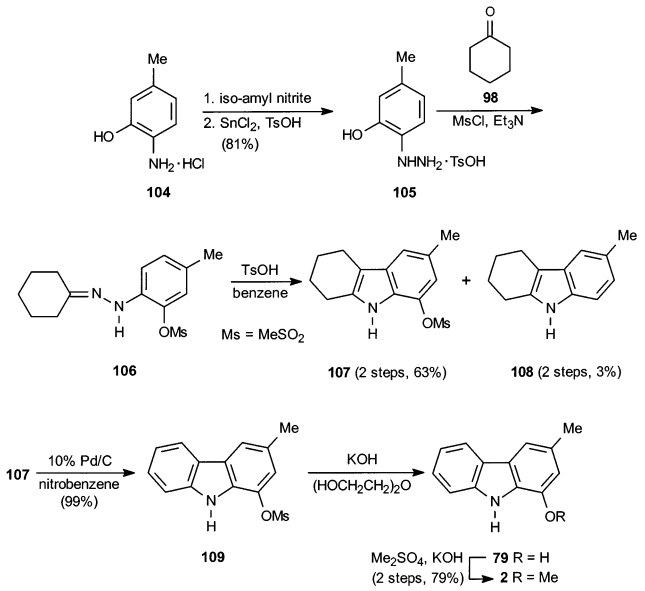
was transformed to 4-bromo-2-methoxyphenylhydrazine **97** over two steps involving diazotization and reduction with tin(II) chloride. The hydrazine **97** and cyclohexanone **98** were refluxed in 25% acetic acid to give 3-bromo-1-methoxy-5,6,7,8-tetrahydrocarbazole **99** in 50% yield. Finally, dehydrogenation of the tetrahydrocarbazole **99** with chloranil and subsequent formylation with *N*-methylformanilide afforded murrayanine (**4**) in two steps and 14% overall yield (Scheme 27).[95]

Chakraborty et al. reported the synthesis of murrayanine (**4**) starting from phenyldiazonium chloride **100a** and 2-hydroxymethylene-5-methylcyclohexanone **101**. The hydrazone **102** was obtained under Japp−Klingemann conditions from **100a** and **101** and transformed to 1-oxo-3-methyl-1,2,3,4-tetrahydrocarbazole **103** by Fischer indolization. The dehydrogenation of compound **103** with Pd/C in an evacuated sealed tube furnished 1-hydroxy-3-methylcarbazole **79**. After *O*-methylation, the corresponding *O*-methyl derivative (murrayafoline A) **2** was transformed to 1-methoxy-3-hydroxymethylcarbazole **3** by reacting with *N*-bromosuccinimide and catalytic amounts of benzoyl peroxide followed by an in situ alkaline hydrolysis of the intermediate bromo derivative. In 1985, Pezzuto et al. isolated 1-methoxy-3-hydroxymethylcarbazole **3**, named koenoline, from the root bark *M. koenigii*.[73] Finally, oxidation of koenoline (**3**)

Scheme 28



Scheme 29

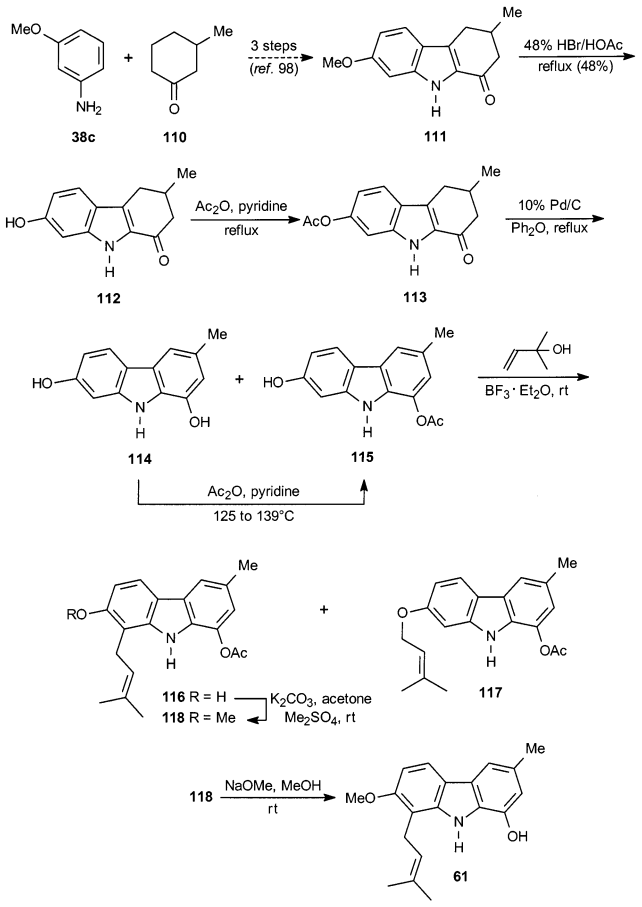


with active manganese dioxide gave murrayanine (**4**) (Scheme 28).[96]

Total Synthesis of Murrayafoline A. Murakami and co-workers reported the total synthesis of murrayafoline A (**2**) by the classical Fischer indolization of the *O*-methanesulfonyl (mesyl) derivative **106**. Compound **106** was prepared from the corresponding aminophenol **104** via the 2-hydrazino-5-methylphenol **105**. Fischer indolization of the *O*-mesylphenylhydrazone derivative **106** afforded the tetrahydrocarbazoles **107** and **108** in 63% and 3% yield, respectively. Dehydrogenation (10% Pd/C in nitrobenzene) of the mesyloxy compound **107** provided 1-mesyloxy-3-methylcarbazole **109**. Hydrolysis of the mesyl group of **109** with potassium hydroxide in diethylene glycol afforded the 1-hydroxycarbazole **79**. Finally, *O*-methylation of **79** gave murrayafoline A (**2**) (Scheme 29).[97] This synthesis provides murrayafoline A (**2**) in six steps and 40% overall yield based on the aminophenol **104**.

Total Synthesis of Murrayafoline B. Ramesh and Kapil reported the total synthesis of murrayafo-

Scheme 30



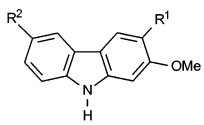
line B (**61**) starting from 7-methoxy-3-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole **111**, which was obtained from 3-methoxyaniline **38c** and 3-methylcyclohexanone **110** by Japp−Klingemann reaction and Fischer indolization.[98] Demethylation of the tetrahydrocarbazole **111** to **112** and subsequent acetylation afforded the 7-acetoxy derivative **113**. Aromatization of **113** with 10% Pd/C in diphenyl ether furnished a mixture of five different carbazoles with the two hydroxycarbazole derivatives **114** and **115** as major products. Acetylation converted compound **114** to **115**. Installation of the prenyl group at C-8 by condensation of the 1-acetoxycarbazole **115** with 2-methylbut-3-en-2-ol in the presence of Lewis acid provided a mixture of the carbazole derivatives **116** and **117**. *O*-Methylation of compound **116** with dimethyl sulfate gave 1-acetoxy-7-methoxy-3-methyl-8-(3,3-dimethylallyl)carbazole **118**. Finally, hydrolysis of **118** with sodium methoxide in methanol at room temperature afforded murrayafoline B (**61**) (Scheme 30).[99]

Additional total syntheses of 1-oxygenated tricyclic carbazole alkaloids are described in section XI.6.

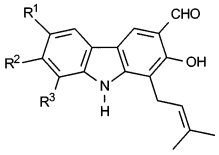
2. 2-Oxygenated Tricyclic Carbazole Alkaloids

Among the large number of carbazole alkaloids that have been isolated from *M. koenigii* by Chakraborty and co-workers are also the 2-oxygenated derivatives, like 2-hydroxy-3-methylcarbazole (**7**),[26] the corresponding aldehyde mukonal (**8**),[27] and the

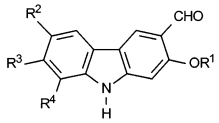
Scheme 31



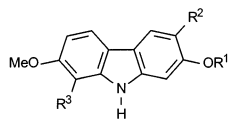
119 2-Methoxy-3-methylcarbazole
R^1 = Me; R^2 = H
120 Glycozolidine
R^1 = Me; R^2 = OMe
121 Glycozolidol
R^1 = Me; R^2 = OH
122 Glycozolidal
R^1 = CHO; R^2 = OMe



123 Heptazoline
R^1, R^2 = H; R^3 = OH
124 6-Methoxyheptaphylline
R^1 = OMe; R^2, R^3 = H
125 7-Methoxyheptaphylline
R^1, R^3 = H; R^2 = OMe



126 *O*-Methylmukonal (Glycosinine)
R^1 = Me; R^2, R^3, R^4 = H
127 7-Methoxy-*O*-methylmukonal
R^1 = Me; R^2, R^4 = H; R^3, = OMe
128 7-Methoxymukonal
R^1, R^2, R^4 = H; R^3 = OMe
129 Clausanitin
R^1, R^2, R^4 = H; R^3 = prenyl
130 Atanisatin
R^1 = Me; R^2, R^3 = H; R^4 = prenyl
131 Lansine
R^1, R^3, R^4 = H; R^2 = OMe

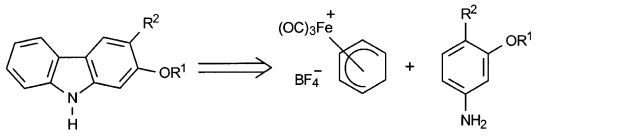


132 Isomurrayafoline B
R^1, R^2 = Me; R^3 = prenyl
133 Murrayaline A
R^1, R^2 = Me; R^3 = CHO
134 Murrayaline B
R^1 = H; R^2 = Me; R^3 = CHO
135 Murrayaline C
R^1 = H; R^2, R^3 = CHO
136 Murrayaline D
R^1 = H; R^2 = CHO; R^3 = geranyl

methyl ester mukonidine (**9**) (Scheme 1).[32] These alkaloids were isolated from different parts of *M. koenigii*. In 1993, Wu et al. isolated mukonidine (**9**) from the root bark of *Clausena excavata*.[100] However, the spectral data of mukonidine isolated by the groups of Chakraborty[27,32] and Wu[100] were not identical. In 1985, Bhattacharyya and Chowdhury isolated 2-methoxy-3-methylcarbazole (**119**) from the seeds of *M. koenigii*.[25] In 1966, Chakraborty et al. reported the isolation of glycozolidine (**120**) from the root bark of *Glycosmis pentaphylla*.[101,102] Two decades later, Chowdhury et al. reported the isolation of glycozolidol (**121**)[103] and glycozolidal (**122**)[104] from the roots of *G. pentaphylla* (Scheme 31).

Various heptaphylline derivatives that differ in the C-ring substitution pattern of the carbazole nucleus were isolated from different *Clausena* species, including heptaphylline (**10**) (see Scheme 2),[29] heptazoline (**123**),[105] 6-methoxyheptaphylline (**124**) (which is in fact 1-prenyllansine),[24] and 7-methoxyheptaphylline (**125**).[106] *O*-Methylmukonal (**126**) and 7-methoxy-*O*-methylmukonal (**127**) were isolated in 1990 by Lange and co-workers from *Murraya siamensis*.[107a] Two years later, Bhattacharyya et al. obtained *O*-methylmukonal **126** from the dried roots of *G. pentaphylla* and called it glycosinine.[107b] 7-Methoxymukonal (**128**) was isolated along with 7-methoxyheptaphylline (**125**), which has an additional prenyl group at C-1.[106] Clausanitin (**129**) and atanisatin (**130**) were isolated from *C. anisata*.[108] Lansine (**131**), which is a 6-methoxy derivative of mukonal, was isolated from the leaves of *C. lansium*.[109] Furukawa et al. isolated isomurrayafoline B (**132**)[110] and murrayaline A−D (**133**−**136**)[111,112] from *M. euchrestifolia* (Scheme 31).

Scheme 32

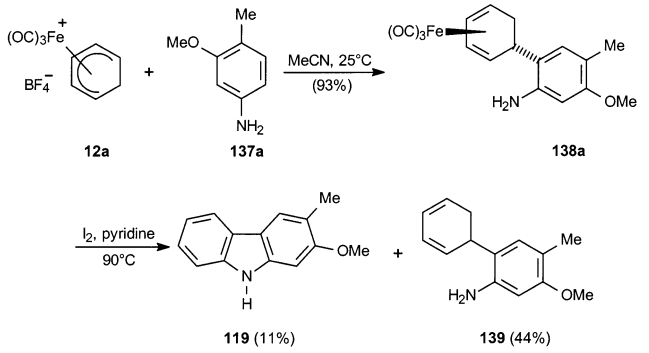


119 2-Methoxy-3-methylcarbazole
R^1, R^2 = Me
9 Mukonidine
R^1 = H; R^2 = COOMe

12a

137a R^1, R^2 = Me
137b R^1 = H; R^2 = COOMe

Scheme 33



12a **137a** **138a**

119 (11%) **139** (44%)

The isolation of additional 2-oxygenated tricyclic carbazole alkaloids is described in section XI.5.2.

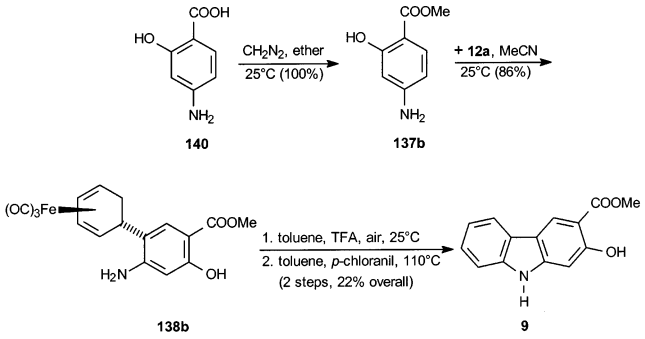
2.1. Iron-Mediated Total Synthesis of 2-Methoxy-3-methylcarbazole and Mukonidine

The retrosynthetic analysis of the 2-oxygenated carbazole alkaloids, e.g. 2-methoxy-3-methylcarbazole (**119**) and mukonidine (**9**), based on an iron-mediated approach led to the iron-complexed cation **12a** and the arylamines **137** as precursors (Scheme 32).

The electrophilic aromatic substitution of **137a** with the iron-complexed cation **12a** provided the iron complex **138a** in almost quantitative yield. The reaction of complex **138a** with very active manganese dioxide resulted in slow decomposition of the starting material. However, reaction of complex **138a** with iodine in pyridine gave 2-methoxy-3-methylcarbazole (**119**) in 11% yield, along with the cyclohexa-1,3-diene **139** in 44% yield (Scheme 33).[39]

For the total synthesis of mukonidine (**9**), the required amine **137b** was obtained quantitatively from commercial 4-aminosalicylic acid **140** using diazomethane. The reaction of the arylamine **137b** with the iron-complexed cation **12a** under the usual conditions led to the iron complex **138b**. The high yield of the C−C bond formation was ascribed to the high nucleophilicity of the *o*-amino position of the aromatic nucleus resulting from the hydroxy group in the 3-position of the arylamine. The oxidation of complex **138b** with very active manganese dioxide did not afford mukonidine (**9**). However, cyclization of complex **138b** in toluene/TFA in the presence of air at room temperature provided the corresponding dihydrocarbazole complex, which was transformed to mukonidine (**9**) by aromatization and demetalation on refluxing in toluene with *p*-chloranil (Scheme 34).[39,87] The spectral data of the synthetic mukonidine

Scheme 34



140 **137b**

138b **9**

(**9**)[87] were in good agreement with those reported by the group of Wu for the natural product.[100]

2.2. Molybdenum-Mediated Total Synthesis of 2-Oxygenated Carbazoles

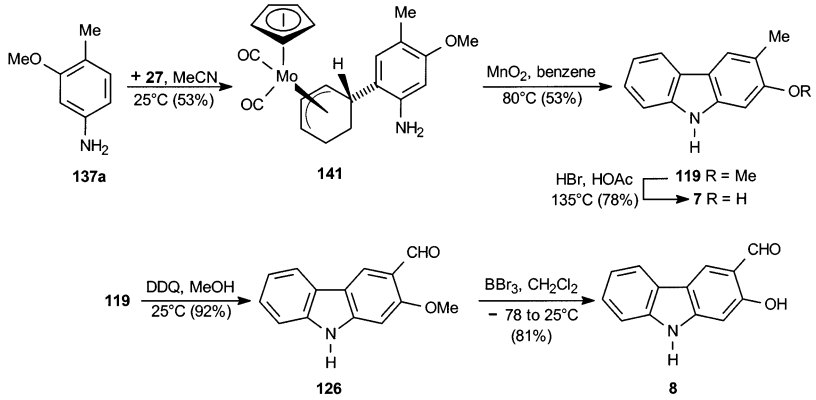
The access to 2-oxygenated carbazole alkaloids using the iron-mediated synthesis is only limited in its application.[39] To overcome the problem, a molybdenum-mediated approach was developed as a complementary method. This alternative synthesis of carbazole derivatives involves the oxidative cyclization of an arylamine at a dicarbonyl[η^5-cyclopentadienyl]-molybdenum-coordinated η^3-cyclohexenyl ligand.

The reaction of dicarbonyl(η^4-cyclohexa-1,3-diene)-(η^5-cyclopentadienyl)molybdenum hexafluorophosphate **27** with the arylamine **137a** provides regio- and stereoselectively the molybdenum complex **141** in 53% yield. Oxidative cyclization of complex **141** with concomitant aromatization using activated manganese dioxide afforded 2-methoxy-3-methylcarbazole (**119**) in 53% yield (Scheme 35).[113] In contrast, cyclization of the corresponding tricarbonyliron complex **138a** to **119** was achieved in a maximum yield of 11% on a small scale using iodine in pyridine as the oxidizing agent (see Scheme 33).[39] 2-Methoxy-3-methylcarbazole (**119**) led to some further 2-oxygenated carbazole alkaloids such as 2-hydroxy-3-methylcarbazole **7**, *O*-methylmukonal (**126**), and mukonal (**8**) by simple transformations. The oxidation of **119** with DDQ afforded *O*-methylmukonal (**126**), which on demethylation with boron tribromide provided mukonal (**8**). Cleavage of the ether in **119** with HBr/HOAc gave 2-hydroxy-3-methylcarbazole (**7**) (Scheme 35).[113]

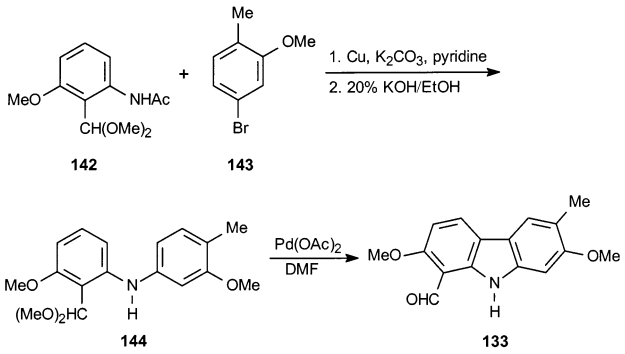
2.3. Palladium-Mediated Total Synthesis of Murrayaline A

Furukawa et al. reported the total synthesis of murrayaline A (**133**) starting from the acetanilide derivative **142** and 5-bromo-2-methylanisole (**143**). Ullmann−Goldberg coupling of **142** and **143** followed by alkaline hydrolysis provided the diarylamine **144**. The palladium-mediated cyclodehydrogenation of the diarylamine **144** afforded murrayaline A (**133**) (Scheme 36).[79] The yields of the individual steps were not given; however, this is the only synthesis of murrayaline A (**133**) reported so far. Using a similar approach, Chakraborty and co-workers reported the synthesis of glycozolidine (**120**) in poor yield by a thermal cyclodehydrogenation of a functionalized *N*,*N*-diarylamine in the presence of iodine at 350 °C.[78]

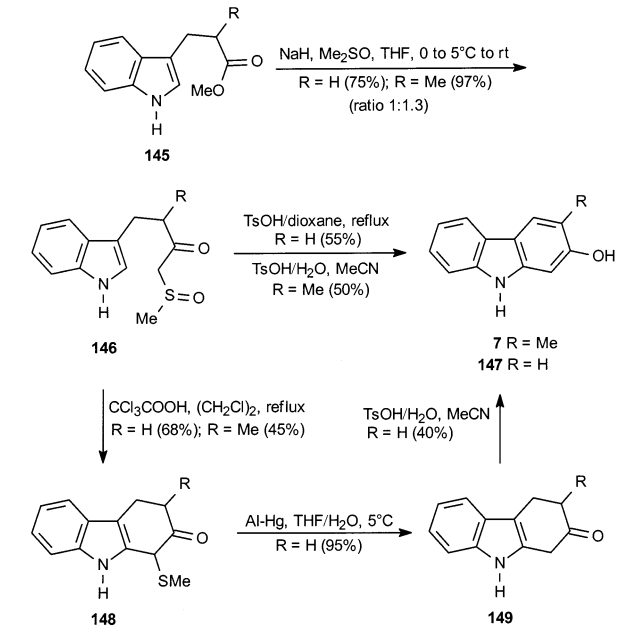
Scheme 35



Scheme 36



Scheme 37

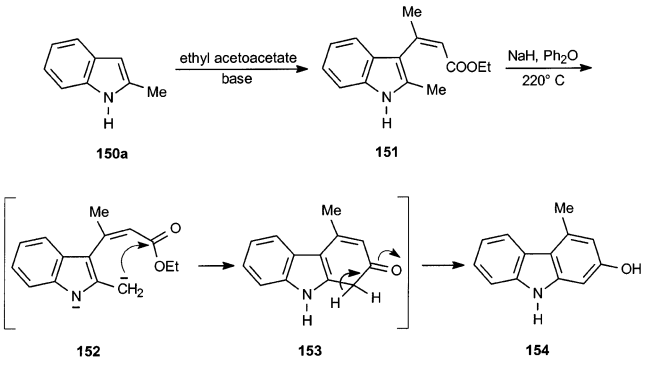


2.4. Acid-Catalyzed Cyclization of β-Keto Sulfoxides

Oikawa and Yonemitsu reported the synthesis of 2-hydroxy-3-methylcarbazole (**7**) by acid-catalyzed cyclization of the β-keto sulfoxide **146**. The key step in this synthesis is an intramolecular nucleophilic attack at the indole ring by the carbocation derived from the β-keto sulfoxide **146** in the presence of acid.

Compound **146** was synthesized from methyl 3-indolepropionate **145** and dimethyl sulfoxide under Corey's conditions.[114] Reaction of **146** with 0.5 equiv of trichloroacetic acid in boiling dichloroethane gave 1-methylthio-2-oxo-1,2,3,4-tetrahydrocarbazole **148**. By reductive desulfurization, **148** was converted to 2-oxo-1,2,3,4-tetrahydrocarbazole **149**. Finally, on treatment with toluenesulfonic acid in boiling acetonitrile, **149** gave 2-hydroxycarbazole **147**. However, this sequence failed to give the 2-hydroxy-3-methylcarbazole (**7**). Alternatively, the β-keto sulfoxide **146** was transformed directly to 2-hydroxy-3-methylcarbazole (**7**) and 2-hydroxycarbazole **147** by treatment with toluenesulfonic acid in dioxane under reflux in 50% and 55% yield, respectively (Scheme 37).[115]

Scheme 38



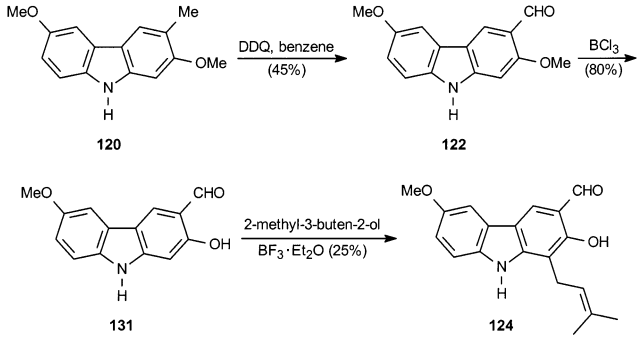
2.5. Base-Induced Thermal Cyclization of a 2-Methyl-3-vinylindole

Bergman and co-workers reported the synthesis of 2-hydroxy-4-methylcarbazole **154** from 2-methylindole **150a** using a base-induced thermal cyclization of the ester **151** as the key step. Condensation of 2-methylindole **150a** and ethyl acetoacetate provided compound **151**. The cyclization of **151** with NaH at 220°C afforded directly 2-hydroxy-4-methylcarbazole **154**, probably involving the intermediates **152** and **153** (Scheme 38).[116]

2.6. Total Synthesis of Lansine, 6-Methoxyheptaphylline, Heptazoline, and Heptaphylline

Sharma and Kapil reported the total synthesis of lansine (**131**) and 6-methoxyheptaphylline (1-prenyllansine) (**124**) starting from 2,6-dimethoxy-3-methylcarbazole (glycozolidine) (**120**). The synthesis of lansine (**131**) involves an oxidation followed by a regioselective demethylation. Thus, oxidation of glycozolidine (**120**) with DDQ provides 2,6-dimethoxycarbazole-3-carbaldehyde (glycozolidal) (**122**), which on selective demethylation with boron trichloride

Scheme 39



afforded lansine (**131**) in 80% yield. For the synthesis of 6-methoxyheptaphylline (**124**), lansine (**131**) was subjected to a Lewis acid-promoted condensation with 2-methyl-3-buten-2-ol (Scheme 39).[117]

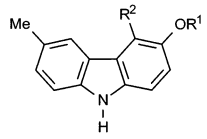
The same authors applied a similar reaction sequence to the total synthesis of heptazoline (8-hydroxyheptaphylline) (**123**) (Scheme 31).[118] In this synthesis the required 2,8-dimethoxy-3-methylcarbazole was obtained by reductive cyclization of 3′,4-dimethoxy-3-methyl-6-nitrobiphenyl with triethyl phosphite.[119] Joshi and co-workers synthesized heptaphylline (**10**) in low yield from 2-hydroxycarbazole (**147**) by formylation and subsequent prenylation.[29b]

3. 3-Oxygenated Tricyclic Carbazole Alkaloids

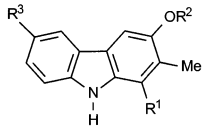
Since 1966, several carbazole alkaloids oxygenated in the 3-position were isolated from different natural sources. Glycozoline (**155**) was the first 3-oxygenated carbazole alkaloid isolated by Chakraborty from the root bark of *G. pentaphylla* (Scheme 40).[120] In 1983, Mukherjee et al. isolated from the same plant source the *O*-demethyl derivative of glycozoline and named it glycozolinine.[121] In the following year, Chowdhury et al. isolated the same alkaloid from the same source and renamed it glycozolinol (**156**).[122] In 1989, Reisch and co-workers reported the isolation of glycomaurrol (**157**), a 4-prenylglycozolinol, from the stem bark of *Glycosmis mauritiana*.[123]

Hyellazole (**158**) and chlorohyellazole (**159**) are two unusual nonbasic marine carbazole alkaloids isolated by Moore et al. from the blue-green algae *H. caespitosa*.[124] These alkaloids possess structures that are entirely different from the carbazole alkaloids isolated from terrestrial plants. Kato et al. isolated carazostatin **160** from *Streptomyces chromofuscus*. This natural product was assigned as 1-heptyl-3-hydroxy-2-methyl-9*H*-carbazole and represents a novel radical scavenger that is more active than butylated hydroxytoluene (BHT).[125] Carazostatin exhibits a strong inhibitory activity against free-radical-induced lipid peroxidation, and in liposomal membranes, it shows a stronger antioxidant activity than α-tocopherol.[126] Seto et al. isolated the antiostatins A_1 (**161**) to A_4 (**164**) and B_2 (**165**) to B_5 (**168**) from *Streptomyces cyaneus* 2007-SV_1.[127] These alkaloids showed a strong inhibitory activity against lipid peroxidation induced by free radicals.[128] In 1997, Seto et al. reported the isolation of the novel neuronal cell protecting substances carbazomadurin A (**169**) and B (**170**) from *Actinomadura madurae* 2808-SV1.[129] The isolation

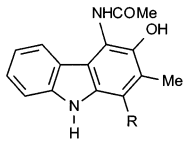
Scheme 40



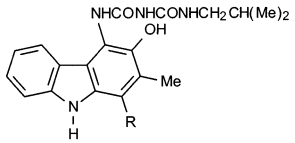
155 Glycozoline
R^1 = Me; R^2 = H
156 Glycozolinol (Glycozolinine)
R^2, R^3 = H
157 Glycomaurrol
R^1 = H; R^2 = prenyl



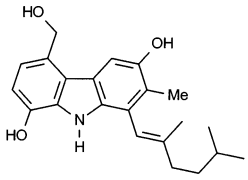
158 Hyellazole
R^1 = Ph; R^2 = Me; R^3 = H
159 Chlorohyellazole
R^1 = Ph; R^2 = Me; R^3 = Cl
160 Carazostatin
R^1 = $(CH_2)_6Me$; R^2, R^3 = H



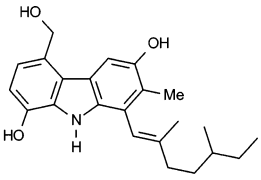
161 Antiostatin A_1
R = $(CH_2)_4Me$
162 Antiostatin A_2
R = $(CH_2)_2CH(Me)CH_2Me$
163 Antiostatin A_3
R = $(CH_2)_4CH(Me)_2$
164 Antiostatin A_4
R = $(CH_2)_6Me$



165 Antiostatin B_2
R = $(CH_2)_5Me$
166 Antiostatin B_3
R = $(CH_2)_4CH(Me)_2$
167 Antiostatin B_4
R = $(CH_2)_6Me$
168 Antiostatin B_5
R = $(CH_2)_5CH(Me)_2$

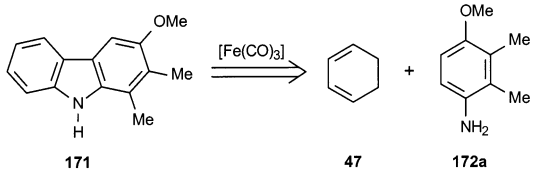


169 Carbazomadurin A



170 Carbazomadurin B

Scheme 41



of additional 3-oxygenated tricyclic carbazole alkaloids is described in section XI.5.3.

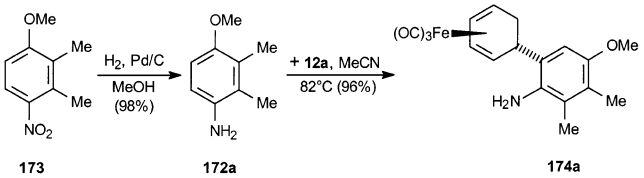
3.1. Iron-Mediated Synthesis of 4-Deoxycarbazomycin B

The precursors for an iron-mediated synthesis of 4-deoxycarbazomycin B (**171**), a degradation product of the natural product carbazomycin B, are cyclohexa-1,3-diene **47** and the corresponding arylamine **172a** (Scheme 41).

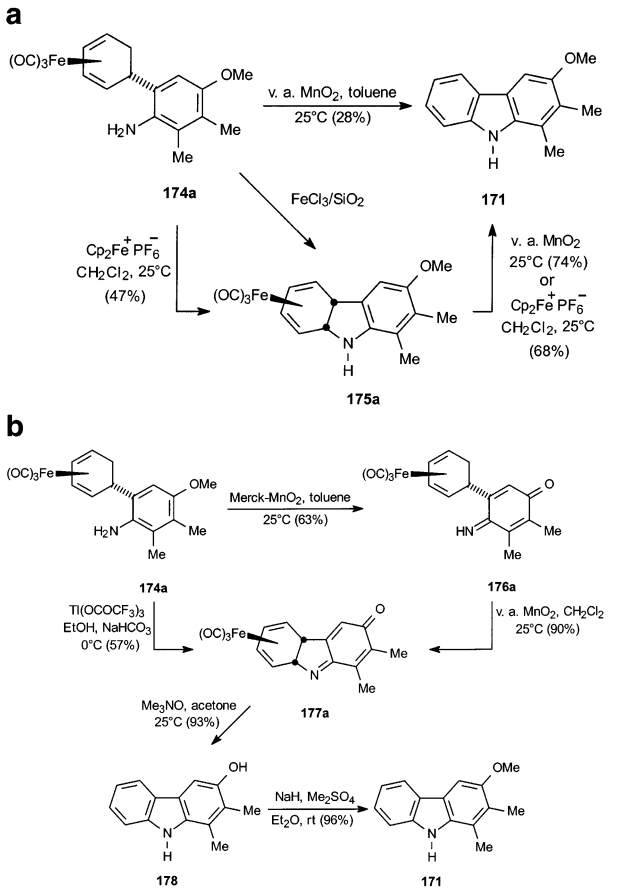
The arylamine **172a** was obtained on a large scale by hydrogenation of the commercial nitroaryl derivative **173**. Electrophilic aromatic substitution of the arylamine **172a** using the iron-complexed cation **12a** provided regio- and stereoselectively the iron complex **174a** in almost quantitative yield (Scheme 42).

The direct one-pot transformation of complex **174a** to 4-deoxycarbazomycin B (**171**) was achieved in 28% yield by an iron-mediated oxidative cyclization with very active manganese dioxide. This reaction involves

Scheme 42



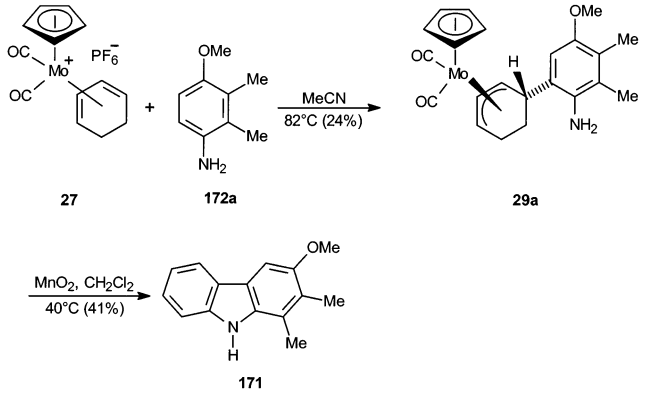
Scheme 43



a sequence of cyclization, aromatization, and demetalation. The same conversion was also achieved stepwise by application of more selective oxidizing reagents (Scheme 43, part a). The cyclizing dehydrogenation to the 4a,9a-dihydro-9*H*-carbazole **175a** is probably initiated by a single-electron transfer (SET) oxidation of the 18-electron complex **174a** to an intermediate 17-electron radical cation (cf. Scheme 4).[13] The iron-mediated arylamine cyclization provides 4-deoxycarbazomycin B (**171**) in three steps and 33% overall yield based on the iron complex salt **12a**.[130,131]

For the synthesis of 4-deoxycarbazomycin B (**171**) via the iron-mediated quinone imine cyclization, the oxidation of complex **174a** to the 4b,8a-dihydrocarbazol-3-one **177a** could be achieved by two different methods: (1) by a two-step procedure with isolation of the intermediate noncyclized quinone imine **176a** by sequential application of two differently activated manganese dioxides and (2) by a direct one-pot transformation of the iron complex **174a** to **177a**. These conversions represent the first examples of chemoselective oxidation of an aromatic ring in the presence of a tricarbonyliron−diene unit. The two-

Scheme 44



step transformation of complex **174a** to the tricarbonyliron-complexed 4b,8a-dihydrocarbazol-3-one **177a** was achieved by treatment of **174a** with commercial manganese dioxide leading to the noncyclized quinone imine **176a**. Cyclization of **176a** with very active manganese dioxide afforded **177a**. The direct one-pot quinone imine cyclization was achieved by oxidation of **174a** with thallium trifluoroacetate in buffered ethanol.[36] Demetalation of the tricarbonyliron-complexed 4b,8a-dihydrocarbazol-3-one **177a** using trimethylamine *N*-oxide afforded directly the 3-hydroxycarbazole **178**. Finally, *O*-methylation of the 3-hydroxycarbazole **178** gave 4-deoxycarbazomycin B (**171**) in 96% yield (Scheme 43, part b).[130,131] The route via the iron-mediated quinone imine cyclization provides 4-deoxycarbazomycin B (**171**) in four steps and 49% overall yield based on the iron complex salt **12a**. A comparison with the results of the iron-mediated arylamine cyclization (Scheme 43, part a) shows the superiority of the quinone imine cyclization for the total synthesis of the carbazomycin alkaloids.

3.2. Molybdenum-Mediated Synthesis of 4-Deoxycarbazomycin B

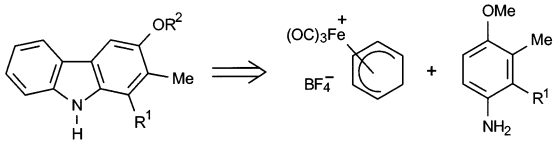
The molybdenum-mediated synthesis of 4-deoxycarbazomycin B (**171**) involves the annulation of the arylamine **172a** at the dicarbonyl[η^5-cyclopentadienyl]molybdenum-complexed η^3-cyclohexenyl ligand. Electrophilic substitution of the arylamine **172a** with dicarbonyl(η^4-cyclohexadiene)(η^5-cyclopentadienyl)-molybdenum hexafluorophosphate **27** provided regio- and stereoselectively the molybdenum complex **29a** in 24% yield. Oxidative cyclization of complex **29a** with concomitant aromatization using activated manganese dioxide afforded 4-deoxycarbazomycin B (**171**) in 41% yield (Scheme 44).[113]

3.3. Iron-Mediated Total Synthesis of Carazostatin and Hyellazole

The total syntheses of carazostatin (**160**) and hyellazole (**158**) based on the iron-mediated annulation require the iron complex salt **12a** and the arylamines **172b** and **172c** as precursors (Scheme 45).

For the synthesis of carazostatin (**160**), the required arylamine **172b** was synthesized starting from 1-methoxycyclohexa-1,3-diene **179** and methyl 2-decynoate **180**. The key step in this route is the Diels−

Scheme 45

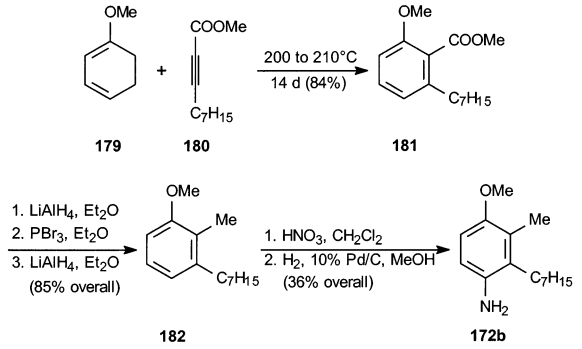


160 Carazostatin
$R^1 = (CH_2)_6Me$; $R^2 = H$
158 Hyellazole
$R^1 = Ph$; $R^2 = Me$

12a

172b $R^1 = (CH_2)_6Me$
172c $R^1 = Ph$

Scheme 46



179 **180** **181**

182 **172b**

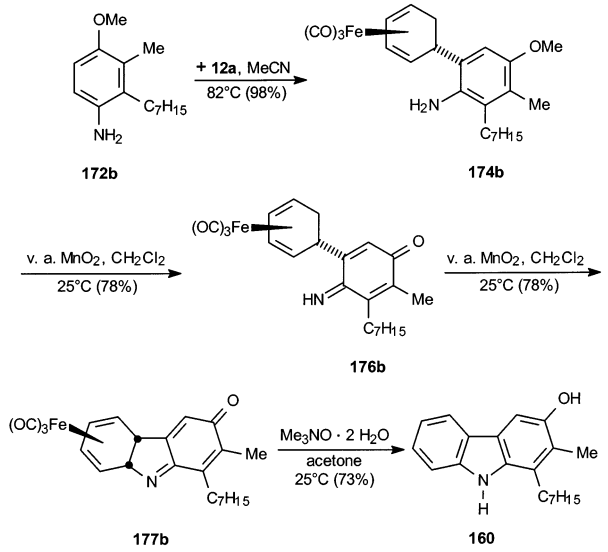
Alder cycloaddition of **179** with **180** to give methyl 2-heptyl-6-methoxybenzoate **181**.[132] Compound **181** was converted to the 3-heptyl-2-methylanisole **182** in 85% overall yield. Finally, the anisole **182** was transformed to the arylamine **172b** by nitration and subsequent catalytic hydrogenation (Scheme 46). This simple sequence provides the arylamine **172b** in six steps with 26% overall yield.

The electrophilic aromatic substitution of **172b** with the iron-coordinated cation **12a** afforded the iron complex **174b** in 98% yield. The iron-mediated quinone imine cyclization of complex **174b** by sequential application of two differently activated manganese dioxides provided the iron-coordinated 4b,8a-dihydrocarbazol-3-one **177b**. Demetalation of the iron complex **177b** with concomitant tautomerization using trimethylamine *N*-oxide afforded carazostatin (**160**) (Scheme 47).[133] The iron-mediated total synthesis provides carazostatin (**160**) in four steps and 43% overall yield based on the iron complex salt **12a**.

The arylamine **172c**, required for the total synthesis of the marine alkaloid hyellazole (**158**), was synthesized by a Diels−Alder reaction of 1-methoxycyclohexa-1,3-diene **179** and ethyl phenylpropynoate **183**. The biphenyl derivative **185** thus obtained was transformed to the arylamine **172c** by the same sequence of steps as shown in Scheme 46. The arylamine **172c** was obtained in six steps and 7% overall yield based on 1-methoxycyclohexa-1,3-diene **179** (Scheme 48).[134,135]

The drawback of the sequence described above is the low yield (30%) of the desired regioisomer **185** in the Diels−Alder reaction. Therefore, the overall yield of the intermediate biphenyl derivative **186** by the route shown in Scheme 48 is limited to 20%. However, Azzena et al. reported a new synthesis of the biphenyl derivative **186** starting from 1,2-dimethoxy-3-methoxymethoxybenzene **187**. The key step in this approach is a Suzuki cross-coupling of the triflate **190**

Scheme 47

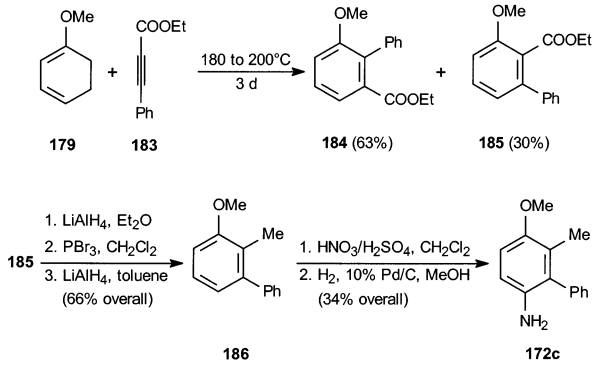


172b **174b**

176b

177b **160**

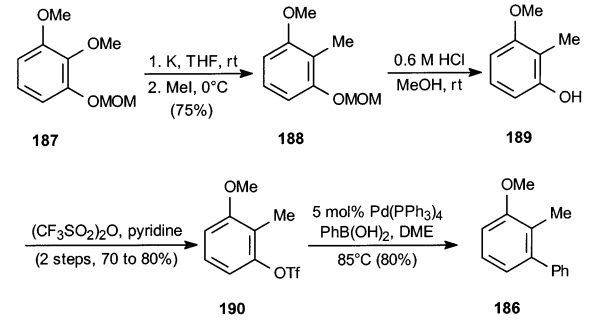
Scheme 48



179 **183** **184** (63%) **185** (30%)

186 **172c**

Scheme 49



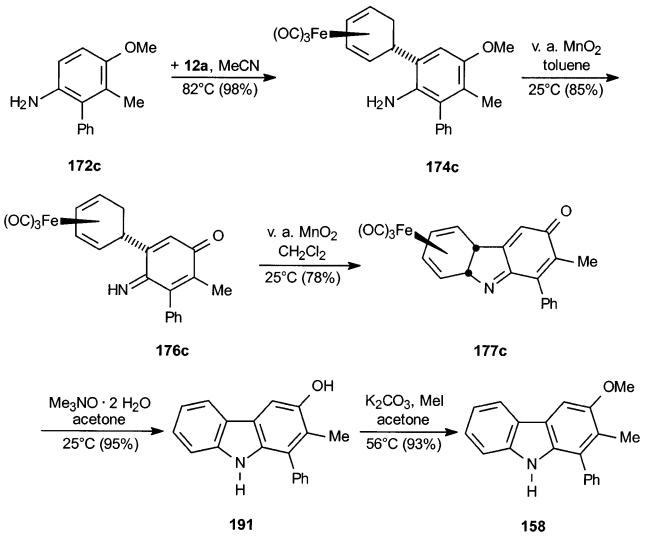
187 **188** **189**

190 **186**

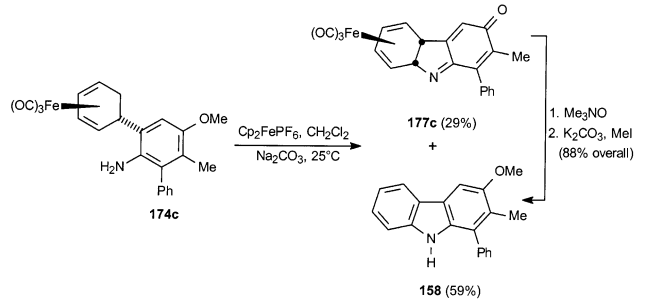
with phenylboronic acid using 5 mol % of $Pd(PPh_3)_4$ (Scheme 49).[136] This alternative method provided the biphenyl derivative **186** in four steps and 48% overall yield based on compound **187**.

Electrophilic substitution at the arylamine **172c** using the complex salt **12a** provided the iron complex **174c** quantitatively. Sequential highly chemoselective oxidation of the iron complex **174c** with two differently activated manganese dioxides provided the tricarbonyliron-complexed 4b,8a-dihydrocarbazol-3-one **177c** via the intermediate noncyclized quinone imine **176c**. Demetalation of the tricarbonyliron-complexed 4b,8a-dihydrocarbazol-3-one **177c**, followed by selective *O*-methylation, provided hyellazole (**158**), which was obtained in five steps and 57% overall yield based on **12a** (Scheme 50).[134,135]

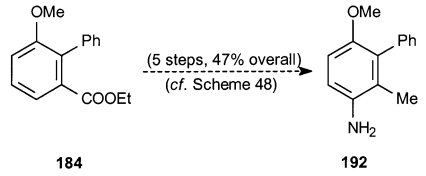
Scheme 50



Scheme 51



Scheme 52

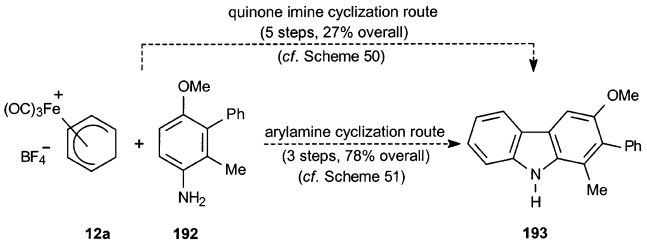


An alternative method for the oxidative cyclization of the arylamine-substituted tricarbonyl(η^4-cyclohexa-1,3-diene)iron complex **174c** is the iron-mediated arylamine cyclization. Using ferricenium hexafluorophosphate in the presence of sodium carbonate this one-pot reaction provides directly hyellazole (**158**) along with complex **177c**, which was additionally converted to the natural product (Scheme 51).[134,135] Thus, hyellazole (**158**) was synthesized in three steps and 83% overall yield based on the iron complex salt **12a**.

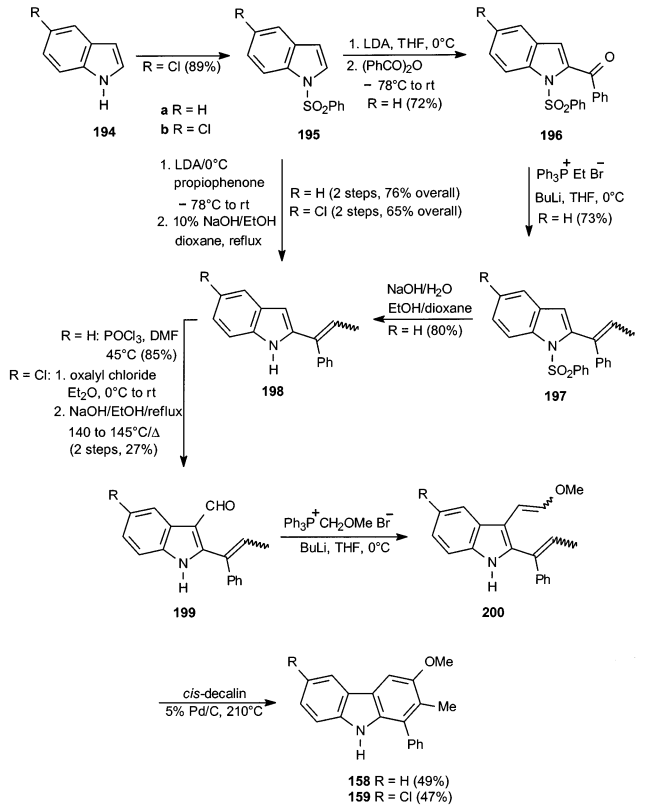
The arylamine **192** was used as a precursor for the synthesis of isohyellazole (3-methoxy-1-methyl-2-phenyl-9*H*-carbazole) **193**, a nonnatural regioisomer of hyellazole (**158**). Ethyl 3-methoxy-2-phenylbenzoate **184**, the major isomer of the Diels−Alder cycloaddition shown in Scheme 48, was transformed to the arylamine **192** in five steps and with 47% overall yield using the same sequence as described for the synthesis of **172c** (Scheme 52).[135]

The iron-mediated quinone imine cyclization afforded isohyellazole (**193**) via the corresponding 3-hydroxycarbazole in five steps and 27% overall yield based on **12a** (cf. the total synthesis of hyellazole,

Scheme 53



Scheme 54

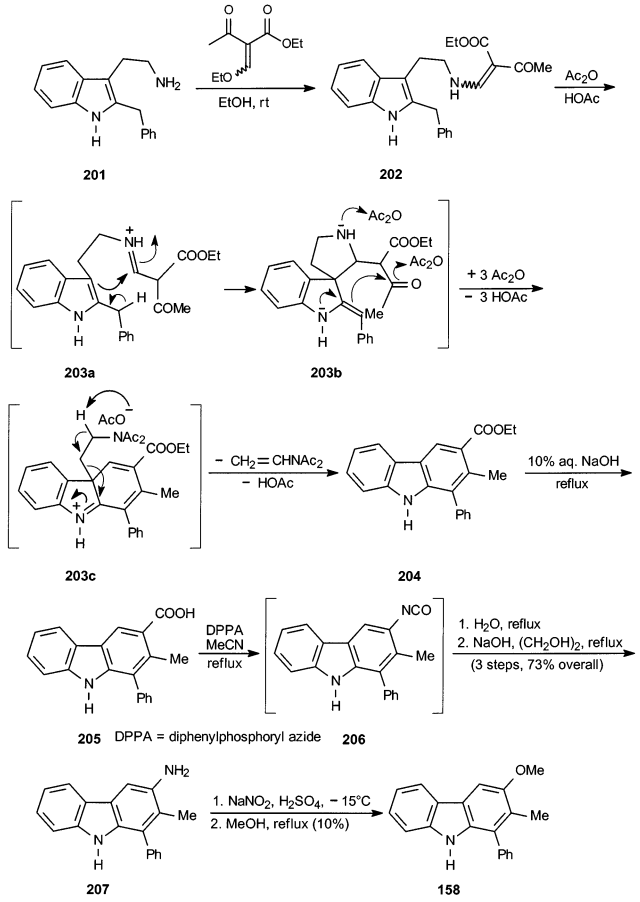


Scheme 50). Alternatively, isohyellazole (**193**) was synthesized by the iron-mediated arylamine cyclization (cf. the total synthesis of hyellazole, Scheme 51). This route provides isohyellazole (**193**) in three steps and 78% overall yield based on **12a** (Scheme 53).[135] Obviously, the route via the iron-mediated arylamine cyclization is more suitable for the syntheses of hyellazole (**158**) and isohyellazole (**193**) than the quinone imine cyclization route.

3.4. Total Synthesis of Hyellazole and 6-Chlorohyellazole by Electrocyclization of 2,3-Divinylindoles

Kano et al. reported the first total synthesis of hyellazole (**158**) and 6-chlorohyellazole (**159**) via thermal electrocyclization of the substituted 2,3-divinyl indoles **200** (Scheme 54). The 2,3-divinylindoles **200** were obtained starting from *N*-phenylsulfonylindole **195a** and 5-chloroindole **194b**, respectively. The initial condensation of **195a** and **195b** with propiophenone provided the 2-vinylindoles **198**. A sequence of Vilsmeier and Wittig reactions of **198a** via the intermediate indole-3-carbaldehyde **199a** afforded the 2,3-divinylindole **200a** required for the total synthesis of hyellazole (**158**). The indole-3-

Scheme 55

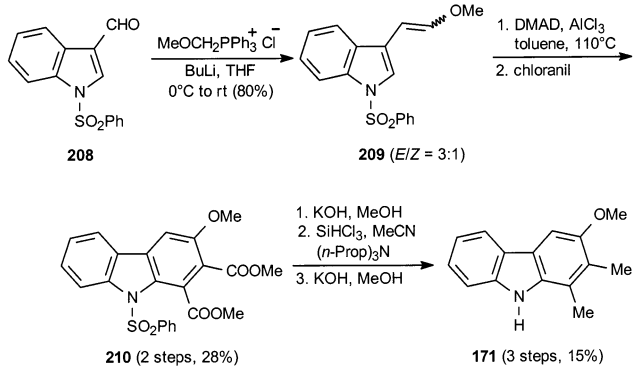


carbaldehyde **199b** required for the total synthesis of 6-chlorohyellazole (**159**) was obtained by reaction with oxalyl chloride and subsequent decarboxylation of the intermediate keto acid, since the direct formylation of **198b** by Vilsmeier reaction was unsuccessful. Finally, Wittig reaction of the indole-3-carbaldehyde **199b** with (methoxymethylene)triphenylphosphorane gave the 2,3-divinylindole **200b**. The electrocyclic ring closure of the 2,3-divinylindoles **200** was achieved by heating in *cis*-decalin as solvent in the presence of 5% Pd/C as dehydrogenation catalyst. Under these conditions, hyellazole (**158**) and 6-chlorohyellazole (**159**) were obtained in 49% and 47% yield, respectively. This synthesis provided hyellazole (**158**) in five steps and 32% overall yield based on **195a**.[137,138] 6-Chlorohyellazole (**159**) was obtained in seven steps with 7% overall yield starting from **194b**.[138]

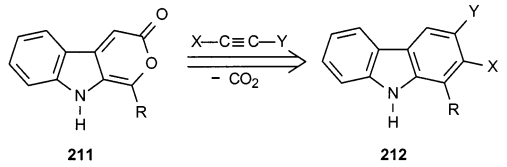
3.5. Total Synthesis of Hyellazole by Annulation of a 2,3-Disubstituted Indole

Takano et al. reported a simple total synthesis of hyellazole (**158**) using the annulation of the 2,3-disubstituted indole **202** as the key step (Scheme 55). Condensation of 2-benzyltryptamine **201**[139] with ethyl (2-ethoxymethylene)acetoacetate gave quantitatively the enamine **202**. On treatment with acetic anhydride/acetic acid (3:2), the enamine **202** cyclized to the carbazole **204**. This one-pot transformation is believed to proceed via the intermediates **203a**−**c**, which promote the crucial cyclization and the removal of the ethylamine side chain. Hydrolysis of the

Scheme 56



Scheme 57



ester afforded the carboxylic acid **205**. The carboxylic group was transformed to an amino group via the intermediate isocyanate **206**. Finally, the amino group of the carbazole **207** was converted to a methoxy group by diazotization and subsequent reaction with methanol. In this total synthesis, hyellazole (**158**) was obtained in five steps and 6% overall yield starting from 2-benzyltryptamine **201**.[140]

3.6. Synthesis of 4-Deoxycarbazomycin B by Diels–Alder Reaction of a 3-Vinylindole

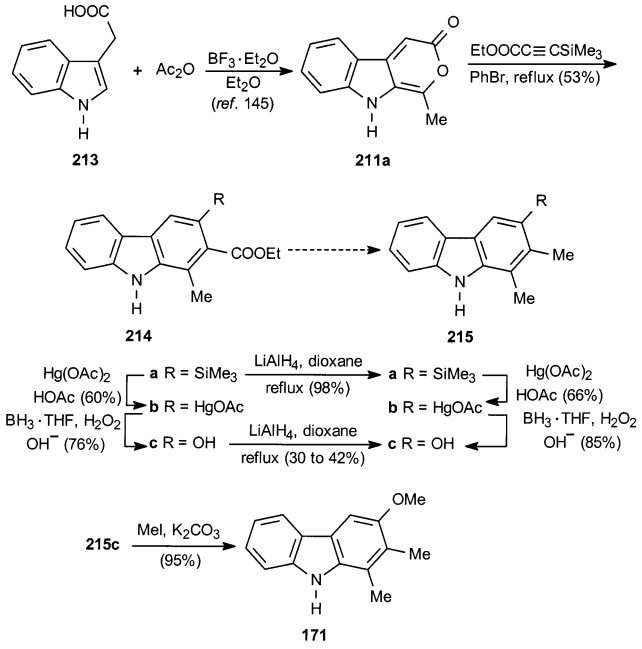
Pindur et al. reported the first synthesis of 4-deoxycarbazomycin B (**171**) by [4 + 2] cycloaddition of a 3-vinylindole and dimethyl acetylenedicarboxylate (DMAD). The required (*E*/*Z*)-3-vinylindole **209** was prepared by a Wittig reaction of the *N*-protected indole-3-carbaldehyde **208**. Diels−Alder reaction of **209** with DMAD and dehydrogenation using chloranil gave the trisubstituted carbazole **210**. Finally, removal of the protecting group and transformation of the ester groups to methyl groups provided 4-deoxycarbazomycin B (**171**) in 15% overall yield (Scheme 56).[141]

3.7. Diels–Alder Reaction of 1-Substituted Pyrano[3,4-b]-indol-3-ones

Moody et al. reported the synthesis of 3-oxygenated carbazole alkaloids (4-deoxycarbazomycin B, hyellazole, and carazostatin) based on his pyrano[3,4-*b*]-indol-3-one methodology (Scheme 57). This synthetic strategy uses 1-substituted pyrano[3,4-*b*]indol-3-ones **211** as stable equivalents of indole-2,3-quinodimethanes in Diels−Alder reactions with alkynes to afford carbazole derivatives by concomitant loss of carbon dioxide.[142−144]

For the synthesis of 4-deoxycarbazomycin B (**171**), 1-methylpyrano[3,4-*b*]indol-3-one **211a** was prepared starting from indole-3-acetic acid **213** and acetic anhydride.[145] The highly regioselective Diels−Alder reaction of **211a** and ethyl 3-trimethylsilylpropynoate in refluxing bromobenzene provided, by concomitant loss of carbon dioxide, the trisubstituted carbazole

Scheme 58



214a in 53% yield. The 3-trimethylsilylcarbazole **214a** served as a crucial intermediate for further transformations, since the silyl group can be substituted by a variety of electrophiles. Thus, the transformation of the trimethylsilyl group of the carbazole **214a** into a hydroxy group was achieved by a two-step sequence employing mild oxidizing conditions in 46% yield. The reduction of the ester group could be achieved either after or before the transformation of the trimethylsilyl group into the hydroxy function. Better results were obtained by the latter alternative. Finally, *O*-methylation of the hydroxycarbazole **215c** with iodomethane in the presence of potassium carbonate gave 4-deoxycarbazomycin B **171** in 95% yield (Scheme 58).[146,147]

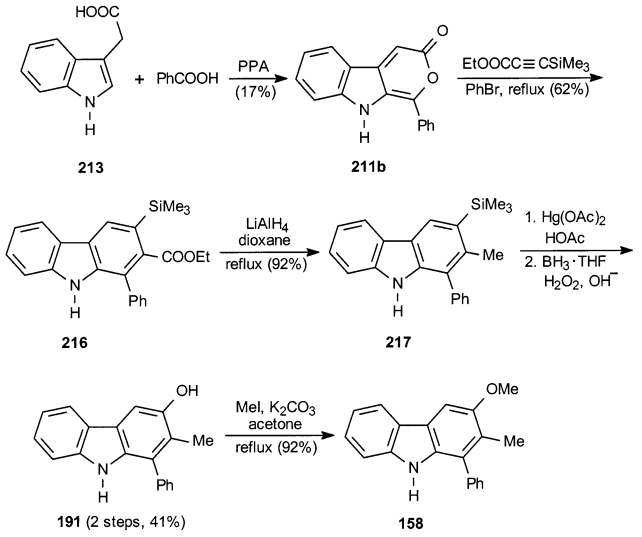
Due to the structural similarity of 4-deoxycarbazomycin B (**171**) to hyellazole (**158**) the Diels−Alder methodology was also applied to the total synthesis of hyellazole (**158**). The reaction of 1-phenylpyrano-[3,4-*b*]indol-3-one **211b** with ethyl 3-trimethylsilylpropynoate afforded the 3-trimethylsilylcarbazole **216**. The final transformation to hyellazole (**158**) via the intermediate 3-hydroxycarbazole **191** was achieved by the same sequence of steps as described above for 4-deoxycarbazomycin B (**171**). This method provides hyellazole (**158**) in five steps and 22% overall yield based on **211b** (Scheme 59).[146,147]

Moody extended his versatile Diels−Alder route to the total synthesis of carazostatin (**160**) with 1-heptylpyrano[3,4-*b*]indol-3-one **211c** as the pyranoindole component. Using a similar reaction sequence as shown in Scheme 59, carazostatin (**160**) was obtained in six steps and 24% overall yield starting from indole-3-acetic acid **213** (Scheme 60).[148,149]

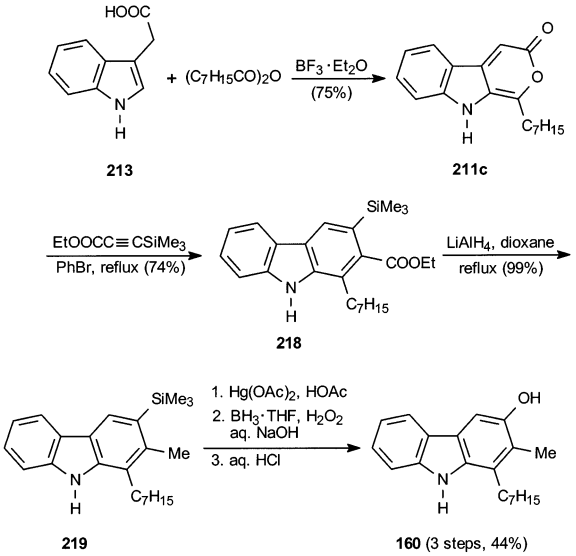
3.8. Benzannulation of Indoles

Synthesis of Hyellazole, 4-Deoxycarbazomycin B, and Carazostatin by Electrocyclization of 3-(Buta-1,3-dienyl)indoles. Sakamoto and his group reported the syntheses of hyellazole (**158**),

Scheme 59



Scheme 60

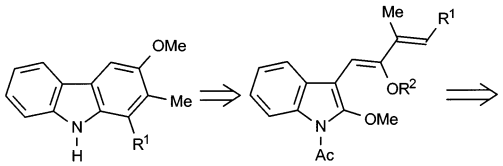


4-deoxycarbazomycin B (**171**), and carazostatin (**160**) based on the benzannulation of indoles. This method involves an electrocyclization of the 3-(buta-1,3-dienyl)indoles **220**, which derive from the indolin-3-one **221** and the phosphorus ylides **222** (Scheme 61).

The Wittig reaction of the readily available 1,2-dihydroindol-3-one **221** with the phosphoranes **222** afforded the enones **223**, which were treated with trimethylsilyl iodide (TMSI) in the presence of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) to give the trimethylsilylenol ethers **220** (Scheme 62).[150,151]

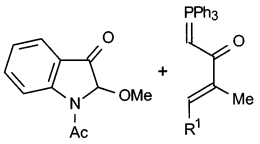
The electrocyclic reaction of the enol ether **220a** in boiling *cis*-decalin (bp 195 °C) gave the 3-siloxycarbazole **225a** and the desilylated product **226a** in 53% and 13% yield, respectively (Scheme 63). The reaction sequence probably involves isomerization of the enol ether **220a**, followed by electrocyclization and aromatization of the intermediate dihydrocarbazole **224a** by elimination of methanol. Removal of the silyl group from the 3-siloxycarbazole **225a** with tetrabutylammonium fluoride (TBAF) afforded the 3-hydroxycarbazole **226a**. The cyclization of **220b** led, via the intermediate **224b** followed by aromatization

Scheme 61



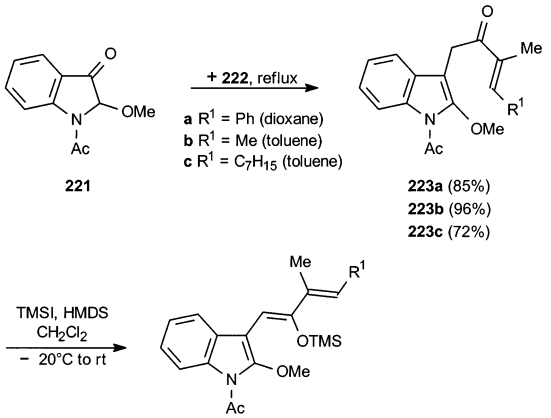
158 Hyellazole
R^1 = Ph
171 4-Deoxycarbazomycin B
R^1 = Me
160 Carazostatin
R^1 = C_7H_{15}

220



221 **222**

Scheme 62



221

a R^1 = Ph (dioxane)
b R^1 = Me (toluene)
c R^1 = C_7H_{15} (toluene)

223a (85%)
223b (96%)
223c (72%)

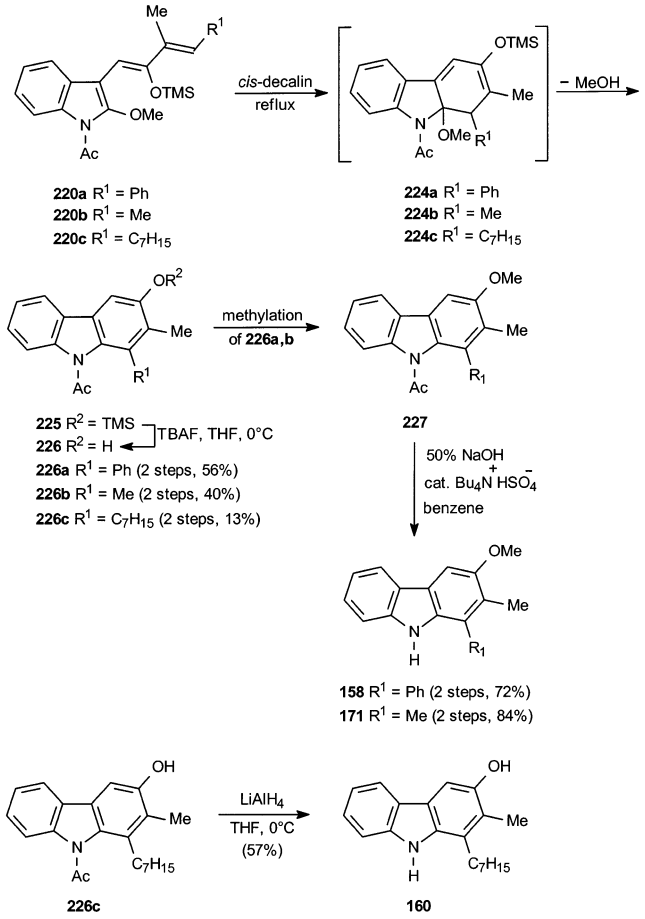
220a (80%)
220b (98%)
220c (75%)

and desilylation of the 3-siloxycarbazole **225b**, to the corresponding 3-hydroxycarbazole **226b** in 40% yield. The 3-hydroxycarbazoles **226** were methylated to give *N*-acetylhyellazole **227a** and *N*-acetyl-4-deoxycarbazomycin B **227b**. Finally, deacetylation with sodium hydroxide under phase-transfer conditions afforded hyellazole (**158**) and 4-deoxycarbazomycin B (**171**).[152]

The same method was applied to the total synthesis of carazostatin (**160**) (Scheme 63). The electrocyclic reaction of the 3-(buta-1,3-dienyl)indole **220c** followed by aromatization afforded the 3-siloxycarbazole **225c**, which on desilylation led to *N*-acetylcarazostatin **226c**. Removal of the acetyl group by reduction with lithium aluminum hydride provided carazostatin (**160**). The electrocyclization route leads to carazostatin (**160**) in five steps and 4% overall yield based on 1-acetyl-2-methoxyindol-3-one **221**.[153]

Total Synthesis of Hyellazole. Danheiser and co-workers developed a new aromatic annulation for the total synthesis of hyellazole (**158**) by irradiation of the α-diazo ketone **229** in the presence of 1-methoxypropyne. This reaction proceeds via the Wolff rearrangement of the α-diazo ketone **229** to generate a heteroarylketene, followed by a cascade of three pericyclic reactions (Scheme 64).

Scheme 63



220a R^1 = Ph
220b R^1 = Me
220c R^1 = C_7H_{15}

224a R^1 = Ph
224b R^1 = Me
224c R^1 = C_7H_{15}

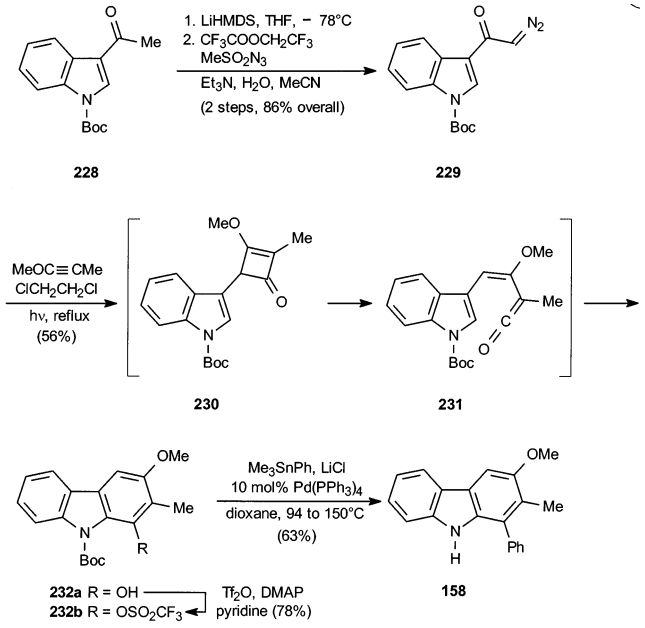
225 R^2 = TMS
226 R^2 = H
226a R^1 = Ph (2 steps, 56%)
226b R^1 = Me (2 steps, 40%)
226c R^1 = C_7H_{15} (2 steps, 13%)

227

158 R^1 = Ph (2 steps, 72%)
171 R^1 = Me (2 steps, 84%)

226c **160**

Scheme 64



228 **229**

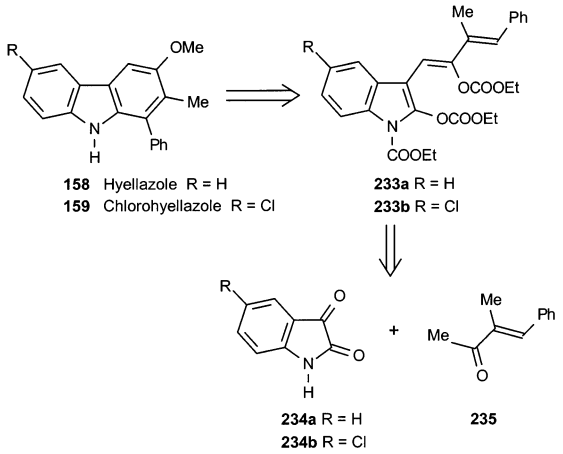
230 **231**

232a R = OH
232b R = OSO_2CF_3

158

A diazo transfer to *N*-Boc-3-acetylindole **228** provided the α-diazo ketone **229**. Irradiation of **229** and 1-methoxypropyne in a solution of 1,2-dichloroethane gave the hydroxycarbazole **232a**. Mechanistically, this annulation involves a photochemical Wolff rearrangement of the α-diazo ketone **229** to generate a vinylketene intermediate, which combines with 1-methoxypropyne in a regiospecific [2 + 2] cycload-

Scheme 65



dition. Further irradiation results in a 4π-electrocyclic ring opening of the cyclobutenone **230** to the dienylketene **231** and subsequent 6π-electrocyclization to afford a 2,4-cyclohexadienone that tautomerizes to the hydroxycarbazole **232a**. After conversion of the hydroxycarbazole **232a** to the triflate **232b**, the phenyl group was introduced at C-1 by a Stille cross-coupling reaction[154] with trimethylphenylstannane in the presence of a catalytic amount of tetrakis(triphenylphosphane)palladium to afford hyellazole (**158**) in 63% yield. The coupling reaction occurs with concomitant cleavage of the Boc group. By this method hyellazole (**158**) is available in six steps and 19% overall yield based on the 3-acetylindole **228**.[155]

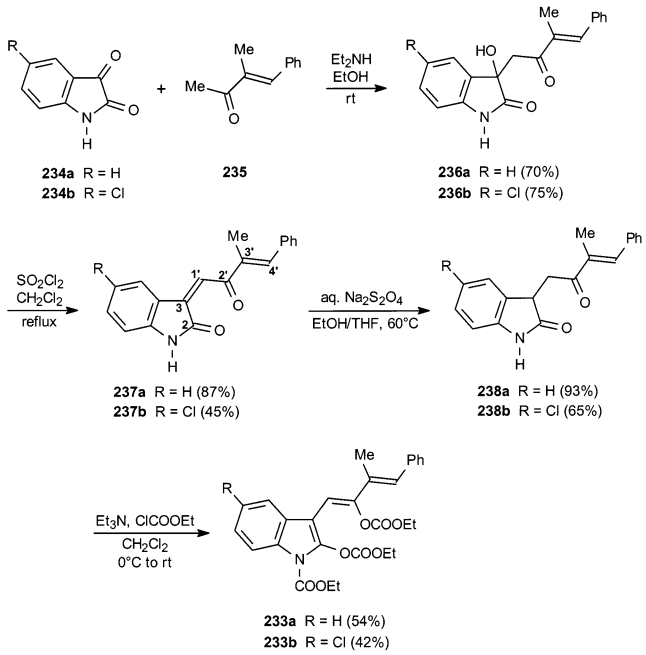
Total Synthesis of Hyellazole and 6-Chlorohyellazole. Using a modification of Sakamoto's synthetic protocol (cf. Scheme 61), Beccalli's group reported the synthesis of the 3-methoxycarbazole alkaloids hyellazole (**158**) and 6-chlorohyellazole (**159**) (Scheme 65). This method requires a good leaving group at the 2-position of the indole moiety of the 3-(buta-1,3-dienyl)indoles **233** to facilitate the aromatization of the intermediate dihydrocarbazole.

The key intermediates **233** required for the thermal cyclization were prepared from the readily available indole-2,3-diones **234**. Condensation of the indole-2,3-diones **234** with 3-methyl-4-phenylbut-3-en-2-one **235** afforded the 3-hydroxy derivatives **236**. The dehydration of **236**, followed by selective reduction of the 3,1′-double bond of the compounds **237**, provided the 3-alkyl derivatives **238**. Finally, the compounds **238** were transformed to the 3-(buta-1,3-dienyl)indoles **233** by reaction with an excess ethyl chloroformate (Scheme 66).

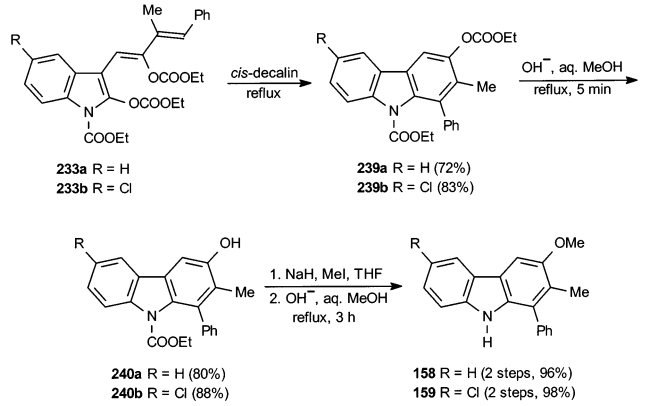
The thermal cyclization of the 3-(buta-1,3-dienyl)-indoles **233** in refluxing *cis*-decalin provided the carbazoles **239**. Selective hydrolysis of the 3-carbonate, methylation of the corresponding 3-hydroxycarbazoles **240** with methyl iodide in the presence of sodium hydride, and subsequent alkaline hydrolysis under reflux gave hyellazole (**158**) and 6-chlorohyellazole (**159**) (Scheme 67).[156]

Total Synthesis of Carazostatin. Ogasawara's group developed a new total synthesis of carazostatin (**160**) from *N*-carbethoxy-2-iodoaniline **241** and 1-decyne employing two aromatic annulation reactions

Scheme 66



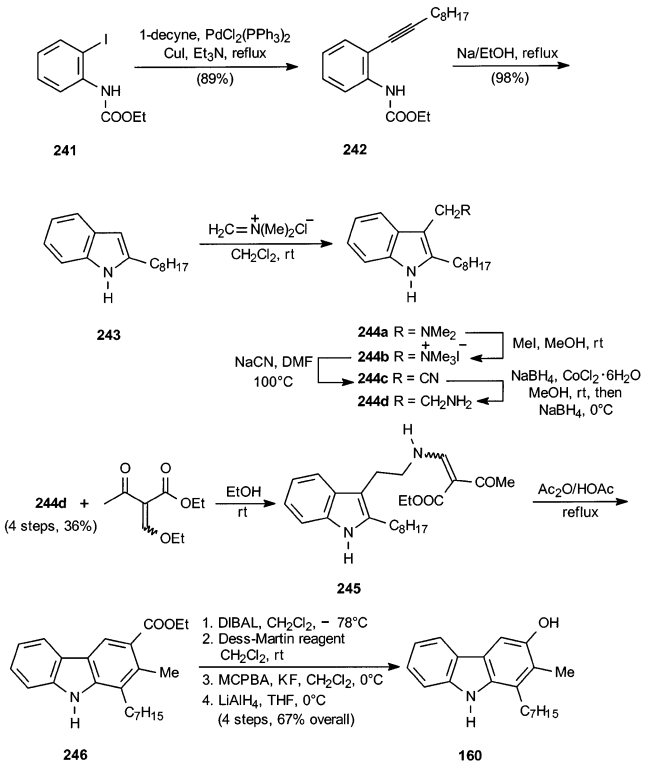
Scheme 67



as key steps (Scheme 68). The palladium-mediated cross-coupling of *N*-carbethoxy-2-iodoaniline **241** and 1-decyne afforded the arylacetylene **242** in 89% yield. Aromatic annulation of the arylacetylene **242** by a base-induced indolization provided 2-octylindole **243**. Following a standard procedure, 2-octylindole **243** was transformed to 2-octyltryptamine **244d** in four steps. The condensation of 2-octyltryptamine **244d** with ethyl (2-ethoxymethylene)acetoacetate provided the conjugated enamine **245** required for the second aromatic annulation. In a one-pot operation, compound **245** was transformed to the carbazole **246** by refluxing in a 5:3 mixture of acetic anhydride and acetic acid (cf. Scheme 55). Finally, using the indicated four-step sequence ($-$COOEt $\rightarrow$ $-CH_2OH$ $\rightarrow$ $-$CHO $\rightarrow$ $-$OCHO $\rightarrow$ $-$OH) the carbazole **246** was converted to the natural product carazostatin (**160**).[157]

Synthesis of 4-Deoxycarbazomycin B, Carazostatin, and Hyellazole by Electrocyclization of 2,3-Divinylindoles. Hibino et al. reported the synthesis of the 3-oxygenated carbazole alkaloids 4-deoxycarbazomycin B (**171**), carazostatin (**160**), and hyellazole (**158**) using new benzannulation methods based on the thermal electrocyclization of 2,3-divi-

Scheme 68

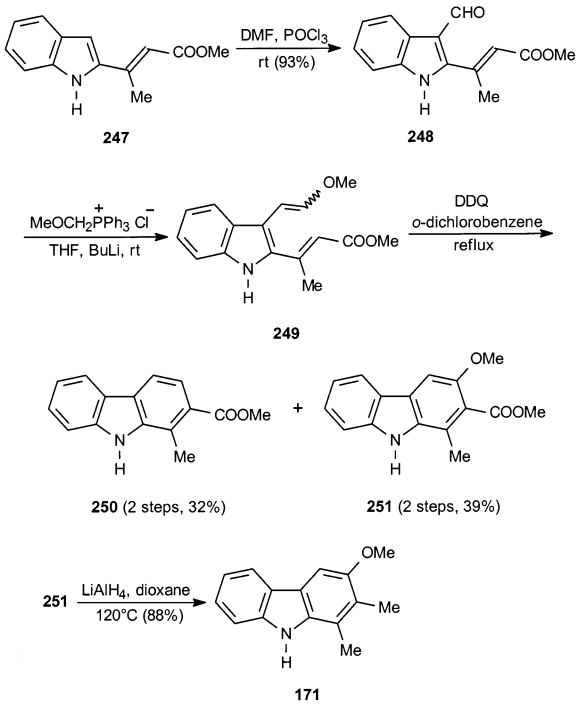


nylindoles and the electrocyclization of 2,3-difunctionalized indoles via allene intermediates.

The 2,3-divinylindole **249** required for the synthesis of 4-deoxycarbazomycin B (**171**) was prepared starting from methyl indolyl-2-butenoate **247**. Vilsmeier formylation of compound **247** provided the indole-3-carbaldehyde **248**, which by Wittig reaction with methoxymethylenetriphenylphosphorane gave the 2,3-divinylindole **249**. Thermal electrocyclization of **249** by heating in *o*-dichlorobenzene under reflux in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded the desired carbazole **251**, along with the demethoxylated derivative **250**. Finally, reduction of the carbazole **251** with lithium aluminum hydride provided 4-deoxycarbazomycin B (**171**) in 88% yield (Scheme 69).[158]

The 3-alkenyl-2-propargylindole **254**, used as precursor for the total synthesis of carazostatin (**160**) and hyellazole (**158**), was prepared in five steps and 51% overall yield starting from 2-formylindole **252**. The thermal electrocyclization of **254** via the intermediate allene **255** was achieved by heating in *tert*-butyl alcohol in the presence of potassium *tert*-butoxide and provided the expected carbazole **256** (41% yield) along with the *N*-deprotected carbazole **257** (43% yield). However, by alkaline hydrolysis of **256** (75% yield) the carbazole **257** could be obtained as the sole product. Subsequent cleavage of the MOM ether of **257** using trimethylsilyl chloride and sodium iodide, followed by treatment with trifluoromethanesulfonic anhydride (Tf_2O) and pyridine, afforded the triflate **258**. The introduction of either the heptyl side chain or the phenyl group at C-1 by a Suzuki cross-coupling reaction transformed the triflate **258** to the carbazoles **259** and **260**, respectively. Finally, cleavage of the ethyl ether of **259** using boron tribromide

Scheme 69



afforded carazostatin (**160**) in 11 steps and 14% overall yield. Cleavage of the ethyl ether of **260** followed by *O*-methylation of the hydroxycarbazole **191** provided hyellazole (**158**) in 12 steps and 15% overall yield (Scheme 70).[159]

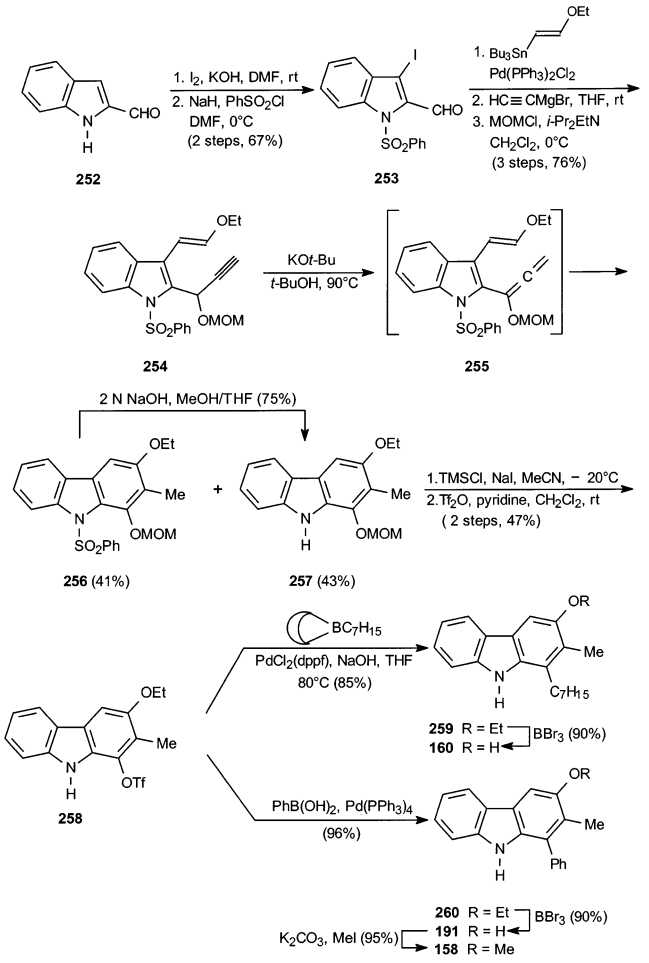
Chowdhury and co-workers developed two routes to 4-deoxycarbazomycin B **171** by a Fischer−Borsche synthesis and a palladium(II)-mediated oxidative cyclization, respectively.[160] They also described the significant inhibitory activity of 4-deoxycarbazomycin B (**171**) against various Gram-positive and -negative bacteria.[160a]

4. 3,4-Dioxygenated Tricyclic Carbazole Alkaloids

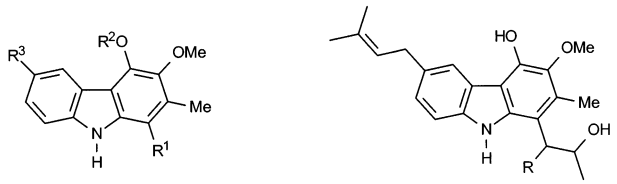
A broad range of structurally diverse 3,4-dioxygenated carbazole alkaloids such as the carbazomycins A−F (**261**−**266**) and the neocarazostatins A−C (**267**−**269**) were isolated from different *Streptomyces* species (Scheme 71).

The carbazomycins are an unprecedented class of antibiotics with a carbazole framework. In 1980, Nakamura et al. reported the isolation of carbazomycins A (**261**) and B (**262**) from *Streptoverticillium ehimense* H 1051-MY 10.[161] Subsequently, the same authors reported the structural elucidation[162,163] and the biogenesis of these novel alkaloids.[164] Carbazomycins A and B inhibit the growth of phytopathogenic fungi and have antibacterial and antiyeast activities. Moreover, carbazomycin B (**262**) is an inhibitor of 5-lipoxygenase.[165] In 1987, Nakamura et al. isolated the carbazomycins C (**263**), D (**264**), E (**265**), and F (**266**) from the same source (*S. ehimense* H 1051-MY 10).[166] Carbazomycin C was also shown to inhibit 5-lipoxygenase.[165] In 1986, Marumo et al. reported already the isolation of the carbazomycins E (carbazomycinal) (**265**) and F (**266**) (6-methoxycarbazomycinal) from a different *Streptoverticillium* species of the strain KCC U-0166.[167] In 1991, Kato

Scheme 70



Scheme 71



261 Carbazomycin A
R^1, R^2 = Me; R^3 = H
262 Carbazomycin B
R^1 = Me; R^2, R^3 = H
263 Carbazomycin C
R^1 = Me; R^2 = H; R^3 = OMe
264 Carbazomycin D
R^1, R^2 = Me; R^3 = OMe
265 Carbazomycin E
R^1 = CHO; R^2, R^3 = H
266 Carbazomycin F
R^1 = CHO; R^2 = H; R^3 = OMe

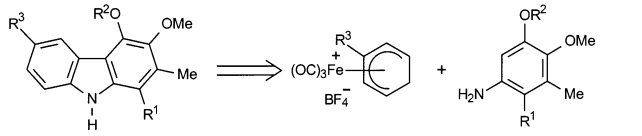
267 Neocarazostatin A
R = OH
268 Neocarazostatin B
R = H
269 Neocarazostatin C
R = OMe

et al. isolated the neocarazostatins A−C (**267**−**269**)[79] from the culture of *Streptomyces* sp. strain GP 38. The neocarazostatins were shown to exhibit strong inhibitory activities against lipid peroxidation induced by free radicals.[168]

4.1. Iron-Mediated Total Synthesis of the Carbazomycins A–E and (±)-Neocarazostatin B

Our approach for the total synthesis of the carbazomycins A−E (**261**−**265**) and (±)-neocarazostatin B

Scheme 72

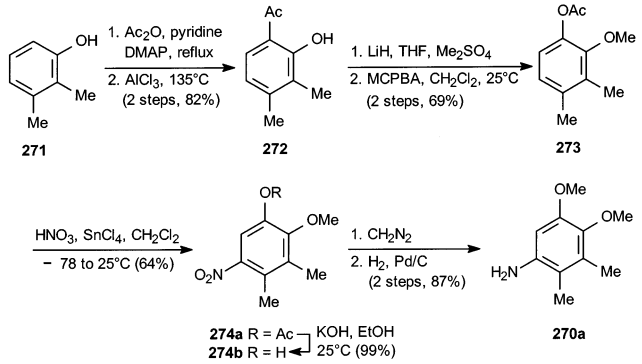


261 Carbazomycin A
R^1, R^2 = Me; R^3 = H
262 Carbazomycin B
R^1 = Me; R^2, R^3 = H
263 Carbazomycin C
R^1 = Me; R^2 = H; R^3 = OMe
264 Carbazomycin D
R^1, R^2 = Me; R^3 = OMe
265 Carbazomycin E
R^1 = CHO; R^2, R^3 = H

12a R^3 = H
12b R^3 = OMe

270a R^1, R^2 = Me
270b R^1 = Me; R^2 = H
270c R^1 = CHO; R^2 = H

Scheme 73

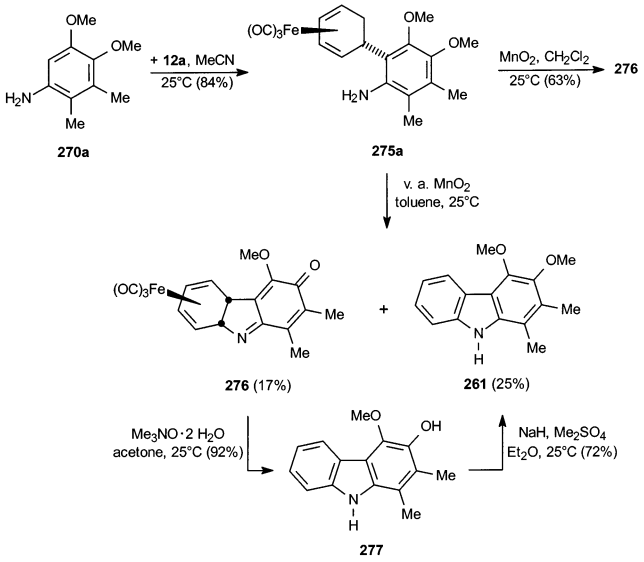


(**268**) was based on the iron-mediated construction of the carbazole ring system via consecutive C−C and C−N bond formation. Retrosynthetic analysis of the carbazomycins A−E (**261**−**265**) based on this approach leads to the iron complex salts **12** and the fully funtionalized arylamines **270** as synthetic precursors (Scheme 72).

Total Synthesis of Carbazomycin A and B. The arylamine **270a** required for the total synthesis of carbazomycin A (**261**) was prepared starting from 2,3-dimethylphenol **271**. The regioselective introduction of the second oxy substituent in the position ortho to the hydroxy group was initiated by acetylation of **271** and subsequent ortho-selective Fries rearrangement of the intermediate acetoxy derivative to the desired acetophenone **272**. Methylation of **272** followed by a regioselective Baeyer−Villiger oxidation afforded the acetoxy compound **273**. Regioselective nitration of **273** using the preformed complex of fuming nitric acid and $SnCl_4$ at −78 °C afforded the desired nitro derivative **274a** in 64% yield. After deacetylation the corresponding phenol, **274b** was methylated and subjected to hydrogenation to give the arylamine **270a**. This synthesis provided the arylamine **270a** in eight steps and 31% overall yield (Scheme 73).[130,169,170]

Electrophilic aromatic substitution of the arylamine **270a** using the iron complex salt **12a** afforded the iron complex **275a**, a hexasubstituted benzene derivative, in high yield. Oxidative cyclization of complex **275a** in toluene at room temperature with very active manganese dioxide afforded carbazomycin A (**261**) in 25% yield along with the tricarbonyliron-complexed 4b,8a-dihydro-3*H*-carbazol-3-one **276** (17%

Scheme 74



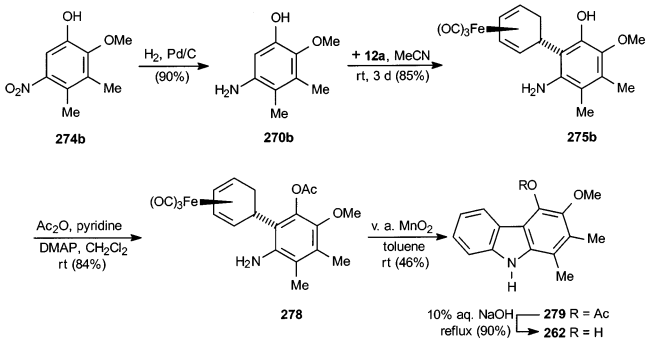
yield). The quinone imine **276** was also converted to carbazomycin A (**261**) by a sequence of demetalation and *O*-methylation (Scheme 74).[130,170] The synthesis via the iron-mediated arylamine cyclization provides carbazomycin A (**261**) in two steps and 21% overall yield based on **12a**.

A selective oxidation of the iron complex **275a** with commercial manganese dioxide in dichloromethane at room temperature afforded selectively the iron-complexed 4b,8a-dihydro-3*H*-carbazol-3-one **276** in 63% yield. The analogous oxidation in the deoxy series provided only the noncyclized quinone imine (cf. Scheme 43, part b). This contrast may be explained by the different oxidation potential of complex **275a**. Finally, demetalation of the quinone imine **276** to the 3-hydroxycarbazole **277** and subsequent *O*-methylation gave carbazomycin A (**261**) (Scheme 74)[169,170] The synthesis of carbazomycin A (**261**) via the iron-mediated quinone imine cyclization provides the natural product in four steps and 35% overall yield based on **12a**.

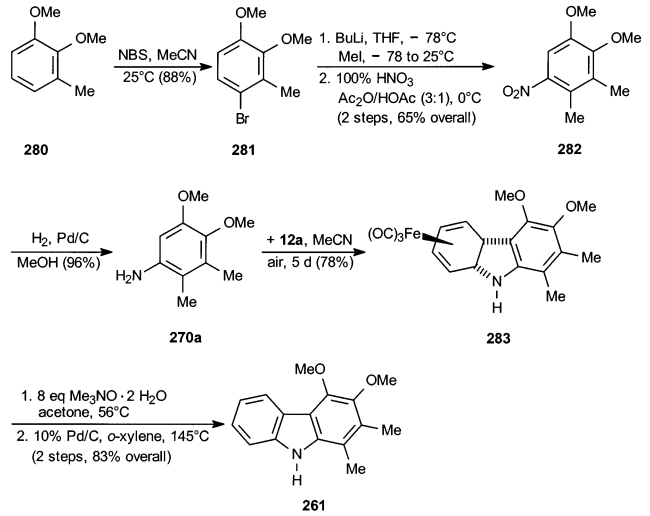
The nitroaryl derivative **274b** can be obtained in six steps and 33% overall yield starting from 2,3-dimethylphenol **271** (see Scheme 73). For the total synthesis of carbazomycin B (**262**), compound **274b** was hydrogenated to give the arylamine **270b** in 90% yield. Electrophilic substitution of the arylamine **270b** with the iron complex salt **12a** provided the iron complex **275b** in 85% yield. The direct one-pot transformation of the iron complex **275b** to carbazomycin B (**262**) by an iron-mediated arylamine cyclization was unsuccessful, probably because the unprotected hydroxyarylamine moiety is too sensitive toward the oxidizing reaction conditions. However, the corresponding *O*-acetyl derivative **278** was transformed to *O*-acetylcarbazomycin B (**279**) in 46% yield. Finally, cleavage of the ester group afforded carbazomycin B (**262**) (Scheme 75).[169,170] The total synthesis of carbazomycin B (**262**) via the iron-mediated arylamine cyclization was completed in four steps and 30% overall yield based on the iron-complexed cation **12a**.

Recently, we described the considerably improved total syntheses of the carbazomycins A (**261**) and B

Scheme 75



Scheme 76

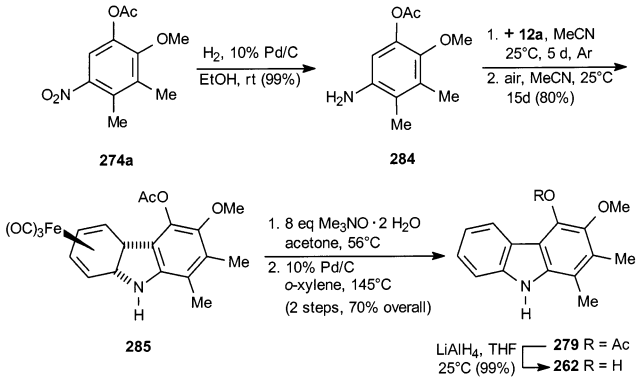


(**262**) using highly efficient synthetic routes to the arylamines **270a** and **270b**. Moreover, we implemented a novel one-pot construction of the carbazole framework by oxidative coupling of the iron-complexed cation **12a** with the arylamines **270a** and **270b** in the air.[171]

The optimized procedure for the synthesis of the arylamine **270a** started from commercially available 3-methylveratrole **280**. The electrophilic bromination of 3-methylveratrole (**280**) led to the corresponding 4-bromo derivative **281**. Halogen−metal exchange of **281** with butyllithium and subsequent methylation by iodomethane afforded 3,4-dimethylveratrole. Regioselective nitration of 3,4-dimethylveratrole using fuming nitric acid in a 3:1 mixture of acetic anhydride and glacial acetic acid provided the 5-nitro derivative **282**. Finally, catalytic hydrogenation of **282** using 10% palladium on activated carbon provided the arylamine **270a** (Scheme 76).[171] This novel route provides the arylamine **270a** in four steps and 55% overall yield based on 3-methylveratrole **280**.

Using a one-pot process of oxidative coupling in the air, the arylamine **270a** was transformed to the tricarbonyl(η^4-4a,9a-dihydro-9*H*-carbazole)iron complex **283** in 78% yield. Finally, demetalation of **283** and subsequent aromatization gave carbazomycin A (**261**) in 83% yield (Scheme 76).[171] This synthesis provided carbazomycin A (**261**) in three steps and 65% overall yield based on **12a** (previous route: four steps and 35% yield based on **12a**).

Scheme 77



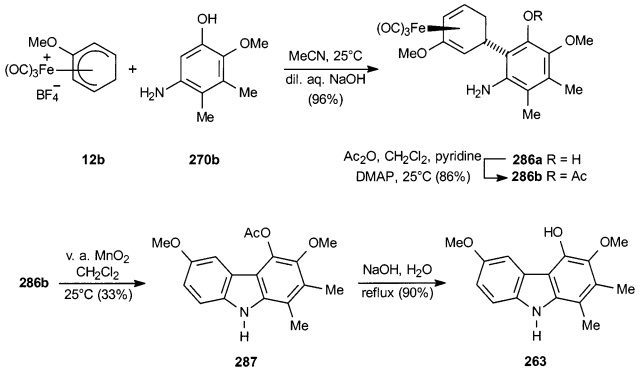
The arylamine **284** required for the improved total synthesis of carbazomycin B (**262**) was prepared in 99% yield by hydrogenation of the nitroaryl derivative **274a** (cf. Scheme 73). Oxidative coupling of the iron complex salt **12a** and the arylamine **284** in the air afforded the tricarbonyl(η^4-4a,9a-dihydro-9*H*-carbazole)iron complex **285** in 80% yield. Demetalation of **285** followed by aromatization and ester cleavage afforded carbazomycin B (**262**) (Scheme 77).[171] Using the oxidative cyclization in air, carbazomycin B (**262**) was obtained in four steps and 55% overall yield based on **12a** (previous synthesis: four steps and 30% overall yield based on **12a**).

Total Synthesis of Carbazomycin C and D. Retrosynthetic analysis of the carbazomycins C (**263**) and D (**264**) based on the iron-mediated construction of the carbazole framework leads to tricarbonyl[3-methoxy-(1−5-η)-cyclohexadienyl]iron tetrafluoroborate **12b** and the arylamines **270b** and **270a** (cf. Scheme 72) as synthetic precursors. Tricarbonyl[3-methoxy-(1−5-η)-cyclohexadienyl]iron tetrafluoroborate **12b** was prepared in three steps from 1,3-dimethoxybenzene.[172] The arylamines **270a** and **270b** were used previously as precursors for the total synthesis of carbazomycin A (**261**) and B (**262**) (see Schemes 73, 75, and 76).

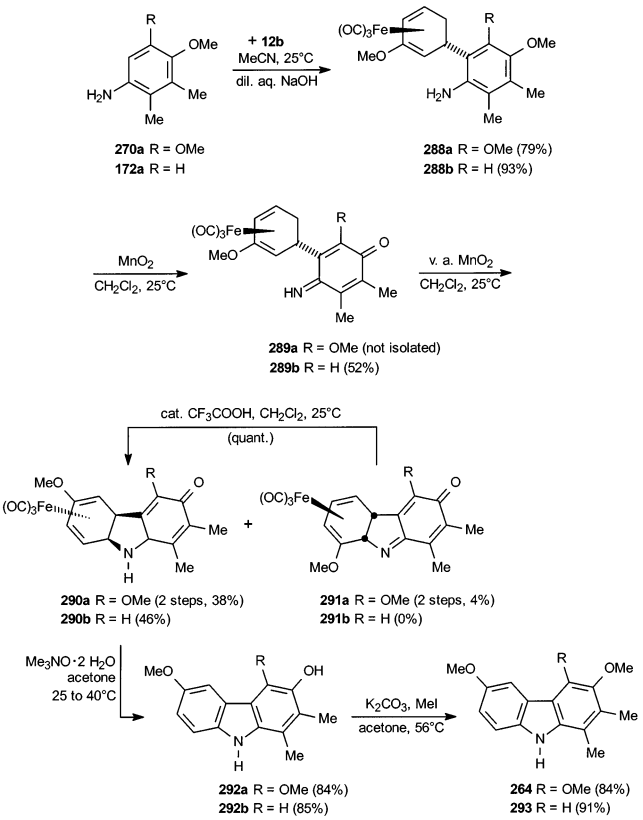
The total synthesis of carbazomycin C (**263**) was achieved by the iron-mediated arylamine cyclization route, as described for the total synthesis of carbazomycin B (**262**) (see Scheme 75). The electrophilic substitution of the arylamine **270b** using the complex salt **12b** afforded the iron complex **286a**, which was transformed to the acetate **286b**. Using very active manganese dioxide, compound **286b** was cyclized to *O*-acetylcarbazomycin C (**287**). Finally, saponification of the ester afforded carbazomycin C (**263**) (four steps and 25% overall yield based on **12b**) (Scheme 78).[173]

The total synthesis of carbazomycin D (**264**) was completed using the quinone imine cyclization route, as described for the total synthesis of carbazomycin A (**261**) (see Scheme 74). The electrophilic substitution of the arylamine **270a** by reaction with the complex salt **12b** provided the iron complex **288a** in 79% yield. Using different grades of manganese dioxide the oxidative cyclization of complex **288a** was achieved in a two-step sequence and afforded the tricarbonyliron complexes **290a** (38%) and **291a** (4%). By a subsequent proton-catalyzed isomerization, the 8-methoxy isomer **291a** could be quantitatively transformed to the 6-methoxy isomer **290a**, due to the regiodirecting effect of the 2-methoxy substituent of the intermediate cyclohexadienyl cation.[173] Demetalation of complex **290a** with trimethylamine *N*-oxide afforded the 3-hydroxycarbazole derivative **292a**, which on *O*-methylation provided carbazomycin D (**264**) (five steps and 23% overall yield based on **12b**) (Scheme 79).[173] Starting from the arylamine **172a** (see Scheme 42) and complex **12b** the nonnatural 4-deoxycarbazomycin C (**293**) was obtained by a similar synthetic sequence in five steps and 17% overall yield (Scheme 79).

Scheme 78

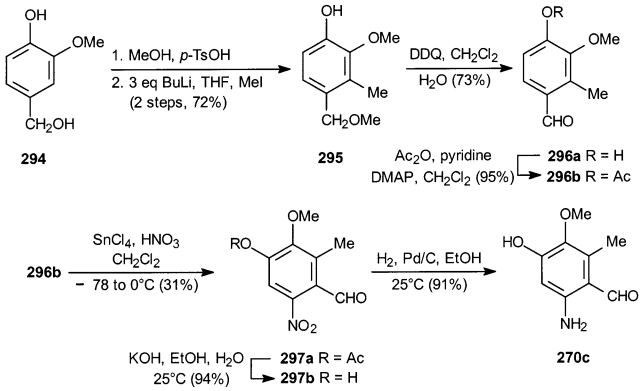


Scheme 79

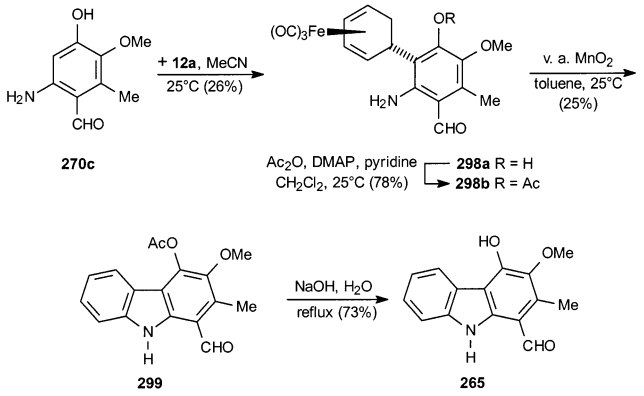


Total Synthesis of Carbazomycin E (Carbazomycinal). The arylamine **270c**, required for the iron-mediated total synthesis of carbazomycin E (**265**) (see retrosynthesis, Scheme 72), was prepared in seven steps starting from vanillyl alcohol (**294**). Vanillyl alcohol (**294**) was transformed to the tetrasubstituted aryl derivative **295** via generation of the benzyl methyl ether followed by ortho-directed lithia-

Scheme 80



Scheme 81



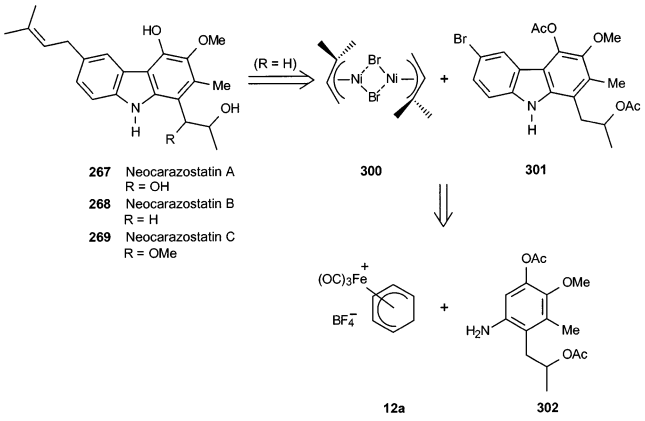
tion and subsequent methylation. After DDQ oxidation of the benzyl methyl ether **295**, the corresponding aldehyde **296a** was converted to the *O*-acetyl derivative **296b**. Nitration of compound **296b** to the nitrobenzaldehyde **297a** was achieved using the complex of tin tetrachloride and fuming nitric acid. Ester cleavage to the nitrophenol **297b** with potassium hydroxide and subsequent catalytic hydrogenation with 10% palladium on activated carbon afforded the desired arylamine **270c** (Scheme 80).[174]

Electrophilic aromatic substitution of the arylamine **270c** using the iron-complex salt **12a** provided the iron complex **298a** in 26% yield. The low yield of complex **298a** was ascribed to the strong electron-withdrawing effect by the formyl group. After acetylation of complex **298a**, the resulting *O*-acetyl derivative **298b** was subjected to the iron-mediated arylamine cyclization to give the *O*-acetyl carbazole **299**. Finally, ester cleavage afforded carbazomycin E (**265**) in 73% yield (Scheme 81).[174] The overall yield for the iron-mediated total synthesis of carbazomycin E (**265**) is low (four steps and 4% overall yield based on **12a**). However, till today it represents the only total synthesis reported for this natural product.

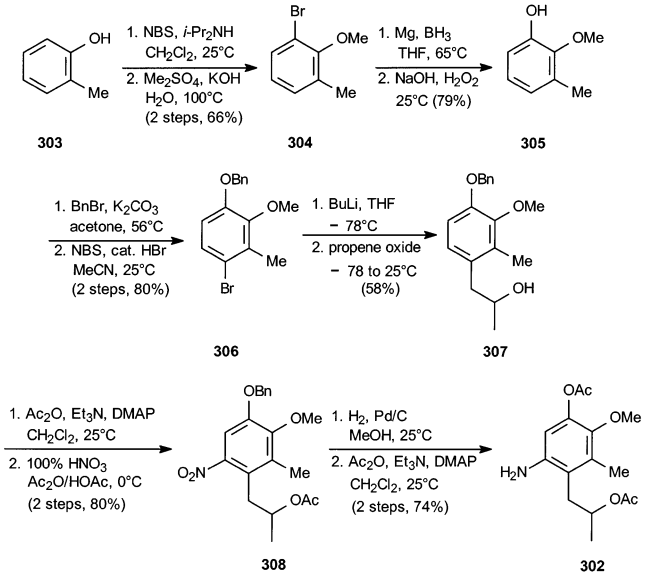
Total Synthesis of (±)-Neocarazostatin B. The retrosynthetic analysis of (±)-neocarazostatin B (**268**) leads to the protected 6-bromocarbazole **301** as the key intermediate. For the regioselective introduction of the prenyl group, a reaction of the 6-bromocarbazole **301** with the dimeric π-prenylnickel bromide complex **300**[175−179] was envisaged (Scheme 82).

The fully functionalized arylamine **302** required for the construction of the carbazole framework was

Scheme 82



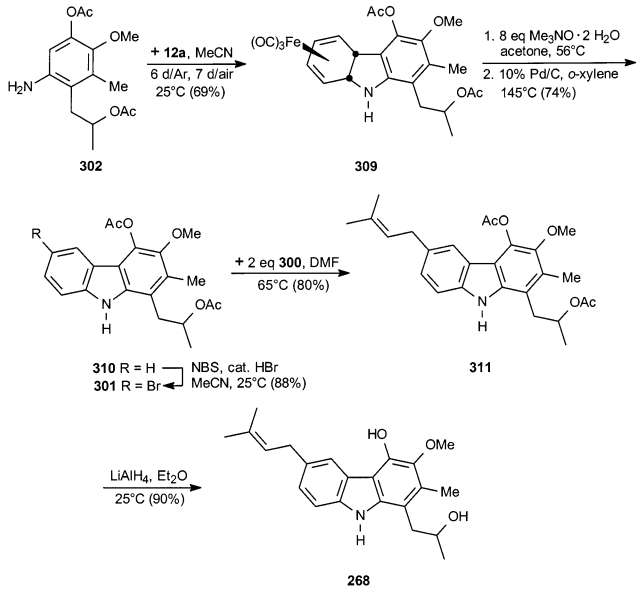
Scheme 83



obtained from *o*-cresol **303**. The diisopropylamine-catalyzed bromination of *o*-cresol **303** with NBS occurred regioselectively ortho to the hydroxy group. Subsequent *O*-methylation with dimethyl sulfate provided the *o*-bromoanisole **304**. Treatment of **304** with magnesium in the presence of diborane followed by oxidation with alkaline hydrogen peroxide led to the *o*-hydroxyanisole **305**. *O*-Benzylation of **305** and subsequent regioselective bromination with NBS provided the bromo derivative **306**. Halogen−metal exchange of **306** with butyllithium followed by reaction with (±)-propene oxide afforded the carbinol **307**. The *O*-acetylation of **307** and subsequent regioselective nitration gave the nitroaryl derivative **308**. Catalytic hydrogenation of **308** with concomitant cleavage of the benzyl ether followed by chemoselective *O*-acetylation of the intermediate aminophenol afforded the arylamine **302** (Scheme 83).[180] Following this route the arylamine **302** is available in 10 steps and 14% overall yield.

A one-pot construction of the carbazole framework was achieved by electrophilic substitution of the arylamine **302** using the iron-complexed cation **12a** combined with the oxidative cyclization in the air. Thus, reaction of the arylamine **302** with 2 equiv of **12a** afforded the iron complex **309** in 69% yield as a

Scheme 84



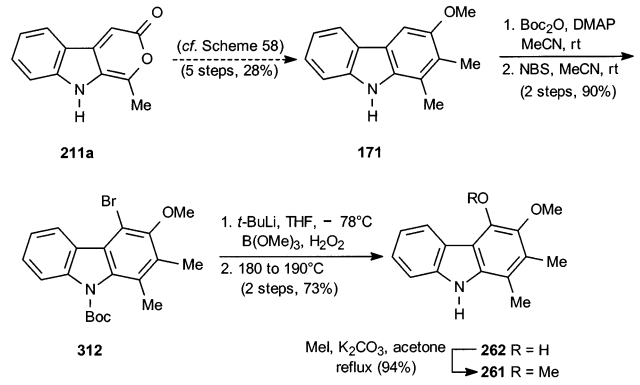
1:1 mixture of two diastereoisomers. Demetalation of complex **309** and subsequent aromatization by catalytic dehydrogenation provided the acetylcarbazole **310** in 74% yield. Regioselective electrophilic bromination of the acetylcarbazole **310** afforded the 6-bromocarbazole **301** in 88% yield. Prenylation of **301** by reaction with the dimeric π-prenylnickel bromide complex **300**[175−179] led to the 6-prenylcarbazole **311**. Finally, reductive cleavage of the ester groups afforded (±)-neocarazostatin B (**268**) in 90% yield (Scheme 84).[180] The iron- and nickel-mediated synthesis described above provided (±)-neocarazostatin B (**268**) in six steps and 32% overall yield based on **12a**.

4.2. Diels–Alder Reaction of 1-Methylpyrano[3,4-b]-indol-3-one

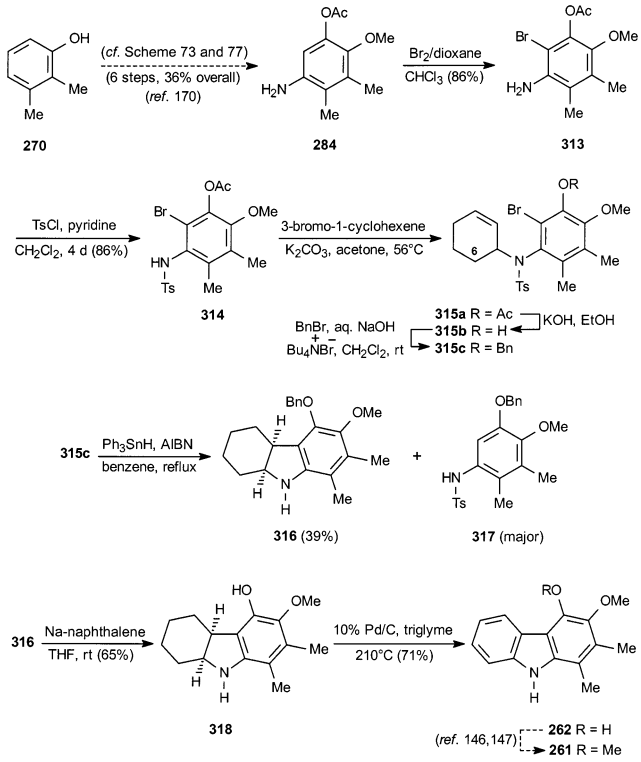
Moody et al. reported the synthesis of the carbazomycins A (**261**) and B (**262**) using his pyrano[3,4-*b*]indol-3-one methodology via 4-deoxycarbazomycin B (**171**) (cf. Scheme 58). Several attempts to introduce the hydroxy group at C-4 in 4-deoxycarbazomycin B (**171**) using various oxidants were unsuccessful, due to either complete decomposition of the hydroxycarbazole or the formation of dimeric 4,4′-biscarbazoles by oxidative dimerization. Therefore, the 4-hydroxy substituent had to be introduced via the corresponding *N*-Boc-protected bromide **312** in a four-step sequence. The conversion of the 4-bromo to the 4-hydroxy substituent was achieved by lithiation, treatment with trimethyl borate, and alkaline hydrogen peroxide workup. Removal of the *N*-Boc group simply by heating led to carbazomycin B (**262**). Carbazomycin B (**262**) was transformed to carbazomycin A (**261**) by chemoselective methylation of the hydroxy group (Scheme 85).[146,147]

On the basis of Moody's conversion of 4-deoxycarbazomycin B (**171**) to carbazomycin A (**261**) and B (**262**), Hibino et al. reported a formal total synthesis of the carbazomycins A (**261**) and B (**262**) via 4-deoxycarbazomycin B (**171**) (see Scheme 69).[158]

Scheme 85



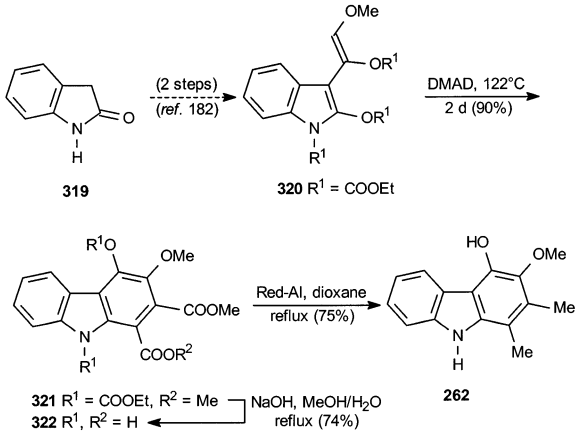
Scheme 86



4.3. Total Synthesis of Carbazomycin B via Radical Cyclization

Clive et al. reported the total synthesis of carbazomycin B (**262**) by radical cyclization of the sulfonamide **315c**, followed by deprotection and dehydrogenation.[181] The bromo sulfonamide **314** required for the preparation of the key intermediate **315c** was obtained from the arylamine **284** (Scheme 86). Alkylation of the bromo sulfonamide **314** with 3-bromo-1-cyclohexene gave two conformational isomers of **315a** (ratio: about 3:2). Hydrolysis followed by benzylation of **315a** gave the sulfonamide **315c**. The inseparable mixture of isomers of **315c** was subjected to a radical cyclization with triphenyltin hydride in refluxing benzene, to give the hexahydrocarbazole **316** in 39% yield. Treatment of the hexahydrocarbazole **316** with sodium−naphthalene gave the corresponding hydroxy derivative **318** as a result of deprotection of the *N*-tosylsulfonyl and the *O*-benzyl group. Dehydrogenation with Pd/C provided carba-

Scheme 87



zomycin B (**262**).[181] *O*-Methylation of **262** is known to form carbazomycin A (**261**) (Scheme 86).[146,147,161]

4.4. Total Synthesis of Carbazomycin B by Diels–Alder Reaction of a 3-Vinylindole

Beccali and co-workers reported a synthesis of carbazomycin B (**262**) by a Diels−Alder cycloaddition using the 3-vinylindole **320** as diene, analogous to Pindur's synthesis of 4-deoxycarbazomycin B. The required 3-vinylindole, (*Z*)-ethyl 3-[(1-ethoxycarbonyloxy-2-methoxy)ethenyl]-2-(ethoxycarbonyloxy)indole-1-carboxylate **320**, was synthesized starting from indol-2(3*H*)one **319**.[182] The Diels−Alder reaction of the diene **320** with dimethyl acetylenedicarboxylate (DMAD) gave the tetrasubstituted carbazole **321** in 90% yield. Compound **321** was transformed to the diacid **322** by alkaline hydrolysis. Finally, reduction of the diacid **322** with Red-Al afforded carbazomycin B (**262**) (Scheme 87).[183]

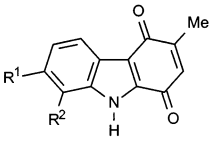
III. Carbazolequinone Alkaloids

The carbazolequinones represent an important family of carbazole alkaloids.[6] They are classified into two subgroups, depending on the position of the quinone moiety in the A-ring of the carbazole nucleus: the carbazole-1,4-quinones, which are combined with the carbazole-1,4-quinols, and the carbazole-3,4-quinones. The 5*H*-benzo[*b*]carbazole-6,11-quinones represent *b*-annulated carbazole-1,4-quinones. However, this class of compounds is covered separately together with the benzoannulated carbazole derivatives (section VI.2.).

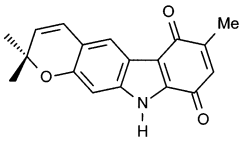
1. Carbazole-1,4-quinone and Carbazole-1,4-quinol Alkaloids

The plants of the genus *Murraya* (Rutaceae) are the major source of carbazole-1,4-quinone alkaloids. In 1983, Furukawa et al. reported the first isolation of a carbazole-1,4-quinone alkaloid, murrayaquinone B (**324**), from the root bark of *M. euchrestifolia* Hayata grown in Taiwan (Scheme 88).[72] In the following years, the same group reported the isolation of various carbazole-1,4-quinone alkaloids such as murrayaquinone A (**323**) and C−E (**325**−**327**) and the pyrayaquinones A−C (**328**−**330**) from the root or the stem bark of the same plant.[72,73,184,185] Among these carbazole-1,4-quinone alkaloids, murrayaquinone A (**323**) has been found to show a cardiotonic activity on the guinea pig papillary muscle.[186] From the biogenetic point of view, it is interesting that a seasonal variation of the carbazolequinone constituents has been observed in *M. euchrestifolia*. Wu et al. isolated and reported the total synthesis of the carbazole-1,4-quinone alkaloid clausenaquinone A (**331**) from the stem bark of *C. excavata*.[187] Clausenaquinone A (**331**) inhibited the growth of tumor cells, like HCT-8, RPMI-7951, and TE-671, with an IC_{50} of 0.92, 0.22, and 3.82 μg/mL and also showed 100 ± 0.8% inhibition of the rabbit platelet aggregation induced by arachidonic acid.[187] Recently, Chowdhury et al. isolated two new carbazole-1,4-quinone alkaloids, koeniginequinone A (**332**) and B (**333**), from the stem bark of *M. koenigii* Spreng.[188] In 1988, Nakamura and his group isolated the antibiotic carbazole alkaloids carbazomycin G (**334**) and H (**335**) (Scheme 88) from *S. ehimense*.[189] They contain the structurally unique carbazole-1,4-quinol substructure.

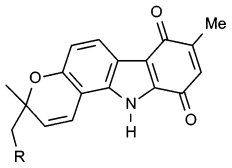
Scheme 88



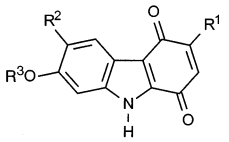
323 Murrayaquinone A
R^1, R^2 = H
324 Murrayaquinone B
R^1 = OMe; R^2 = prenyl
325 Murrayaquinone C
R^1 = OMe; R^2 = geranyl
326 Murrayaquinone D
R^1 = OH; R^2 = geranyl
327 Murrayaquinone E
R^1 = OH; R^2 = prenyl



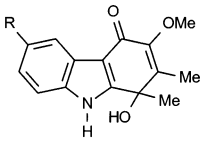
328 Pyrayaquinone A



329 Pyrayaquinone B
R = H
330 Pyrayaquinone C
R = prenyl



331 Clausenaquinone A
R^1= OMe; R^2= Me; R^3= H
332 Koeniginequinone A
R^1, R^3 = Me; R^2= H
333 Koeniginequinone B
R^1, R^3 = Me; R^2= OMe

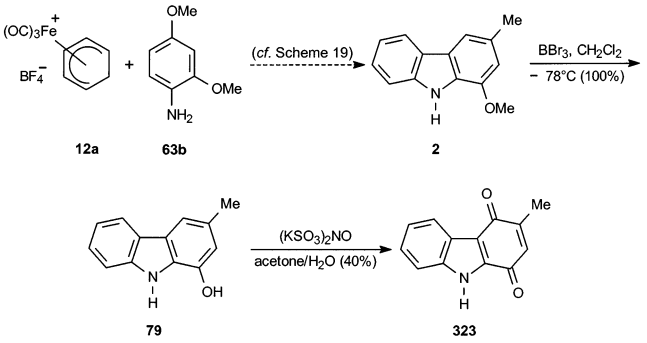


334 Carbazomycin G
R = H
335 Carbazomycin H
R = OMe

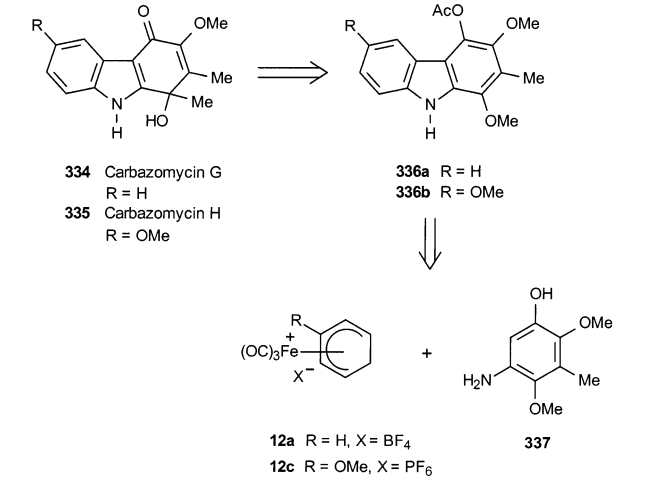
1.1. Iron-Mediated Total Syntheses of Carbazole-1,4-quinones and -quinols

Total Synthesis of Murrayaquinone A. The total synthesis of murrayaquinone A (**323**) was

Scheme 89



Scheme 90



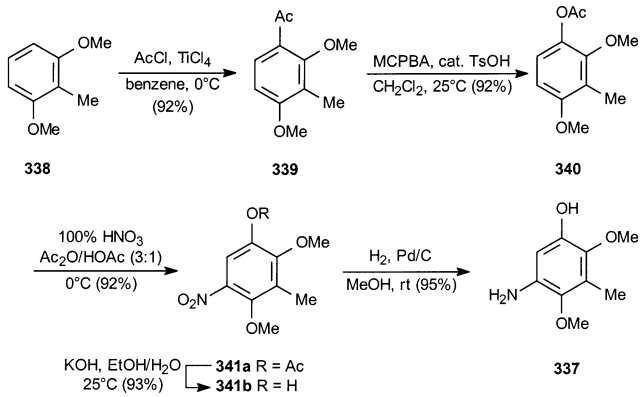
achieved from murrayafoline A (**2**) (see Scheme 19) via the intermediate hydroxycarbazole **79**. Cleavage of the methyl ether in murrayafoline A (**2**) and subsequent oxidation of the resulting 1-hydroxy-3-methyl-9*H*-carbazole **79** with Fremy's salt provided murrayaquinone A (**323**) in 40% yield over two steps (Scheme 89).[86]

Total Synthesis Carbazomycin G and H. The total synthesis of the carbazomycins G (**334**) and H (**335**) based on the iron-mediated approach proceeds via the *O*-acetylcarbazoles **336** as synthetic precursors, which are derived from the iron complex salts **12** and the arylamine **337** (Scheme 90).

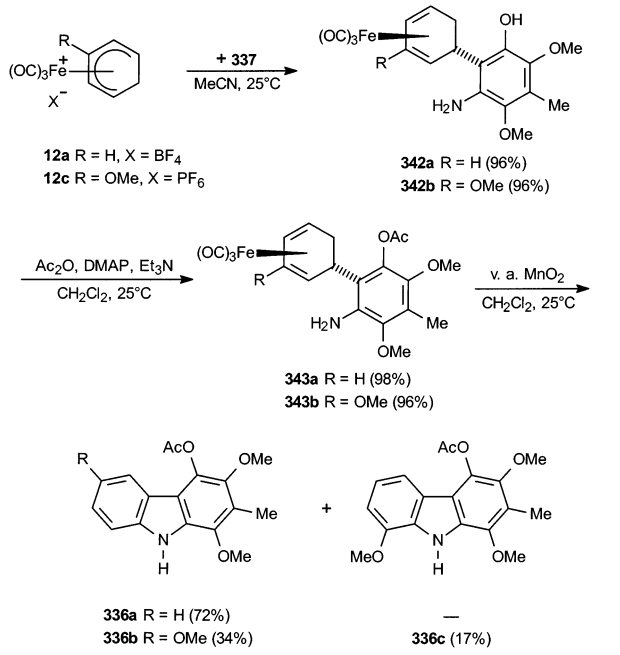
The required arylamine **337** was prepared starting from commercial 2,6-dimethoxytoluene **338**. The titanium tetrachloride-promoted Friedel−Crafts acylation afforded the acetophenone **339**, which was transformed into the acetate **340** by a proton-catalyzed Baeyer−Villiger oxidation. Nitration of **340** with fuming nitric acid in a mixture of acetic anhydride and glacial acetic acid (3:1) gave the 5-nitro derivative **341a**. Finally, ester clevage to the phenol **341b** and catalytic hydrogenation afforded the arylamine **337** (Scheme 91). This route provides the arylamine **337** in five steps and 69% overall yield on a multigram scale.

The reaction of the iron complex salts **12** with the arylamine **337** afforded the iron complexes **342a** and **342b** in 96% yield each. Subsequent *O*-acetylation provided the corresponding acetates **343a** and **343b**. The iron-mediated arylamine cyclization of the *O*-acetyl derivative **343a** using very active manganese

Scheme 91



Scheme 92



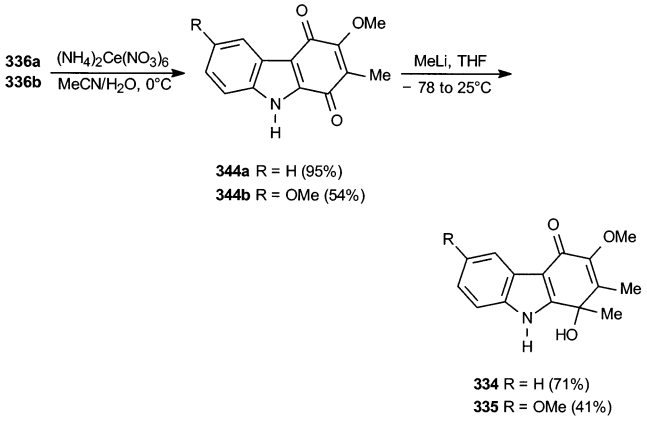
dioxide provided the carbazole **336a** in 72% yield. Under the same reaction conditions, the *O*-acetyl derivative **343b** gave a mixture of the carbazoles **336b** and **336c** in 34% and 17% yield, respectively (Scheme 92).

The oxidation of the *O*-acetylcarbazole derivatives **336a** and **336b** with ceric ammonium nitrate (CAN) to the carbazole-1,4-diones **344** followed by addition of methyllithium afforded carbazomycin G (**334**) and H (**335**) (Scheme 93).[190] The iron-mediated synthesis provides carbazomycin G (**334**) (overall yield: 46%) and H (**335**) (overall yield: 7%) in five steps based on the iron complex salts **12a** and **12c**.

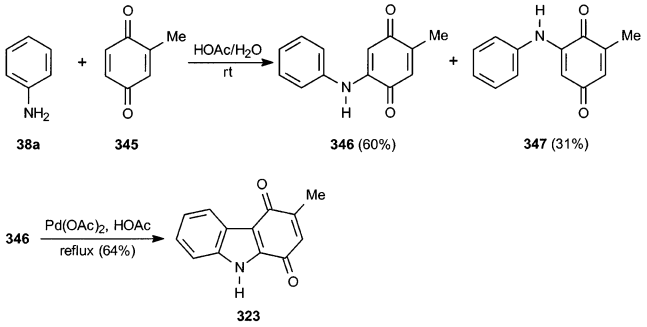
1.2. Palladium-Mediated Total Syntheses of Carbazole-1,4-quinones

Total Synthesis of Murrayaquinone A, Pyrayaquinone A, and Pyrayaquinone B. Furukawa et al. reported the total synthesis of murrayaquinone A (**323**) and pyrayaquinone A (**328**) and B (**329**) by a palladium-mediated oxidative cyclization of the corresponding 2-arylamino-5-methyl-1,4-benzoquinones. 2-Anilino-5-methyl-1,4-benzoquinone **346** was prepared starting from 2-methyl-1,4-benzoquinone **345**

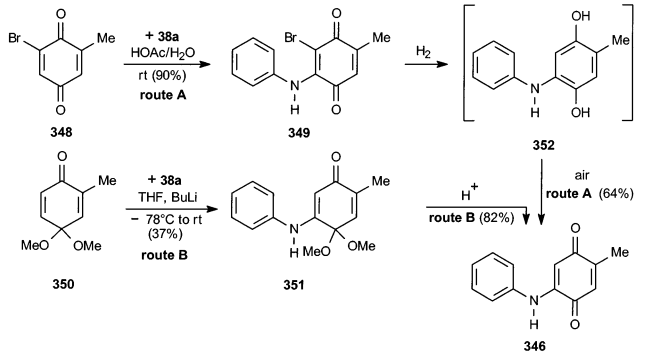
Scheme 93



Scheme 94



Scheme 95

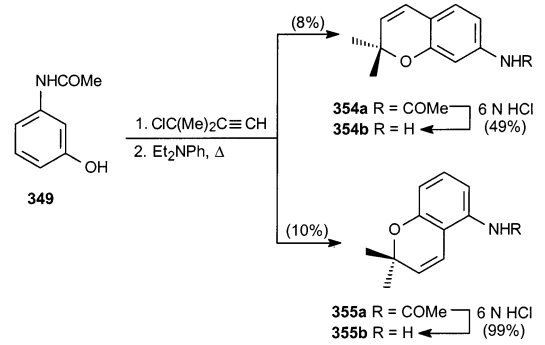


and aniline **38a** along with the regioisomeric 2-anilino-6-methyl-1,4-benzoquinone **347**. The oxidative cyclization of 2-anilino-5-methyl-1,4-benzoquinone **346** with stoichiometric amounts of palladium(II) acetate provided murrayaquinone A (**323**) in 64% yield (Scheme 94).[191]

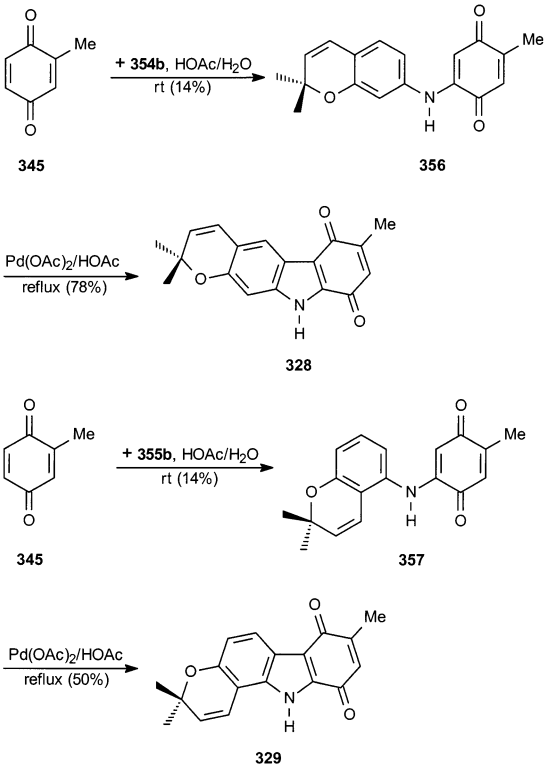
An alternative synthesis of 2-anilino-5-methyl-1,4-benzoquinone **346** was developed by using 2-bromo-6-methyl-1,4-benzoquinone **348** (route A) and 4,4-dimethoxy-2-methylcyclohexa-2,5-dienone **350** (route B) as synthetic equivalents for methyl-1,4-benzoquinone **345** (Scheme 95).

Subsequently, the palladium-mediated oxidative cyclization was applied to the total synthesis of pyrayaquinone A (**328**) and B (**329**). The starting materials, 7-amino- (**354b**) and 5-amino-2,2-dimethyl-2*H*-chromene (**355b**) were synthesized from acetamidophenol **349** and 3-chloro-3,3-dimethyl-1-butyne via etherification and Claisen rearrangement followed by hydrolysis (Scheme 96).[192]

Scheme 96



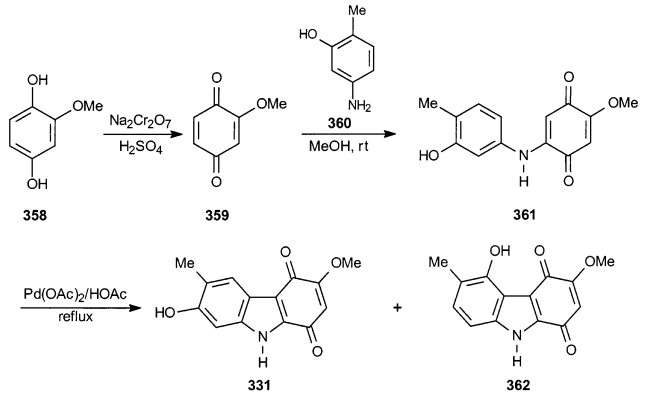
Scheme 97



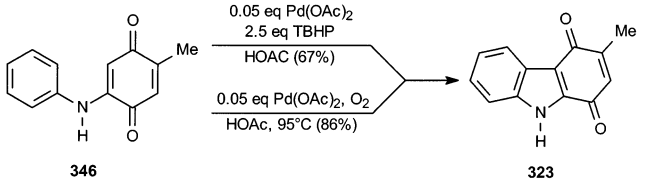
Condensation of the aminochromenes **354b** and **355b** with 2-methyl-1,4-benzoquinone **345** gave 2-(2,2-dimethyl-2*H*-chromen-7-ylamino)- (**356**) and 2-(2,2-dimethyl-2*H*-chromen-5-ylamino)-5-methyl-1,4-benzoquinone (**357**) along with the corresponding 6-methyl isomers. Treatment of the benzoquinones **356** and **357** with stoichiometric amounts of palladium(II) acetate in acetic acid under reflux furnished pyrayaquinone A (**328**) and B (**329**) in 78 and 50% yield, respectively (Scheme 97).[191]

Total Synthesis of Clausenaquinone A. Wu et al. reported the total synthesis of clausenaquinone A (**331**) using a palladium(II)-mediated oxidative cyclization of the 2-arylamino-5-methoxy-1,4-benzoquinone **361**. However, the oxidative cyclization as the key step of this synthesis is nonregioselective. Consequently, equimolar amounts of clausenaquinone A (**331**) and its regioisomer **362** are provided. The reaction of 5-amino *o*-cresol **360** with 2-methoxy-1,4-benzoquinone **359** (prepared by oxidation of methoxyhydroquinone **358**) afforded 2-(3-hydroxy-4-methylanilino)-5-methoxy-1,4-benzoquinone **361**. Cycli-

Scheme 98



Scheme 99



zation of the 2-arylamino-5-methoxy-1,4-benzoquinone **361** with palladium(II) acetate in acetic acid under reflux provided clausenaquinone A (**331**) and the regioisomeric product **362** in a 1:1 ratio (Scheme 98).[187]

1.3. Palladium-Catalyzed Total Syntheses of Carbazole-1,4-quinones and -quinols

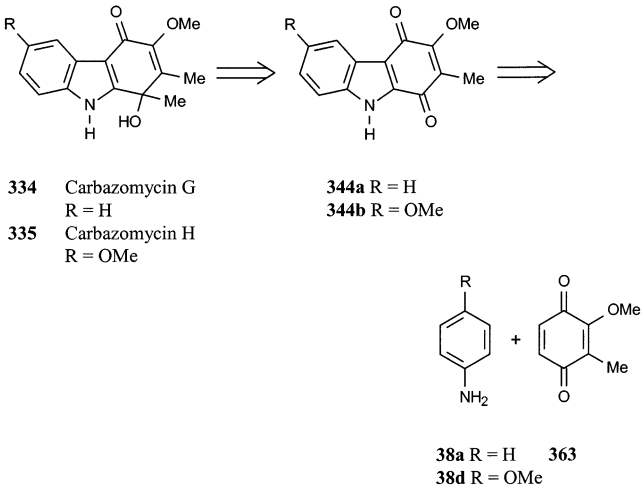
Total Synthesis of Murrayaquinone A. Åkermark et al. applied a catalytic version of the palladium-mediated (stoichiometric) cyclization of 2-anilino-5-methyl-1,4-benzoquinone **346** described by Furukawa (see Scheme 94)[191] to the total synthesis of murrayaquinone A (**323**). For this cyclization, only 5 mol % of palladium(II) acetate and an excess of *tert*-butyl hydroperoxide (TBHP) as oxidant were used (Scheme 99).[193] Subsequently, a catalytic cyclization of **346** to murrayaquinone A (**323**) using oxygen for the reoxidation of palladium was reported (Scheme 99).[194]

Total Synthesis of Carbazomycin G and H. The retrosynthetic analysis of the carbazomycins G (**334**) and H (**335**) based on a palladium-catalyzed approach leads to the carbazole-1,4-quinones **344** as precursors (compare the iron-mediated synthesis, Scheme 93). These intermediates should derive by oxidative cyclization of the arylamino-1,4-benzoquinones, which in turn are prepared from the arylamines **38** (**a**, aniline; **d**, *p*-anisidine) and 2-methoxy-3-methyl-1,4-benzoquinone **363** (Scheme 100).

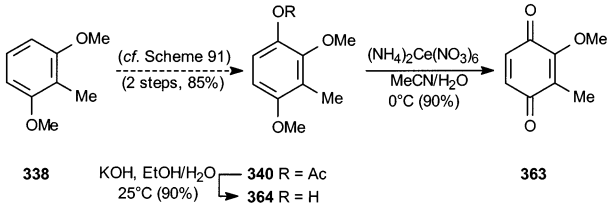
The required 2-methoxy-3-methyl-1,4-benzoquinone **363**[195,196] was obtained from the aryl acetate **340** (Scheme 91) by ester cleavage to the phenol **364** and oxidation with ceric ammonium nitrate in 81% overall yield (Scheme 101).

Addition of 0.5 equiv of the arylamines **38a** and **38d** to the 1,4-benzoquinone **363** provided the corresponding 5-(arylamino)-2-methoxy-3-methyl-1,4-benzoquinones **365a**,**b** with the expected regioselectivity. The oxidative cyclization of the benzoquinones

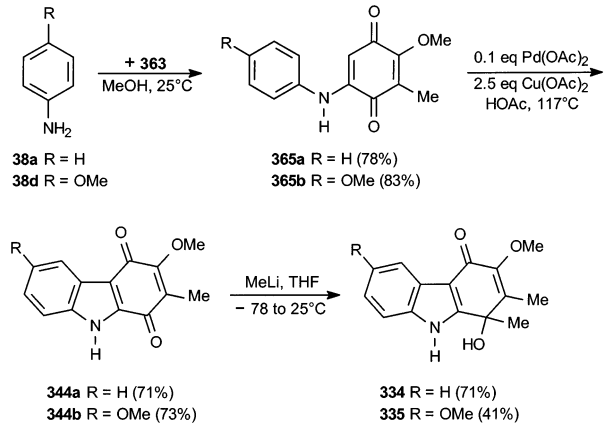
Scheme 100



Scheme 101



Scheme 102



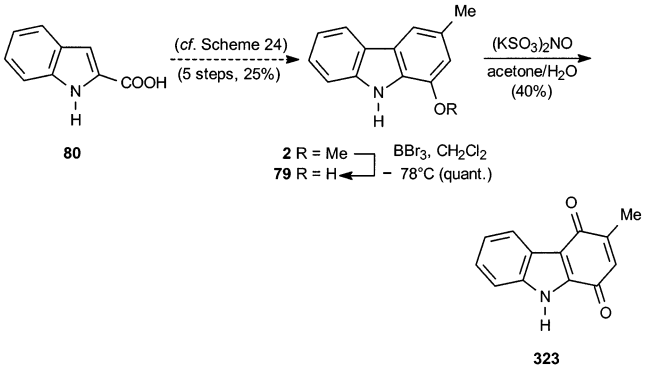
365a,**b** with 10 mol % of palladium(II) acetate in the presence of copper(II) acetate in the air furnished the carbazole-1,4-quinones **344a**,**b**. Regioselective addition of methyllithium to the carbazole-1,4-quinones **344a**,**b** afforded carbazomycin G (**334**) and H (**335**) (Scheme 102).[197] A more recent total synthesis of carbazomycin G is described in section XI.1.

1.4. Total Synthesis of Murrayaquinone A and B by Intramolecular Electrophilic Substitution

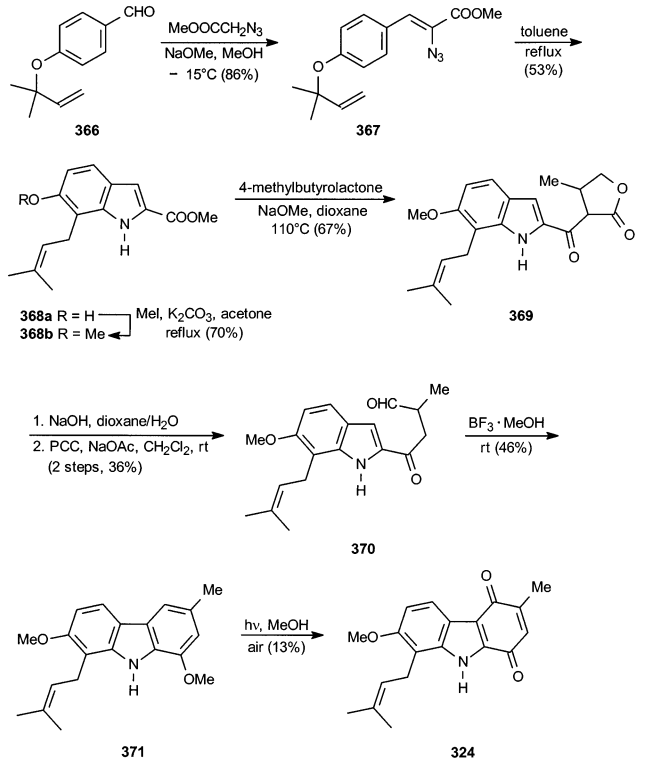
Moody et al. reported the total synthesis of murrayaquinone A (**323**) starting from murrayafoline A (**2**) (see Scheme 24). The demethylation of murrayafoline A (**2**) with boron tribromide in dichloromethane gave the 1-hydroxycarbazole **79** in quantitative yield. Oxidation with Fremy's salt provided murrayaquinone A (**323**) in 40% yield (Scheme 103).[92]

The overall approach for the total synthesis of murrayaquinone B (**324**) is similar to that of murrayaquinone A (**323**) (see Schemes 24 and 103).

Scheme 103



Scheme 104

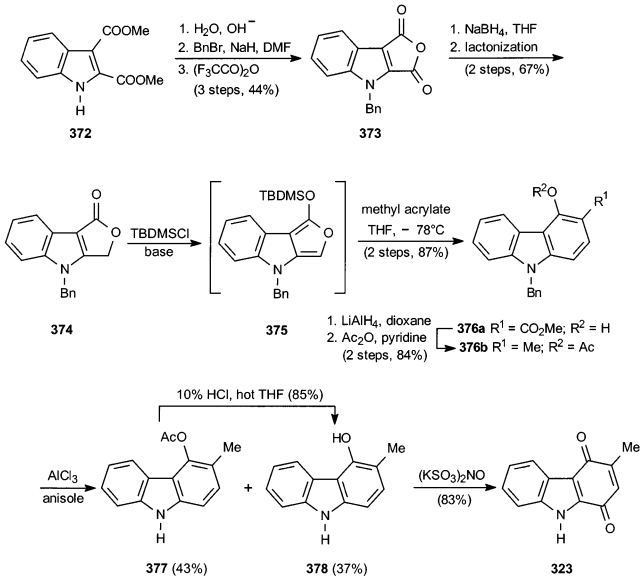


However, the transformation of the 1-methoxycarbazole **371** to murrayaquinone B (**324**) was achieved by a photooxidation due to the problems associated with the regioselective demethylation of the methoxy group at the A-ring. The 1-methoxycarbazole **371** was prepared from 4-(1,1-dimethylallyloxy)benzaldehyde **366** and methyl azidoacetate by the synthesis shown in Scheme 104. This reaction sequence involves a regioselective Claisen rearrangement to give the 7-(3-methylbut-2-enyl)indole **368a**,[198,199] transformation to the aldehyde **370** via the lactone **369**, and formation of the A-ring by a Lewis acid-promoted cyclization. Finally, the direct photooxidation by irradiation of a solution of the 1-methoxycarbazole **371** in methanol in the presence of air provided murrayaquinone B (**324**) in 13% yield (Scheme 104).[200,201]

1.5. Total Synthesis of Murrayaquinone A by Diels–Alder Reaction of a 4H-Furo[3,4-b]indole

Miki et al. reported a total synthesis of murrayaquinone A (**323**) using 4-benzyl-1-*tert*-butyldimethylsiloxy-4*H*-furo[3,4-*b*]indole **375** as an indolo-2,3-quinodimethane equivalent for the cycloaddition reaction with methyl acrylate. 4-Benzyl-3,4-dihydro-1*H*-furo[3,4-*b*]indol-1-one (**374**), the precursor for the 4*H*-furo[3,4-*b*]indole **375**, was prepared in five steps and 30% overall yield starting from dimethyl indole-2,3-dicarboxylate **372**. Alkaline hydrolysis of **372**, *N*-benzylation of the corresponding dicarboxylic acid with benzyl bromide and sodium hydride in DMF, and treatment of the resulting 1-benzylindole-2,3-dicarboxylic acid with trifluoroacetic anhydride gave the anhydride **373**. Reduction followed by lactonization transformed the anhydride **373** to the lactone **374** (Scheme 105).

Scheme 105

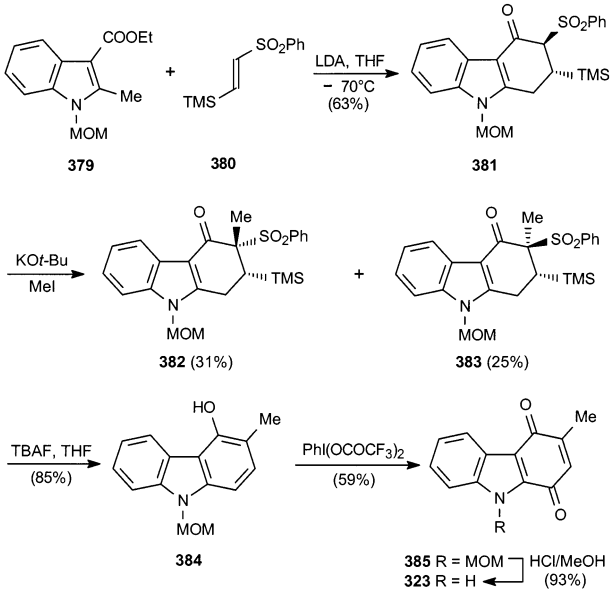


The lactone **374** was transformed to 4-benzyl-1-*tert*-butyldimethylsiloxy-4*H*-furo[3,4-*b*]indole **375** by a base-induced silylation. Without isolation, **375** was treated with methyl acrylate to give the carbazole **376a** with the required regioselectivity. After reduction of the carbazole **376a** with lithium aluminum hydride, the corresponding 3-methylcarbazole was acetylated to give 4-acetoxy-9-benzyl-3-methylcarbazole **376b**. Treatment of **376b** with aluminum trichloride in anisole afforded a mixture of the debenzylated carbazoles **377** and **378** in 43% and 37% yield, respectively. However, by deacetylation with 10% hydrochloric acid compound **377** was converted to 4-hydroxy-3-methylcarbazole **378**. The oxidation of **378** with Fremy's salt provided murrayaquinone A (**323**) in 83% yield (Scheme 105).[202]

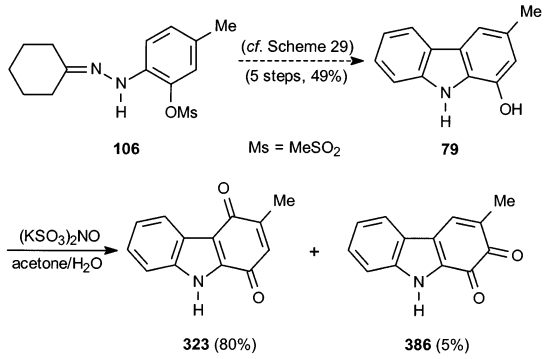
1.6. Total Synthesis of Murrayaquinone A by Anionic [4 + 2] Cycloaddition

Hanaoka et al. reported a total synthesis of murrayaquinone A (**323**) based on an anionic [4 + 2]-cycloaddition of the indole ester **379** with phenyl β-trimethylsilylvinyl sulfone **380**. The reaction of the MOM-protected indole **379** with phenyl β-trimethylsilylvinyl sulfone **380** in the presence of LDA gave the cycloadduct **381** with the desired regioselectivity. Methylation of **381** with methyl iodide in the presence of potassium *tert*-butoxide gave the two dia-

Scheme 106



Scheme 107



stereoisomers **382** and **383** in 31% and 25% yield, respectively. This mixture was treated with tetrabutylammonium fluoride (TBAF) in THF to afford the 4-hydroxycarbazole **384** in 85% yield. Oxidation of **384** with [bis(trifluoroacetoxy)iodo]benzene gave the carbazole-1,4-quinone **385**, which on removal of the methoxymethyl group with hydrochloric acid in methanol provided murrayaquinone A (**323**) in 93% yield (Scheme 106).[203]

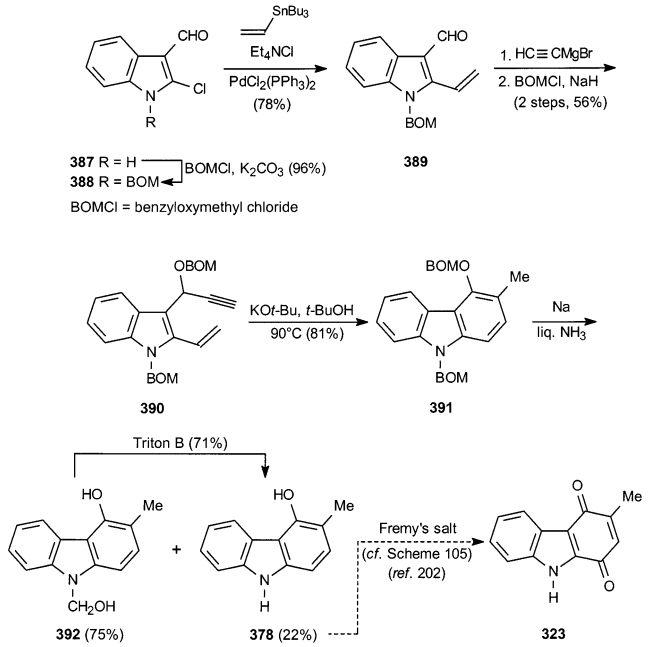
1.7. Total Synthesis of Murrayaquinone A by Fischer Indolization

Murakami et al. described a total synthesis of murrayaquinone A (**323**) via the Fischer indolization of the 2-methanesulfonyloxyphenylhydrazone **106** (see Scheme 29). The oxidation of 1-hydroxy-3-methylcarbazole **79** with Fremy's salt afforded murrayaquinone A (**323**) as the major product (80% yield) along with the isomeric carbazole-1,2-quinone **386** in 5% yield (Scheme 107).[97]

1.8. Formal Synthesis of Murrayaquinone A by Benzannulation of Indole

Hibino et al. reported a formal synthesis of murrayaquinone A (**323**) from 2-chloro-3-formylindole **387** by an electrocyclization involving an intermediate allene, a 2-vinyl substituent, and the indole 2,3-

Scheme 108



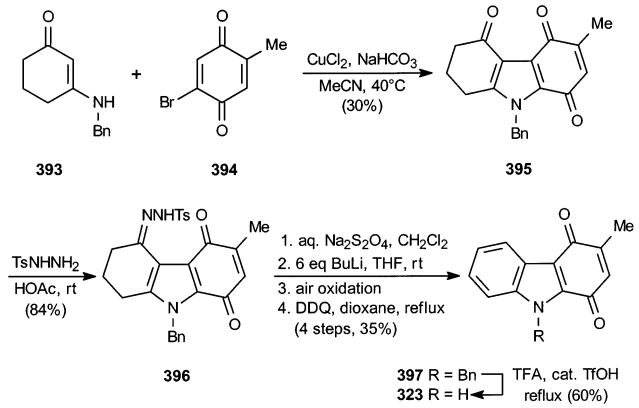
bond. The 2-ethenyl-3-propargylindole **390**, a precursor of the intermediate hexatriene system for the electrocyclization, was prepared from 2-chloro-3-formylindole **387** in five steps (Scheme 108). The key step in this sequence is the palladium(0)-catalyzed cross-coupling reaction of the *N*-BOM-indole **388** with tributylvinyltin to give the 3-formyl-2-vinylindole **389**. Addition of ethynylmagnesium bromide to compound **389**, followed by treatment with benzyloxymethyl chloride (BOMCl), afforded the 2-ethenyl-3-propargylindole **390**.

The thermal electrocyclization of compound **390** in the presence of potassium *tert*-butoxide (KO*t*-Bu) at 90 °C provided the 3-methyl-4-oxycarbazole **391** in 81% yield. Deprotection of **391** under Birch reaction conditions gave a mixture of *N*-hydroxymethyl-4-hydroxy-3-methylcarbazole **392** and 4-hydroxy-3-methylcarbazole **378** in 75% and 22% yield, respectively. However, **392** was transformed to **378** with Triton B in a yield of 71% (Scheme 108).[204] The carbazole **378** represents a known precursor for murrayaquinone A (**323**) (see Scheme 105).[202]

1.9. Total Synthesis of Murrayaquinone A by Bromoquinone–Enaminone Annulation

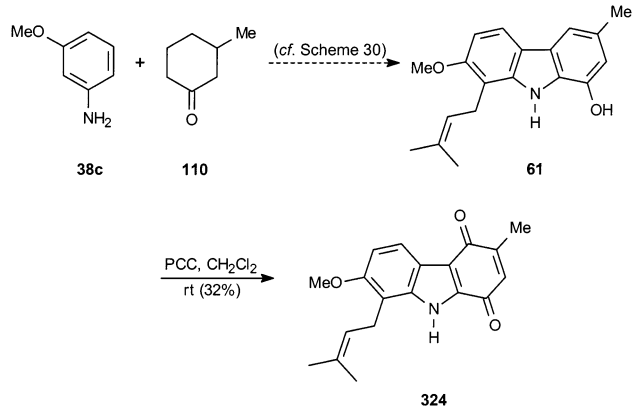
Murphy et al. developed a new annulation route for the total synthesis of murrayaquinone A (**323**) starting from the *N*-benzylenaminone **393** and 5-bromo-2-methyl-1,4-benzoquinone **394**. For the aromatization of the C-ring they applied the Shapiro deoxygenation−olefination reaction.[205] The annulation reaction of **393** and **394** involving Michael addition, followed by in situ reoxidation and dehalocyclization, provided the hexahydrocarbazoletrione **395** in 30% yield. Compound **395** was transformed to *N*-benzylmurrayaquinone A (**397**) using Shapiro's deoxygenation−olefination and subsequent dehydrogenation with DDQ (29% overall yield). Finally, debenzylation of **397** with trifluoroacetic acid and

Scheme 109



393 394 395 396 397 323

Scheme 110



38c 110 61 324

traces of trifluoromethanesulfonic acid afforded murrayaquinone A (**323**) (Scheme 109).[206]

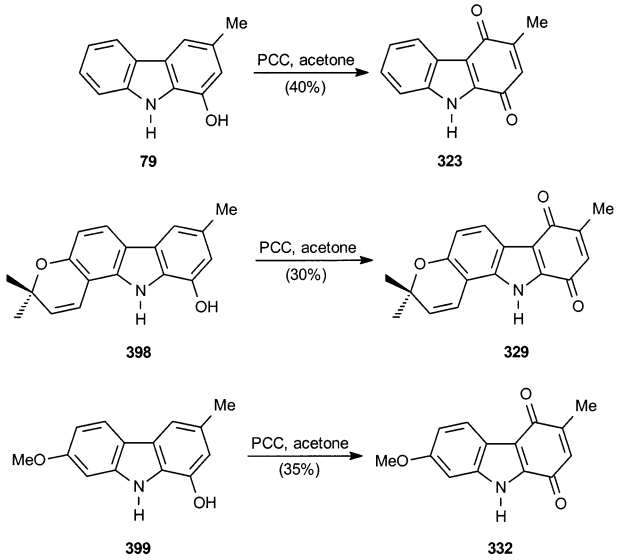
1.10. Fischer Indolization of Phenylhydrazones

Total Synthesis of Murrayaquinone A and B, Pyrayaquinone A and B, and Koeniginequinone A. In 1986, Ramesh and Kapil reported a total synthesis of murrayaquinone B (**324**) by oxidation of murrayafoline B (**61**) with pyridinium chlorochromate (PCC) (Scheme 110).[99] Murrayafoline B (**324**) was synthesized by using the Japp−Klingemann reaction and Fischer indolization as key steps starting from 3-methoxyaniline **38c** and 3-methylcyclohexanone **110** (see Scheme 30).[98,99]

The same procedure was applied to the total synthesis of murrayaquinone A (**323**), pyrayaquinone B (**329**), and 7-methoxy-3-methylcarbazole-1,4-quinone (**332**) starting from the corresponding hydroxycarbazole derivatives **79**,[96] **398**, and **399**[99] (Scheme 111).[207] In 1998, Chowdhury et al. reported the isolation of 7-methoxy-3-methylcarbazole-1,4-quinone **332** from the stem bark of *M. koenigii* and named it koeniginequinone A.[188]

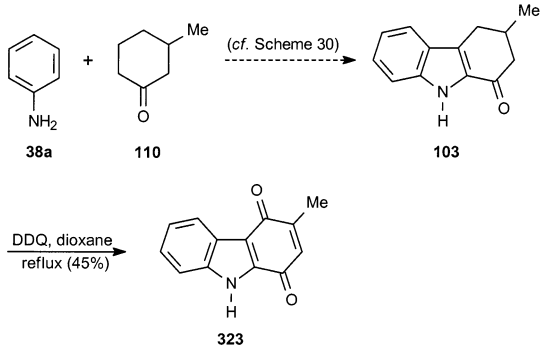
In another approach, Ramesh and Kapil described the total synthesis of murrayaquinone A (**323**), pyrayaquinone A (**328**), pyrayaquinone B (**329**), and koeniginequinone A (**332**) by a direct oxidation of the corresponding 1-oxo-1,2,3,4-tetrahydrocarbazoles **103**, **400**, **401**, and **111** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dioxane under reflux (Schemes 112 and 113). For the synthesis of murrayaquinone A (**323**) the required 1-oxo-1,2,3,4-tetrahydrocarba-

Scheme 111



79 323 398 329 399 332

Scheme 112



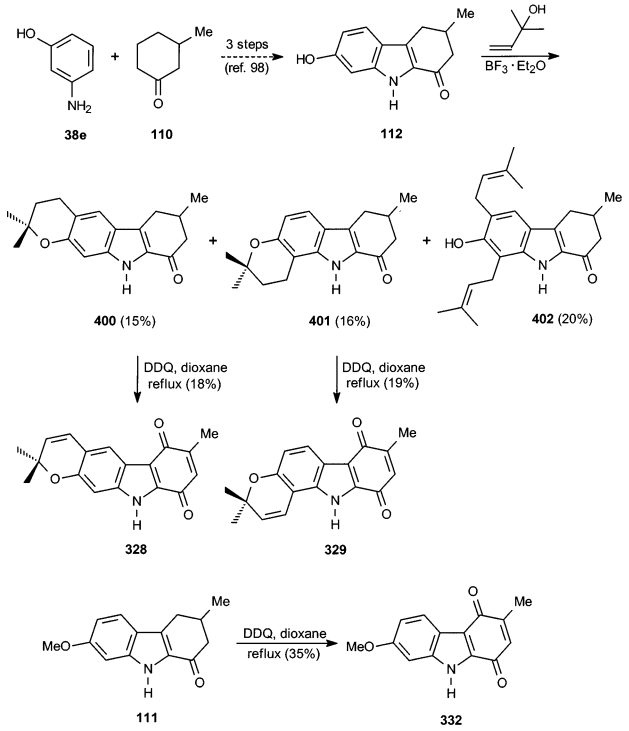
38a 110 103 323

zole **103** was obtained from aniline **38a** and 2-methylcyclohexanone **110** in three steps by Japp−Klingemann reaction and Fischer cyclization (see Scheme 28).[98] The oxidation of the tetrahydrocarbazole **103** with DDQ provided directly murrayaquinone A (**323**) in 45% yield (Scheme 112).[208]

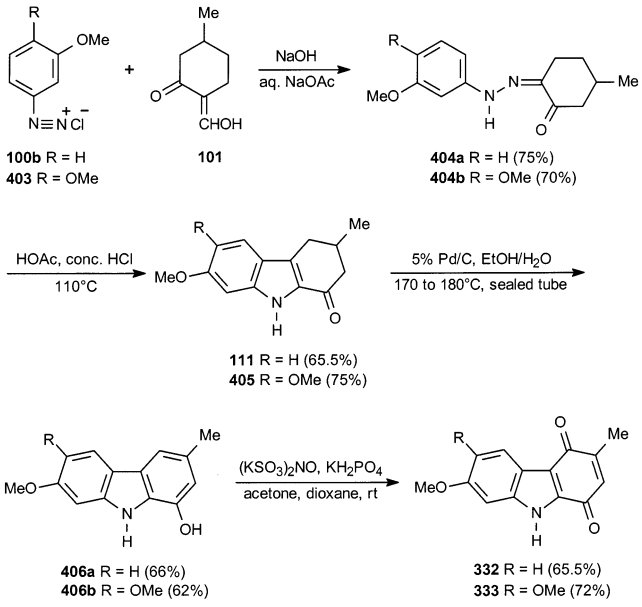
7-Hydroxy-3-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole **112**, the key intermediate for the total synthesis of the pyrayaquinones A (**328**) and B (**329**), was obtained from 3-hydroxyaniline **38e** and 3-methylcyclohexanone **110** by Japp−Klingemann and Fischer reactions (Scheme 113). The annulation of the pyran ring at the C-ring of the tetrahydrocarbazole **112** by reaction with 3-methyl-1-buten-3-ol in the presence of boron trifluoride afforded the regioisomeric pyranocarbazoles **400** and **401**. Oxidation of **400** and **401** with DDQ afforded pyrayaquinone A (**328**) and B (**329**) in 18% and 19% yield, respectively. Starting from 7-methoxy-3-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole **111**, this method was used for the synthesis of koeniginequinone A (**332**) in 35% yield (Scheme 113).[208]

Total Synthesis of Koeniginequinone A and B. In 1998, Saha and Chowdhury have confirmed the structures assigned for koeniginequinone A (**332**) and B (**333**) by synthesis using a Fischer indolization of the corresponding phenylhydrazones **404** as the key step. The phenylhydrazones **404** were obtained by a Japp−Klingemann reaction of 2-hydroxymethylene-

Scheme 113



Scheme 114

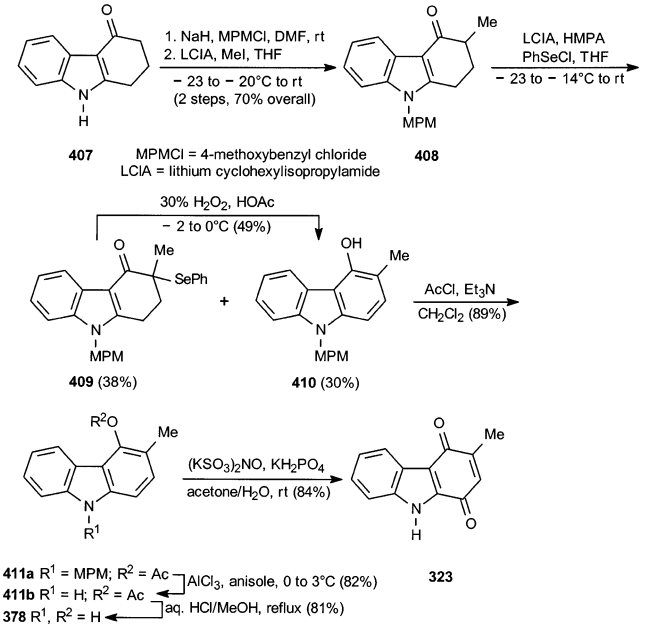


5-methylcyclohexanone **101** and the aryldiazonium chlorides **100b** and **403**, respectively. Aromatization of the 1-oxotetrahydrocarbazoles **111** and **405** with 5% palladium on charcoal at 170−180°C in a sealed tube afforded the 1-hydroxycarbazoles **406**. Finally, oxidation of the 1-hydroxycarbazoles **406** with potassium nitrosodisulfonate (Fremy's salt) provided koeniginequinone A (**332**) and B (**333**) in 65.5% and 72% yield, respectively (Scheme 114).[188]

1.11. Total Synthesis of Murrayaquinone A from 1,2,3,4-Tetrahydrocarbazol-4(9H)-one

Matsuo and Ishida reported the total synthesis of murrayaquinone A (**323**) starting from 1,2,3,4-tetrahydrocarbazol-4(9*H*)-one **407**, which can be prepared by several known literature methods.[209−212] After protection of the tetrahydrocarbazolone **407** at the 1-position, the methylation at C-3 was achieved by deprotonation with lithium cyclohexylisopropylamide (LCIA). To introduce the 2,3-double bond, the enone **408** was successively treated with LCIA and phenylselenenyl chloride in the presence of HMPA to give a mixture of the phenylselenenylated compound **409** and the aromatized product **410** in 38% and 30% yield, respectively. Compound **409** was converted to the fully aromatic compound **410** by treatment with peracetic acid. Oxidation of **410** with Fremy's salt led to the corresponding quinone in good yield; however, all attempts to remove the *N*-protecting group of this quinone intermediate failed. Therefore, the 4-hydroxy group was protected by acetylation to **411a** prior to the deprotection of the nitrogen atom, which gave compound **411b**. Finally, hydrolysis of the ester group to 4-hydroxy-3-methylcarbazole **378** and oxidation with Fremy's salt afforded murrayaquinone A (**323**) (Scheme 115).[213]

Scheme 115



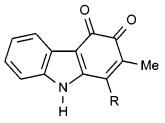
More recently, Chowdhury et al. achieved the synthesis of murrayaquinone A (**323**) by direct photochemical oxidation of 3-methylcarbazole in a solution of methanol using UV light at 254 nm (24% yield).[214] Previous reviews on the isolation and the total synthesis of natural carbazole-1,4-quinones were published in 1994 by Furukawa[215] and more recently by Fillion.[216]

2. Carbazole-3,4-quinone Alkaloids

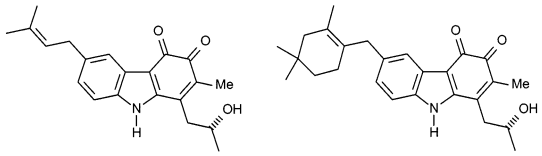
In the past decade, Seto and his group isolated a series of unprecedented carbazole-3,4-quinone alkaloids from different *Streptomyces* species, among them the carbazoquinocins A−F (**412**−**417**), carquinostatin A [(*R*)-**418**], and lavanduquinocin [(*R*)-**419**] (Scheme 116). These compounds are structurally unique because they represent the first carbazole alkaloids containing an *o*-benzoquinone system.

The first example of a carbazole-3,4-quinone alkaloid was carquinostatin A [(*R*)-**418**], isolated in 1993

Scheme 116

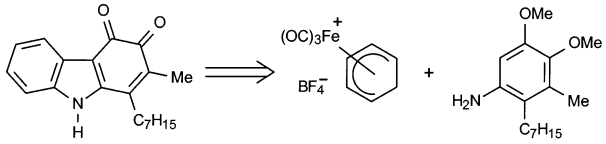


412 Carbazoquinocin A
R = $(CH_2)_2CH(Me)CH_2Me$
413 Carbazoquinocin B
R = $(CH_2)_4CH(Me)_2$
414 Carbazoquinocin C
R = $(CH_2)_6Me$
415 Carbazoquinocin D
R = $(CH_2)_4CH(Me)CH_2Me$
416 Carbazoquinocin E
R = $(CH_2)_5CH(Me)_2$
417 Carbazoquinocin F
R = $(CH_2)_6CH(Me)_2$



(*R*)-**418** Carquinostatin A (*R*)-**419** Lavanduquinocin

Scheme 117



414 Carbazoquinocin C **12a** **420**

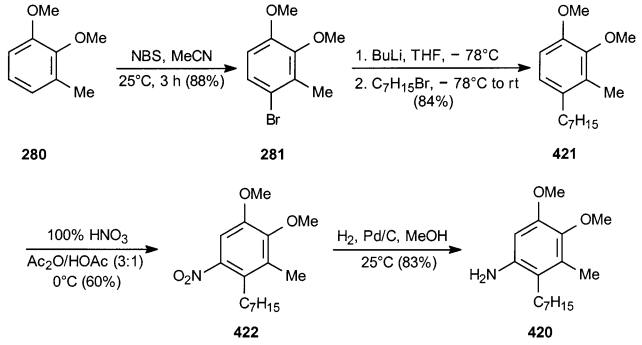
from *Streptomyces exfoliatus* 2419-SVT2. This natural product was shown to be a potent neuronal protecting substance that also exhibits a free radical scavenging activity.[217] Two years later, lavanduquinocin [(*R*)-**419**], a structurally intriguing carbazole-3,4-quinone alkaloid that has a monoterpenoidal β-cyclolavandulyl side chain in the 6-position of the carbazole nucleus and exhibits a strong neuronal cell protecting activity, was isolated from *Streptomyces viridochromogens* 2941-SVS3.[218] In the same year, the carbazoquinocins A−F (**412**−**417**) were isolated from *Streptomyces violaceus* 2448-SVT2. The carbazoquinocins have a strong inhibitory activity against lipid peroxidation.[219]

2.1. Iron-Mediated Total Synthesis of Carbazole-3,4-quinones

For the iron-mediated total synthesis of carbazoquinocin C (**414**) the iron complex salt **12a** and the arylamine **420** were required as precursors (Scheme 117).

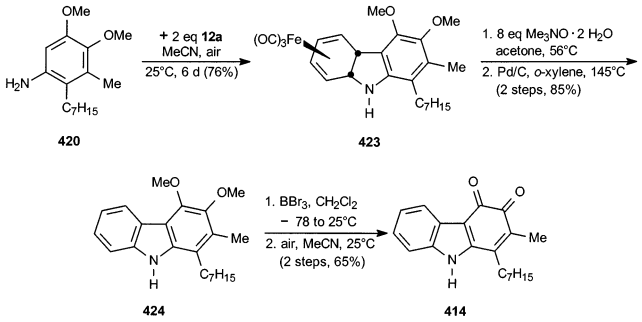
The arylamine **420** was prepared starting from commercial 3-methylveratrole (**280**). Regioselective bromination of the veratrole **280** afforded the 4-bromo derivative **281** in 88% yield. Halogen/metal exchange using butyllithium, followed by alkylation with 1-bromoheptane, provided the 4-heptyl derivative **421**. Regioselective nitration of **421** with fuming nitric acid in a mixture of acetic anhydride and glacial acetic acid (3:1) gave the 5-nitro derivative **422** in 60% yield. A catalytic hydrogenation of the 5-nitro derivative **422** led to the arylamine **420** in 83% yield

Scheme 118



280 **281** **421** **422** **420**

Scheme 119



420 **423** **424** **414**

(Scheme 118).[220] This sequence provided the arylamine **420** in four steps and 37% overall yield.

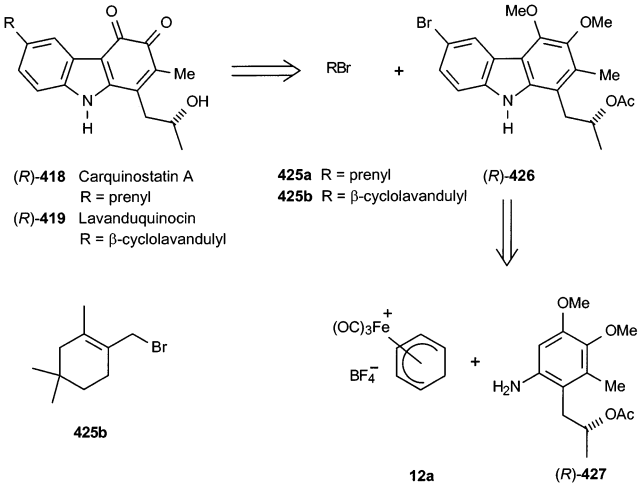
The reaction of the iron complex salt **12a** with the arylamine **420** in the air led directly to the tricarbonyl(η^4-4a,9a-dihydro-9*H*-carbazole)iron complex **423** by a one-pot C−C and C−N bond formation. Demetalation of complex **423** and subsequent aromatization by catalytic dehydrogenation afforded the 3,4-dimethoxycarbazole **424**, a protected carbazoquinocin C. Finally, ether cleavage followed by oxidation in air provided carbazoquinocin C (**414**) (Scheme 119).[220] This synthesis provides carbazoquinocin C (**414**) in five steps and 42% overall yield based on **12a**.

The one-pot C−C and C−N bond formation was subsequently applied to the synthesis of the bromocarbazole **426**, a common precursor of the carbazole-3,4-quinone alkaloids (±)-carquinostatin A [(±)-**418**][221] and (±)-lavanduquinocin [(±)-**419**].[222] More recently, the same methodology was used for the first enantioselective total synthesis of carquinostatin A [(*R*)-**418**] and lavanduquinocin [(*R*)-**419**]. The precursors required for the enantioselective total synthesis of carquinostatin A [(*R*)-**418**] and lavanduquinocin [(*R*)-**419**] are the (*R*)-arylamine (*R*)-**427** and the iron complex salt **12a** (Scheme 120).

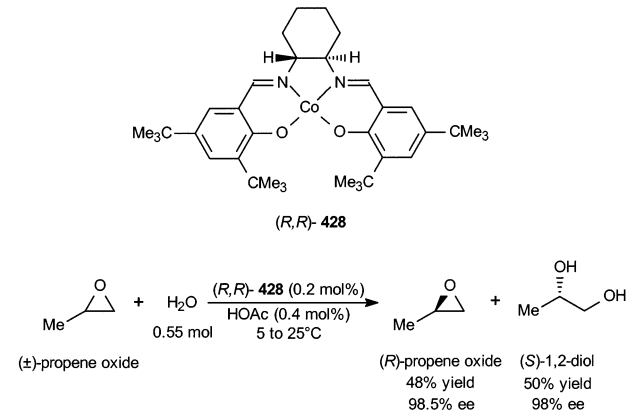
The chiral side chain of the (*R*)-arylamine (*R*)-**427** was derived from (*R*)-propene oxide, which was obtained by Jacobsen's hydrolytic kinetic resolution (HKR) of racemic propene oxide using the (*R,R*)-(Salen)cobalt(II) complex (*R,R*)-**428** (Scheme 121).[223,224]

The (*R*)-arylamine (*R*)-**427** was obtained from commercial 3-methylveratrole **280** in five steps and 59% overall yield. The regioselective bromination of 3-methylveratrole **280** gave the 4-bromo derivative **281** almost quantitatively. Halogen/metal exchange using butyllithium followed by reaction with the (*R*)-propene oxide afforded the (*R*)-carbinol (*R*)-**429a**. Protec-

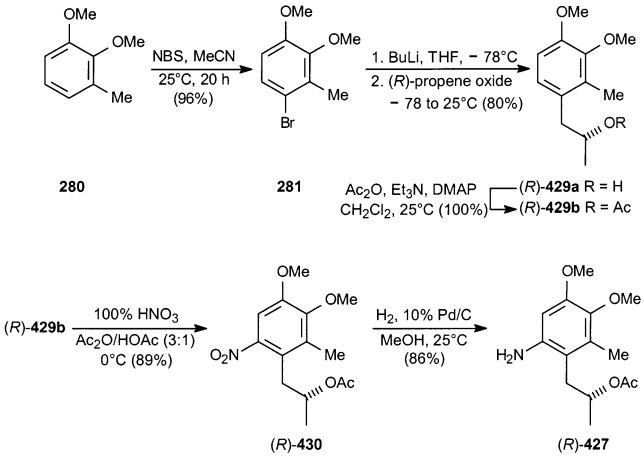
Scheme 120



Scheme 121



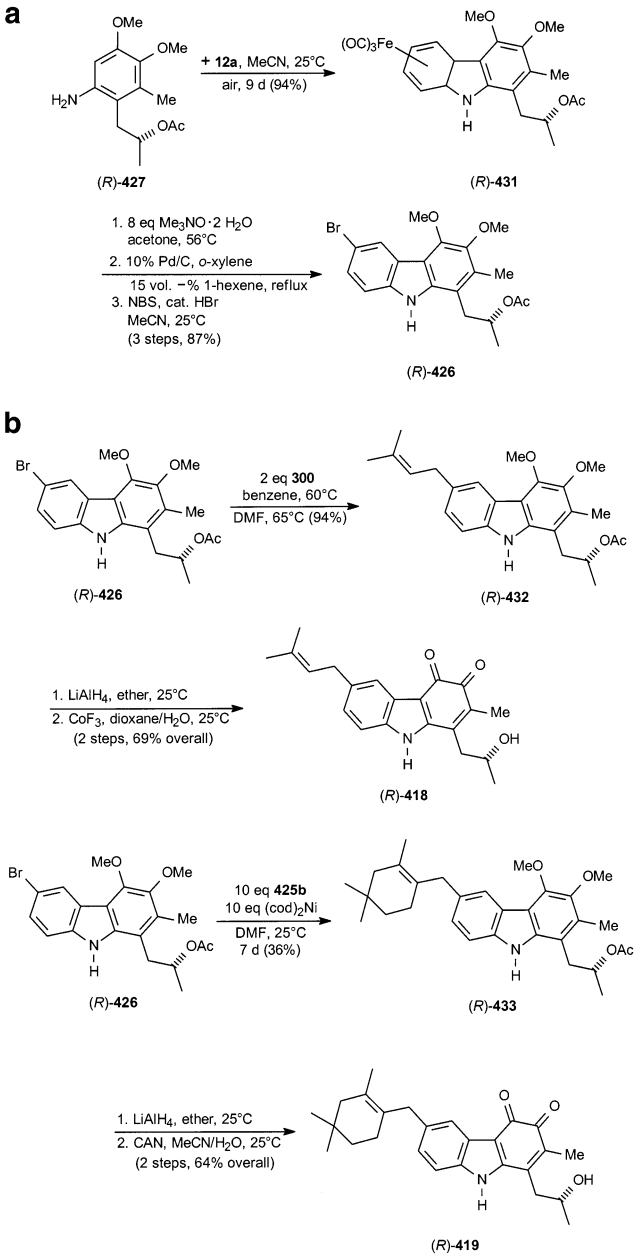
Scheme 122



tion of (*R*)-**429a** as the (*R*)-acetate (*R*)-**429b** and subsequent regioselective nitration led to the (*R*)-nitro compound (*R*)-**430**. Finally, catalytic hydrogenation of (*R*)-**430** provided the (*R*)-arylamine (*R*)-**427** (Scheme 122).

The construction of the carbazole framework was achieved by slightly modifying the reaction conditions previously reported for the racemic synthesis.[221,222] The reaction of the (*R*)-arylamine (*R*)-**427** with the iron complex salt **12a** in the air provided by concomitant oxidative cyclization the tricarbonyliron-complexed 4a,9a-dihydro-9*H*-carbazole (*R*)-**431**. Demetalation of the complex (*R*)-**431** followed by aromatization and regioselective electrophilic bromination afforded the 6-bromocarbazole (*R*)-**426**, which represents a crucial precursor for the synthesis of 6-substituted carbazole 3,4-quinone alkaloids (Scheme 123, part a).

Scheme 123

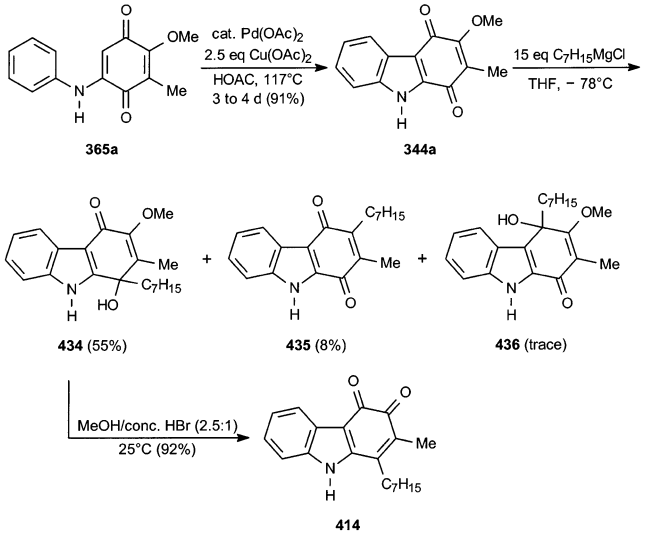


A nickel-mediated cross-coupling[175−179] of the 6-bromocarbazole (*R*)-**426** with prenyl bromide and *β*-cyclolavandulyl bromide **425b**,[225−227] followed by ester cleavage and oxidation with either cobalt(III) fluoride or ceric ammonium nitrate (CAN), afforded carquinostatin A [(*R*)-**418**][228] and lavanduquinocin [(*R*)-**419**],[229] respectively (Scheme 123, part b).

2.2. Palladium-Catalyzed Total Synthesis of Carbazoquinocin C

The total synthesis of carbazoquinocin C (**414**) was achieved by the palladium-catalyzed intramolecular oxidative coupling of 5-anilino-2-methoxy-3-methyl-

Scheme 124



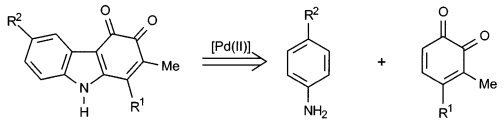
1,4-benzoquinone **365a** to the carbazole-1,4-quinone **344a** and subsequent regioselective introduction of the heptyl side chain. The carbazole-1,4-quinone **344a** was used previously as a key intermediate in the total synthesis of carbazomycin G (**334**) (see Scheme 102).[197] The regioselective introduction of the heptyl side chain at C-1 of the carbazole-1,4-quinone **344a** was achieved by a 1,2-addition of the corresponding Grignard reagent to give the carbazole-1,4-quinol **434** in 55% yield. However, 1,4-addition at C-3 and 1,2-addition at C-4 led to the regioisomeric products **435** and **436** as well. Under acidic reaction conditions, the carbazole-1,4-quinol **434** was smoothly transformed to carbazoquinocin C **414** (Scheme 124).[230]

2.3. Palladium-Mediated Total Synthesis of Carbazoquinocin C and (±)-Carquinostatin A

The retrosynthetic analysis of carbazoquinocin C (**414**) and (±)-carquinostatin A [(±)-**418**] based on the palladium-mediated intramolecular oxidative coupling of arylamino-1,2-benzoquinones provides aniline **38a** and 4-heptyl-3-methyl-1,2-benzoquinone **438a**, as precursors for **414**, and 4-prenylaniline **437** and 4-(2-hydroxypropyl)-3-methyl-1,2-benzoquinone **438b**, as precursors for (±)-**418** (Scheme 125).

Total Synthesis of Carbazoquinocin C. The veratrole **421**, required for the preparation of the 5-anilino-4-heptyl-3-methyl-1,2-benzoquinone **440**, served previously as a precursor for the iron-mediated synthesis of carbazoquinocin C (**414**) (see Scheme 118).[220] Ether cleavage of the veratrole **421** using boron tribromide afforded the catechol **439**. Oxidation of **439** with *o*-chloranil gave the required 1,2-benzoquinone **438a** (see Scheme 125). The 1,2-benzoquinone **438a** proved to be very labile. Therefore, it was tranformed in situ to the anilino-1,2-benzoquinone **440** by addition of 0.5 equiv of aniline **38a** in methanol. The oxidative cyclization using palladium(II) acetate in glacial acetic acid at 55°C transformed compound **440** directly to carbazoquinocin C (**414**) (Scheme 126).[231] The synthesis via the palladium-mediated *o*-quinone cyclization affords carbazoquinocin C (**414**) in three steps and 29% overall yield based on the veratrole **421**.

Scheme 125



414 Carbazoquinocin C
$R^1 = C_7H_{15}$; $R^2 = H$

(±)-**418** (±)-Carquinostatin A
$R^1 = CH_2CH(OH)Me$; R^2 = prenyl

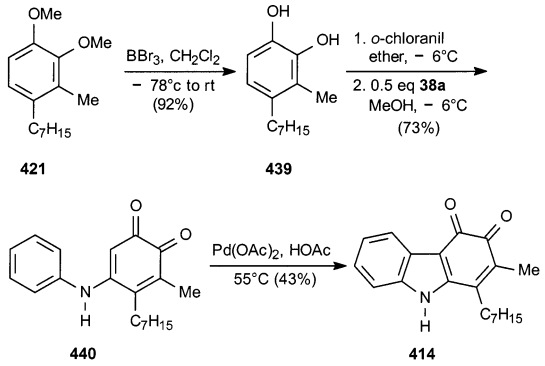
38a $R^2 = H$

437 R^2 = prenyl

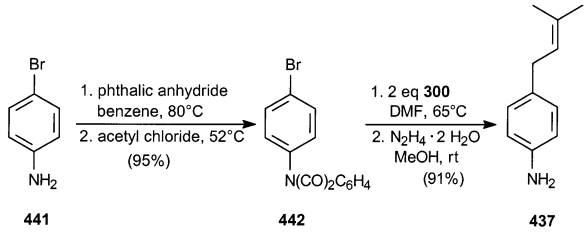
438a $R^1 = C_7H_{15}$

438b $R^1 = CH_2CH(OH)Me$

Scheme 126



Scheme 127



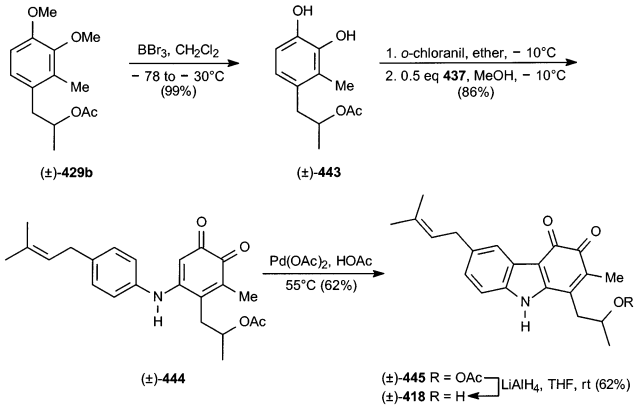
Total Synthesis of (±)-Carquinostatin A. 4-Prenylaniline **437** required for the synthesis of (±)-carquinostatin A [(±)-**418**] (see retrosynthesis in Scheme 125) was obtained by a nickel-mediated cross-coupling of the *N*-protected 4-bromoaniline **442** with bis[μ-bromo(η^3-prenyl)nickel] **300**[175−179] (Scheme 127).

Following a synthetic pathway similar to the one reported for carbazoquinocin C (**414**) (see Scheme 126), the veratrole (±)-**429b** was transformed to the arylamino-1,2-benzoquinone (±)-**444**. By a palladium(II)-mediated oxidative cyclization, compound (±)-**444** was transformed to *O*-acetylcarquinostatin A (±)-**445**. Removal of the acetate by reduction with lithium aluminum hydride provided (±)-carquinostatin A [(±)-**418**] in 62% yield (Scheme 128).[231] Using this method, (±)-carquinostatin A [(±)-**418**] is available in four steps and 33% overall yield based on the veratrole (±)-**429b**.

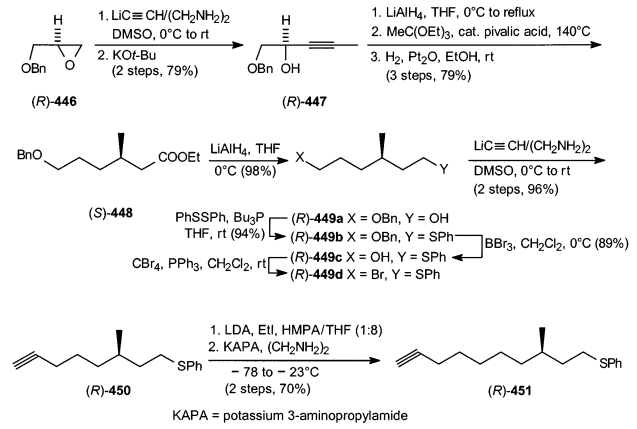
2.4. Total Synthesis of the Carbazoquinocins A–F via Benzannulation of Indoles

On the basis of his aromatic annulation strategy described previously (see Scheme 68),[157] Ogasawara et al. reported in 1996 the first enantioselective total synthesis of the carbazoquinocins A [(*S*)-**412**] and D [(*S*)-**415**]. The required methyl-substituted secondary stereogenic center of the alkyl side chain at C-1 of carbazoquinocin A and D was introduced starting

Scheme 128



Scheme 129

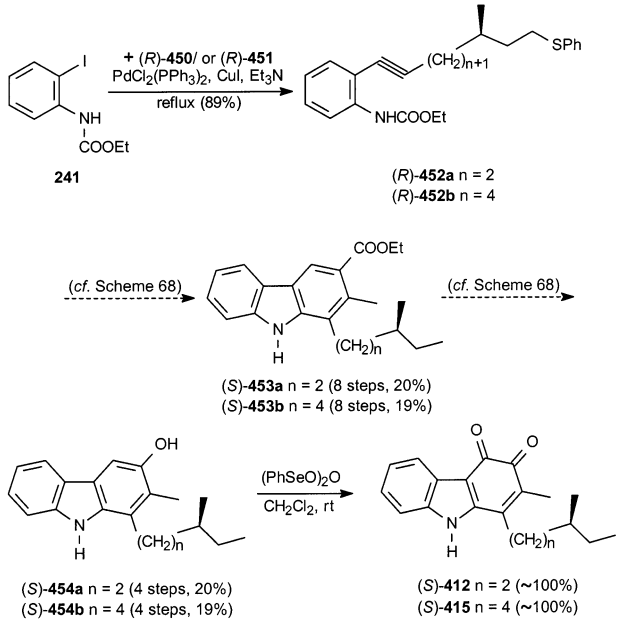


from the *O*-benzyl (*R*)-glycidol (*R*)-**446**.[232−235] Thus, (*R*)-**446** was transformed to ethyl (*S*)-6-benzyloxy-3-methyl-4(*E*)-hexenoate (*S*)-**448** via addition of acetylide, followed by isomerization, stereoselective reduction, and Claisen−Johnson rearrangement. The chiral ester (*S*)-**448** was converted to (*R*)-4-methyl-6-phenylthiohexanol (*R*)-**449c**. The primary alcohol (*R*)-**449c** was then transformed to the terminal acetylene (*R*)-**450**, a common intermediate for the synthesis of carbazoquinocin A [(*S*)-**412**] and D [(*S*)-**415**]. Chain elongation of (*R*)-**450** by two carbon atoms led to (*R*)-**451**, the chiral precursor for carbazoquinocin D [(*S*)-**415**] (Scheme 129).

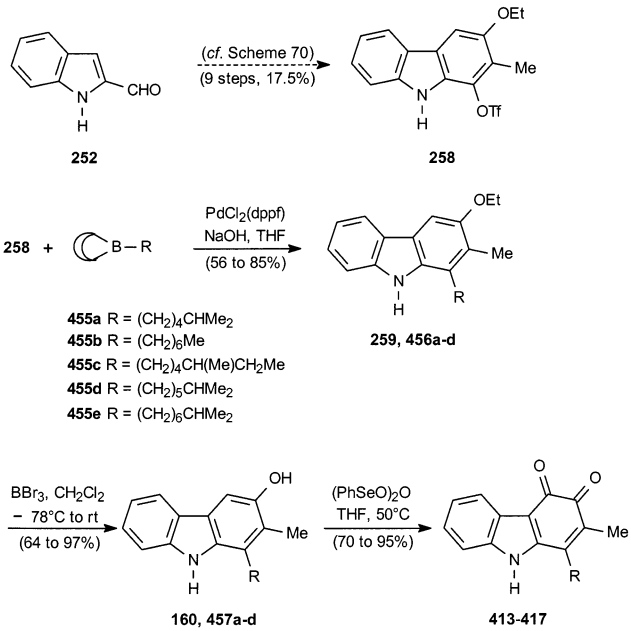
A Sonogashira coupling of the (*R*)-acetylenes (*R*)-**450** and (*R*)-**451** with *N*-carbethoxy-2-iodoaniline **241** afforded the aryl acetylenes (*R*)-**452a** and (*R*)-**452b**. Similar functional group transformations as described previously for the total synthesis of carazostatin (**160**) (see Scheme 68)[157] led to the 3-ethoxycarbonyl-2-methylcarbazoles (*S*)-**453a** and (*S*)-**453b** and subsequently to the 3-hydroxy-2-methylcarbazoles (*S*)-**454a** and (*S*)-**454b**. Finally, oxidation of the 3-hydroxycarbazoles (*S*)-**454a** and (*S*)-**454b** with benzeneseleninic anhydride $(PhSeO)_2O$ provided quantitatively (*S*)-(−)-carbazoquinocin A [(*S*)-**412**] and (*S*)-(−)-carbazoquinocin D [(*S*)-**415**] (Scheme 130).[236]

Hibino et al. reported the total synthesis of the carbazoquinocins B−F (**413**−**417**) by his electrocyclic reaction of allenes previously applied to the total synthesis of carazostatin (**160**) and hyellazole (**158**) (see Scheme 70). The carbazole triflate **258**, an intermediate in the total synthesis of carazostatin

Scheme 130



Scheme 131



and hyellazole (cf. Scheme 70),[159] served also as a common precursor for the total synthesis of the carbazoquinocins B−F (**413**−**417**). A Suzuki cross-coupling reaction of the carbazole triflate **258** with 9-alkyl-9-borabicyclo[3.3.1]nonane (9-alkyl-9-BBN) **455a**−**e** afforded the 1-alkylcarbazoles **259** and **456a**−**d** (56−85% yield). Cleavage of the ether by treatment of **259** and **456a**−**d** with boron tribromide gave the 3-hydroxycarbazoles **160** and **457a**−**d** (64−97% yield). Finally, **160** and **457a**−**d** were oxidized with benzeneseleninic anhydride $(PhSeO)_2O$ to provide the carbazoquinocins B−F (**413**−**417**) in 70−95% yield (Scheme 131).[237] A more recent total synthesis of carbazoquinocin C is described in section XI.2.

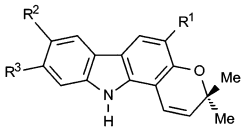
IV. Pyranocarbazole Alkaloids

Girinimbine (**458**), the first member of the pyrano[3,2-*a*]carbazole alkaloids, was isolated from the stem

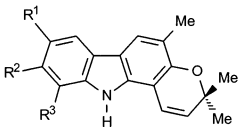
bark of *M. koenigii* Spreng by Chakraborty et al.[2,238] Later it was also isolated from the root bark of *C. heptaphylla* Wt. and Arn. by Joshi et al.[239] On the basis of chemical degradation studies, Chakraborty et al. proposed that the pyran ring and the aromatic methyl group are attached to different benzene rings of the carbazole nucleus.[2] Dutta and Quasim reassigned the structure of girinimbine (**458**) on the basis of NMR studies and proposed that the pyran ring and the methyl group are at the same benzene ring.[240] This structural assignment was additionally supported by Joshi et al.,[239] when they isolated girinimbine from a further natural source. Chakraborty et al. reported the isolation of murrayacine (**459**), a formyl analogue of girinimbine from two different natural sources, *M. koenigii* [238,241] and *C. heptaphylla*.[30] Moreover, Chakraborty et al. isolated heptazolidine (**460**) from *C. heptaphylla* Wt. and Arn.[242,243] Lange et al. isolated a 7-methoxy derivative of murrayacine (**461**) from the roots of *M. siamensis*. Because of the related natural source and an A-ring substitution pattern identical to murrayacine, it was called 7-methoxymurrayacine.[244] Mukherjee et al. isolated mukonicine (**462**) from the leaves of *M. koenigii* and assigned the structure as 6,8-dimethoxygirinimbine.[245] Reisch et al. reported the isolation of mupamine (**463**) from the root bark of *C. anisata* (Willd) Oliv. On the basis of the spectroscopic data, it was assigned as 8-methoxygirinimbine.[246] Different groups isolated koenimbine (**464**) independently from the fruits and leaves of *M. koenigii*, and the structure was assigned as 6-methoxygirinimbine.[247,248] In 1969, Kapil et al. isolated koenigicine (**465**) (7-methoxygirinimbine) from the leaves of *M. koenigii*.[248] It was also isolated by other investigators from the same natural source, and the alternative names koenimbidine[239] and koenidine[249] were given. Along with koenidine from the leaves of *M. koenigii*, Narasimhan et al. isolated koenigine (**466**) and koenine (**467**), which differ in the substitution pattern of the 6,7-position.[249] Chowdhury et al. isolated heptazolicine (**468**) from the roots of *C. heptaphylla*.[250] Furukawa et al. isolated dihydroxygirinimbine (**469**) from the root bark of *M. euchrestifolia* Hayata.[251] It could be shown that the pyran ring of **469** contains a *trans*-1,2-diol moiety. However, the absolute stereochemistry of **469** is still uncertain (Scheme 132).

In 1966, Chakraborty et al. isolated (±)-mahanimbine (**470**) from the stem bark of *M. koenigii* Spreng.[252] Later, Narasimhan et al. isolated **470** from the leaves and fruits of the same plant.[247,253] Joshi et al. isolated (+)-isomahanimbine (**471**) from the leaves of *M. koenigii* Spreng.[239] Kapil et al. isolated (+)-isomahanimbine from the same source and named it as (+)-mahanimbicine.[254] Narasimhan et al. isolated (−)-mahanine (**472**)[249,253] along with (±)-mahanimbine (**470**) from *M. koenigii* Spreng.[253] Chakraborty et al. isolated murrayacinine (**473**), a formyl analogue of (±)-mahanimbine, from the stem bark of *M. koenigii* Spreng.[255] In 1992, Reisch et al. isolated isomahanine (**474**) from the same source as (−)-mahanine.[256] In 1985, Furukawa et al. isolated pyrayafoline A (**475**) from the root bark of *M. euchrestifolia*.[111] From the same natural source, Furukawa et al. isolated in 1991 the other angular pyrayafoline isomers, pyrayafoline C (**476**) and D (**477**),[257] and the linear isomers, pyrayafoline B (**478**)[257] and E (**479**).[112] In 1989, Reisch et al. isolated glycomaurin (**480**) from *Glycosmis mauritiana*.[258] In the following year, Furukawa et al. isolated the same compound from a different natural source, *M. euchrestifolia* Hayata, and named it eustifoline-A.[259] Along with eustifoline-A (**480**), they also reported the isolation of the corresponding prenyl analogue, eustifoline-B (**481**)[259] (Scheme 133). The isolation of additional pyranocarbazole alkaloids is described in section XI.5.4.

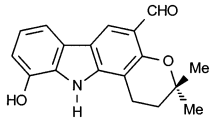
Scheme 132



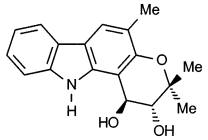
458 Girinimbine
R^1 = Me; R^2, R^3 = H
459 Murrayacine
R^1 = CHO; R^2, R^3 = H
460 Heptazolidine
R^1 = OMe; R^2 = Me; R^3 = H
461 7-Methoxymurrayacine
R^1 = CHO; R^2 = H; R^3 = OMe



462 Mukonicine
R^1, R^3 = OMe; R^2 = H
463 Mupamine
R^1, R^2 = H; R^3 = OMe
464 Koenimbine
R^1 = OMe; R^2, R^3 = H
465 Koenigicine
(Koenimbidine, Koenidine)
R^1, R^2 = OMe; R^3 = H
466 Koenigine
R^1 = OMe; R^2 = OH; R^3 = H
467 Koenine
R^1 = OH; R^2, R^3 = H

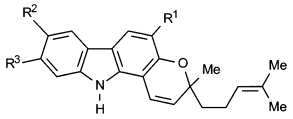


468 Heptazolicine

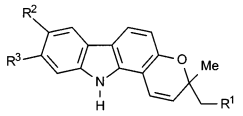


469 Dihydroxygirinimbine

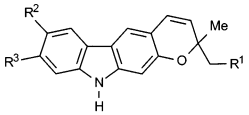
Scheme 133



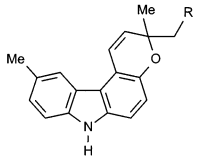
470 (±)-Mahanimbine
R^1 = Me; R^2, R^3 = H
471 (+)-Isomahanimbine [(+)-Mahanimbicine]
R^1, R^3 = H; R^2 = Me
472 (−)-Mahanine
R^1 = Me; R^2 = H; R^3 = OH
473 Murrayacinine
R^1 = CHO; R^2, R^3 = H
474 Isomahanine
R^1 = H; R^2 = Me; R^3 = OH



475 Pyrayafoline A
R^1= H; R^2 = Me; R^3 = OMe
476 Pyrayafoline C
R^1 = H; R^2 = Me; R^3 = OH
477 Pyrayafoline D
R^1 = prenyl; R^2 = Me; R^3 = OH

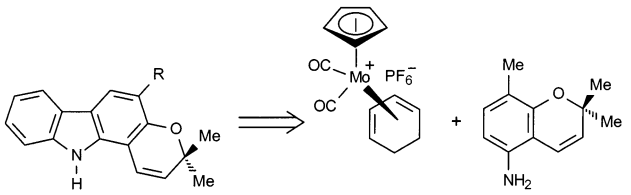


478 Pyrayafoline B
R^1 = H; R^2 = Me; R^3 = OH
479 Pyrayafoline E
R^1 = prenyl; R^2 = Me; R^3 = OH



480 Eustifoline-A (Glycomaurin)
R = H
481 Eustifoline-B
R = prenyl

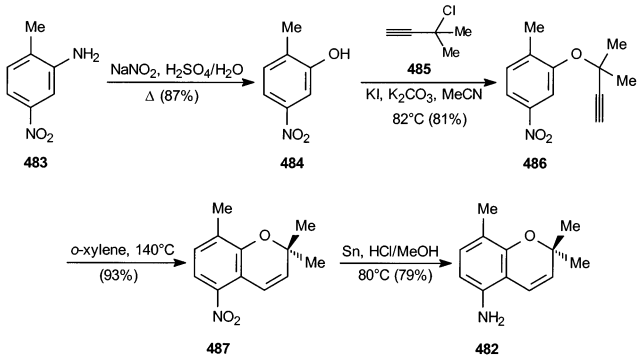
Scheme 134



458 Girinimbine R = Me
459 Murrayacine R = CHO

27 **482**

Scheme 135



483 **484** **485** **486** **487** **482**

1. Molybdenum-Mediated Total Syntheses

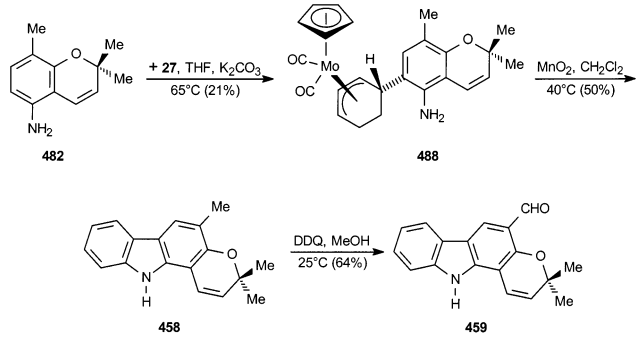
The retrosynthetic analysis of girinimbine (**458**) and murrayacine (**459**) based on a molybdenum-mediated approach provides the molybdenum complex salt **27** and the 5-aminochromene **482** as potential precursors (Scheme 134).

5-Amino-2,2,8-trimethylchromene **482** was prepared starting from commercially available 2-methyl-5-nitroaniline **483** in four steps and 52% overall yield. The reaction of **483** with nitrous acid afforded the phenol **484**, which was alkylated by 3-chloro-3-methylbut-1-yne **485** to the aryl propargyl ether **486**. The key step of this synthesis is the transformation of the aryl propargyl ether **486** to the 5-nitrochromene **487** by a [3,3]-sigmatropic rearrangement and subsequent cyclization.[260] Heating of **486** in *o*-xylene at reflux for 14 h provided the 5-nitrochromene **487** in 93% yield. The reduction of the 5-nitrochromene **487** with tin in methanolic hydrochloric acid afforded the 5-aminochromene **482** (Scheme 135).

The reaction of the 5-aminochromene **482** with the complex salt **27** provided by an electrophilic aromatic substitution regio- and diastereoselectively the molybdenum complex **488**. The oxidative cyclization of complex **488** with concomitant aromatization and demetalation using activated manganese dioxide led directly to girinimbine (**458**) in 50% yield. Oxidation of girinimbine (**458**) with DDQ in methanol[261,262] afforded murrayacine (**459**) in 64% yield (Scheme 136).[263]

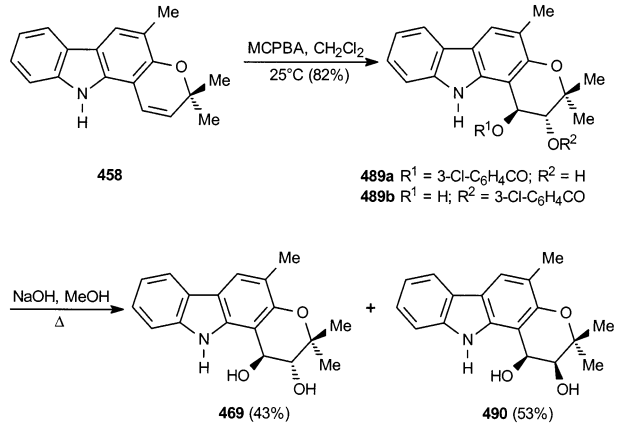
For the transformation of girinimbine (**458**) to dihydroxygirinimbine (**469**), girinimbine was oxidized by MCPBA to give a mixture of the two regioisomeric 3-chlorobenzoic acid esters **489a** and **489b** in 82% yield (ratio 1.5:1). The hydrolysis of the 3-chlorobenzoates **489a** and **489b** with methanolic sodium

Scheme 136



482 **488** **458** **459**

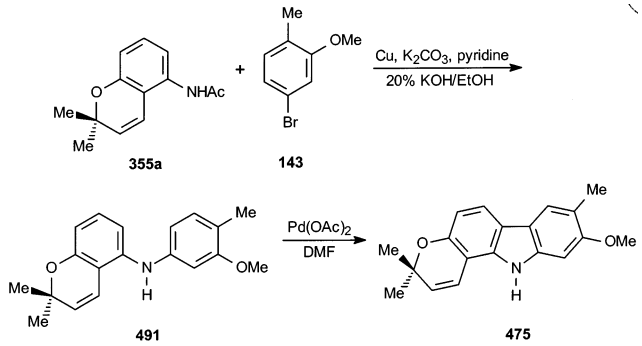
Scheme 137



458 **489a** R^1 = 3-Cl-C_6H_4CO; R^2 = H
489b R^1 = H; R^2 = 3-Cl-C_6H_4CO

469 (43%) **490** (53%)

Scheme 138



355a **143** **491** **475**

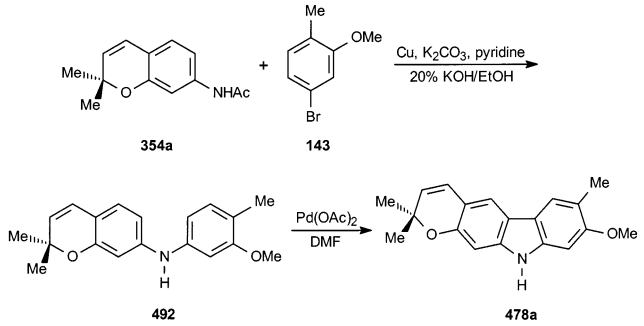
hydroxide provided dihydroxygirinimbine (**469**) in 43% yield along with the corresponding *cis*-diol **490** (Scheme 137).[263]

2. Palladium-Mediated Total Syntheses

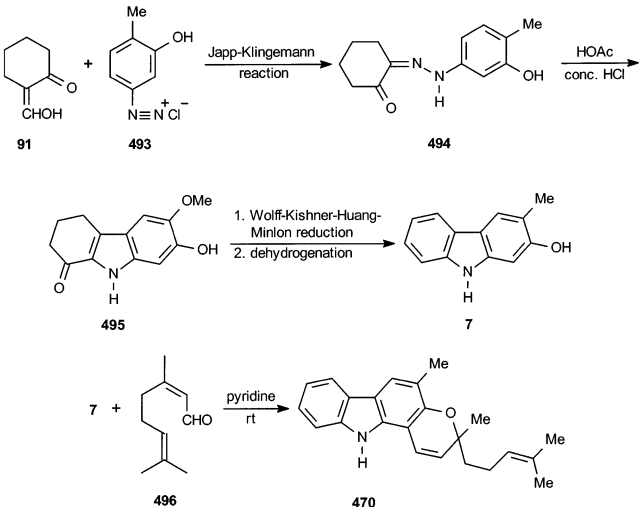
Furukawa et al. reported the total synthesis of pyrayafoline A (**475**) and *O*-methylpyrayafoline B (**478a**) by cyclodehydrogenation of the corresponding diarylamines **491** and **492** with stoichiometric amounts of palladium(II) acetate. Both diarylamines were obtained by using the Goldberg modification of the Ullmann coupling. The diarylamine **491** was obtained by Ullmann coupling of 5-acetylamino-2,2-dimethylchromene **355a**[192] with 5-bromo-2-methylanisole **143**,[264] followed by hydrolysis of the intermediate diarylamide. Oxidative cyclization of the diarylamine **491** using palladium(II) acetate in DMF afforded pyrayafoline A (**475**) (Scheme 138).[79]

Subsequently, the same methodology was also applied to the synthesis of *O*-methylpyrayafoline B

Scheme 139



Scheme 140



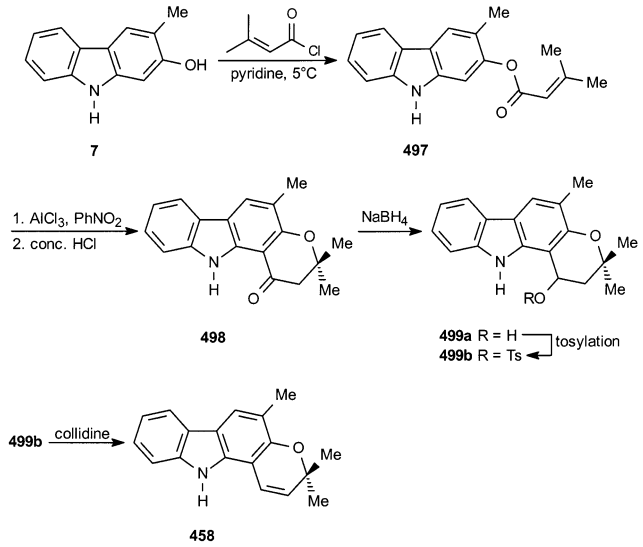
(**478a**). Coupling of 7-acetylamino-2,2-dimethylchromene **354a**[192] with 5-bromo-2-methylanisole **143** and hydrolysis to the diarylamine **492** followed by oxidative cyclization with palladium(II) acetate in DMF provided *O*-methylpyrayafoline B (**478a**) (Scheme 139).[257]

3. Total Syntheses by Fischer Indolization of Phenylhydrazones

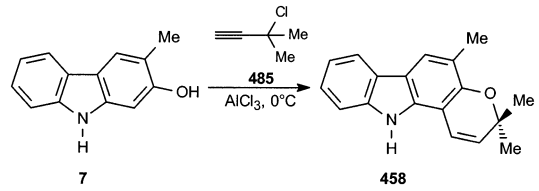
In 1969, Chakraborty et al. reported the total synthesis of (±)-mahanimbine (**470**). First, 2-hydroxy-3-methylcarbazole (**7**) was synthesized from 2-hydroxymethylenecyclohexanone **91** and the diazoaryl compound **493** via the following sequence: Japp−Klingemann reaction, Fischer indolization, Wolff−Kishner reduction, and dehydrogenation. 2-Hydroxy-3-methylcarbazole (**7**) was transformed to (±)-mahanimbine (**470**) in a one-pot process by reaction with citral **496** in the presence of pyridine (Scheme 140).[265−267] In the same year, Dutta et al. reported a total synthesis of (±)-mahanimbine (**470**) from 2-hydroxy-3-methylcarbazole (**7**) using a similar methodology with $SnCl_3$, $FeCl_3$, or polyphosporic acid as condensing agents.[268]

In 1971, Chakraborty and Islam reported the synthesis of girinimbine (**458**) from 2-hydroxy-3-methylcarbazole (**7**)[267] by annulation of a 2,2-dimethyl-Δ^3-pyran ring. The acylation of 2-hydroxy-3-methylcarbazole (**7**) with β,β-dimethylacryloyl chloride afforded the acyl derivative **497**. A Fries rearrangement of compound **497** led to the indolochromanone **498**. Twenty-five years later, Wu et al. isolated

Scheme 141



Scheme 142



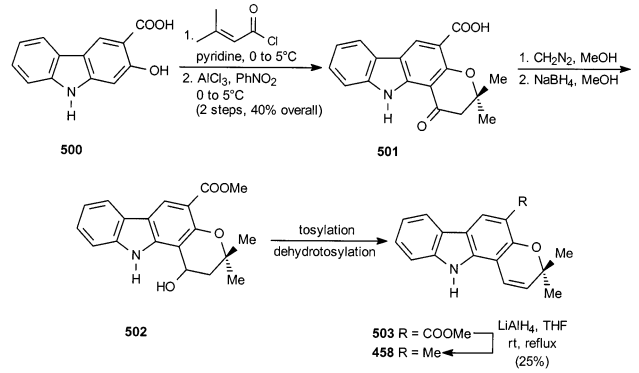
compound **498** from nature and named it euchrestifoline (see section XI.5.4). Finally, the indolochromanone **498** was transformed to girinimbine (**458**) by the sequence reduction, tosylation, and elimination (Scheme 141).[269]

In 1984, Bhattacharyya et al. reported an improved procedure for the transformation of 2-hydroxy-3-methylcarbazole (**7**) to girinimbine (**458**) by annulation of the 2,2-dimethyl-Δ^3-pyran ring in a one-pot operation on reaction with 3-chloro-3-methyl-1-butyne **485** in the presence of a Lewis acid (Scheme 142).[270]

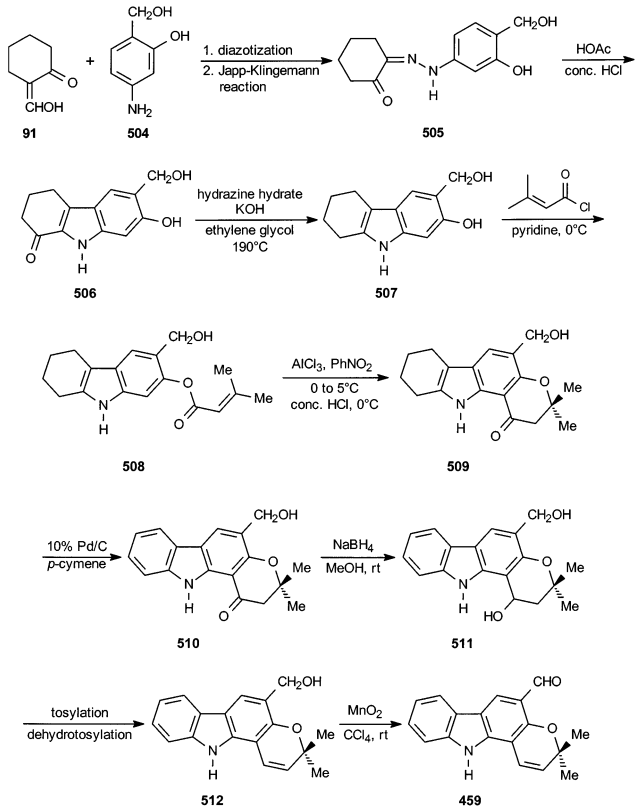
Chakraborty et al. reported a new total synthesis of girinimbine (**458**) starting from 2-hydroxycarbazole-3-carboxylic acid **500**. The reaction of compound **500** with β,β-dimethylacryloyl chloride in the presence of pyridine gave an intermediate *O*-acyl compound that in the presence of aluminum trichloride underwent a Fries rearrangement to the indolochromanone (**501**). Compound **501** was converted to the carbinol **502** by methylation with diazomethane and subsequent reduction with borohydride. Elimination of the carbinol **502** via the tosyl derivative afforded the carbomethoxypyranocarbazole **503**, which was transformed to girinimbine (**458**) by reduction with lithium aluminum hydride (Scheme 143).[271] This method also provides norgirinimbine, a linear isomer of girinimbine.

In 1973, Chakraborty et al. reported the synthesis of murrayacine (**459**), a formyl analogue of girinimbine, by annulation of the 2,2-dimethyl-Δ^3-pyran ring at 2-hydroxy-3-hydroxymethyl-5,6,7,8-tetrahydrocarbazole **507**. The tetrahydrocarbazole **507** was obtained from 2-hydroxymethylenecyclohexanone **91** and 3-hydroxy-4-hydroxymethylaniline **504** by the

Scheme 143



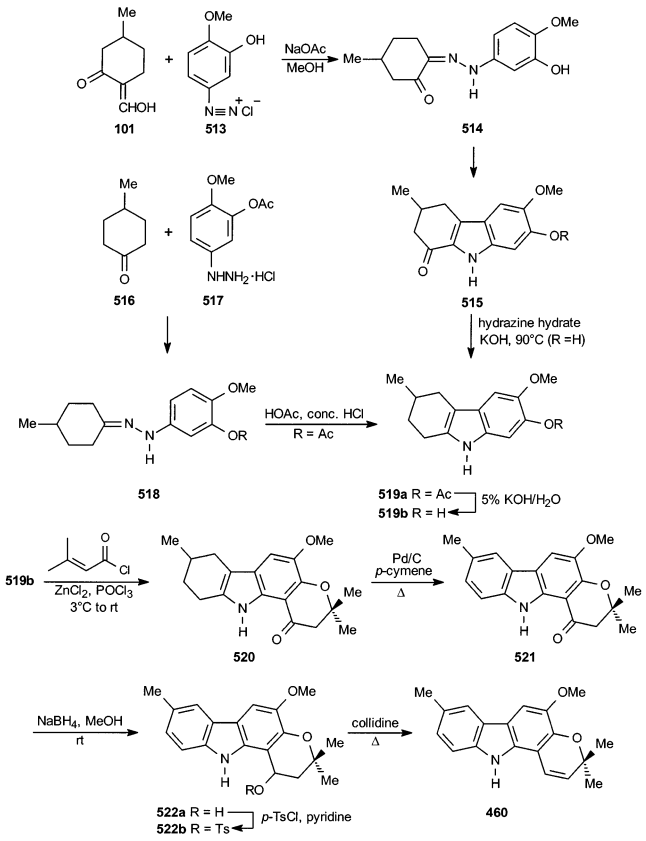
Scheme 144



follwing sequence: diazotization, Japp−Klingemann reaction, Fischer indolization, and Wolff−Kishner reduction. Reaction of the tetrahydrocarbazole **507** with β,β-dimethylacryloyl chloride to the *O*-acyl derivative **508** and subsequent Fries rearrangement provided the chromanone **509**. Aromatization to compound **510** followed by reduction with sodium borohydride gave the corresponding carbinol **511**. Elimination of the carbinol **511** via the corresponding tosyl derivative afforded the chromenoindole **512**, which by oxidation with active manganese dioxide provided murrayacine (**459**) (Scheme 144).[272]

In 1985, Chakraborty et al. reported the total synthesis of heptazolidine (**460**) from 2-hydroxy-3-methoxy-6-methyltetrahydrocarbazole **519b**. Japp−Klingemann reaction of 2-hydroxymethylene-5-methylcyclohexanone **101** and the diazoaryl derivative **513** followed by Fischer indolization of the resulting phenylhydrazone **514** and Wolff−Kishner reduction of the 2-hydroxy-3-methoxy-6-methyl-8-oxotetrahydrocarbazole **515** afforded the tetrahydrocarbazole **519b**. Alternatively, the tetrahydrocarbazole **519b** was obtained by condensation of 4-methylcyclohexanone **516** and 3-acetoxy-4-methoxyphenylhydrazine hydrochloride **517** to the phenylhydrazone **518**, Fischer indolization, and ester cleavage. The total synthesis of heptazolidine (**460**) was completed by annulation of the 2,2-dimethyl-Δ^3-pyran ring and aromatization (Scheme 145).[273] These final transformations involve a similar sequence of steps as shown above for the total syntheses of girinimbine (**458**) (see Schemes 141 and 143) and murrayacine (**459**) (see Scheme 144).

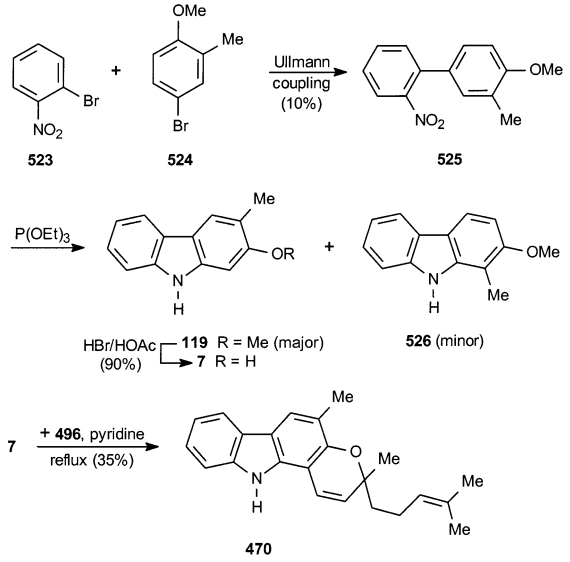
Scheme 145



4. Total Syntheses via Reductive Cyclization of *o*-Nitrobiaryls

Cadogan et al. described a synthesis of the carbazole skeleton by reductive cyclization of *o*-nitrobiaryls with triethyl phosphite. This reaction proceeds via an intermediate arylnitrene that undergoes an insertion into a C−H bond at the ortho position of the second aromatic ring, thus generating a C−N bond.[274,275] In 1969, Popli and co-workers applied this methodology to the total synthesis of (±)-mahanimbine (**470**) from 2-methoxy-3-methylcarbazole (**119**). Ullmann coupling of 2-nitrobromobenzene **523** with 4-bromo-2-methylanisole **524** afforded 4-methoxy-3-methyl-2′-nitrobiphenyl **525**. Reductive cyclization of the nitrobiaryl **525** with triethyl phosphite[274,275] led to a mixture (45% yield) of the isomeric 2-methoxy-3-methylcarbazole **119** (major) and 2-methoxy-1-methylcarbazole **526** (minor). Ether cleavage of 2-methoxy-3-methylcarbazole (**119**) gave 2-hydroxy-

Scheme 146



3-methylcarbazole (**7**). Condensation of the hydroxycarbazole **7** with citral (**496**)[265,266] provided (±)-mahanimbine (**470**) in 35% yield (Scheme 146).[276]

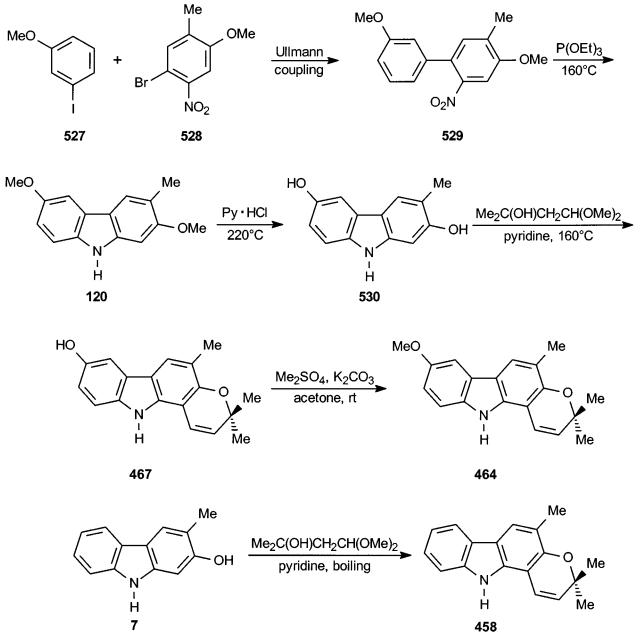
In the following year, Popli et al. reported the total synthesis of koenine (**467**) and koenimbine (**464**) by annulation of the 2,2-dimethyl-Δ^3-pyran ring at 2,6-dihydroxy-3-methylcarbazole **530**.[119] Ullmann coupling of *m*-iodoanisole **527** with 4-bromo-2-methyl-5-nitroanisole **528** led to 4-methoxy-5-methyl-2-nitro-3′-methoxybiphenyl **529**. Reductive cyclization of the nitrobiaryl **529** by treatment with triethyl phosphite gave 2,6-dimethoxy-3-methylcarbazole (**120**). Demethylation of compound **120** with pyridine hydrochloride afforded 2,6-dihydroxy-3-methylcarbazole **530**. The dihydroxycarbazole **530** was transformed to koenine (**467**) in a one-pot process by condensation with 3-hydroxyisovaleraldehyde dimethyl acetal[277] in pyridine. *O*-Methylation of koenine (**467**) provided koenimbine (**464**) (Scheme 147).[119] Similarly, condensation of 2-hydroxy-3-methylcarbazole (**7**) with 3-hydroxyisovaleraldehyde dimethyl acetal gave girinimbine (**458**) (Scheme 147).[119]

In 1972, the same authors reported the synthesis of (±)-*O*-methylmahanine (**533**) starting from 2,7-dihydroxy-3-methylcarbazole **531**. Reaction of **531** with diazomethane afforded by selective 7-*O*-methylation 2-hydroxy-7-methoxy-3-methylcarbazole **532**. Condensation of 2-hydroxy-7-methoxy-3-methylcarbazole **532** with citral (**496**) provided (±)-*O*-methylmahanine **533** (Scheme 148).[278]

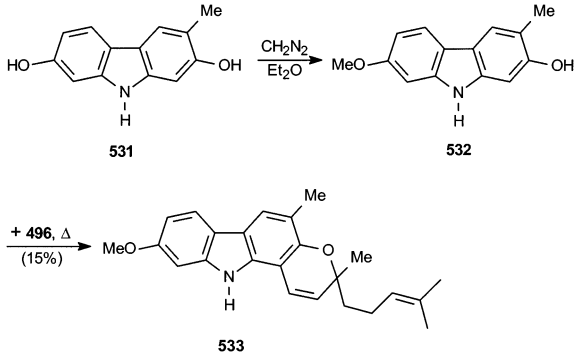
Popli also reported the synthesis of murrayacine (**459**) by oxidation of girinimbine (**458**) with DDQ. On the basis of this transformation, the structure of murrayacine was revised (Scheme 149).[261]

In 1980, Kapil et al. reported the total synthesis of koenigicine (**465**) from 2-hydroxy-6,7-dimethoxy-3-methylcarbazole **541** by application of the methodology described above. Ullmann coupling of 4-iodo-2-methylanisole **534** with 5-bromo-2-methoxy-4-nitroanisole **535** followed by reductive cyclization of the nitrobiaryl **536** afforded the desired 2,6,7-trimethoxy-3-methylcarbazole **538** in 35% yield, along with the isomeric 2,6,7-trimethoxy-1-methylcarbazole

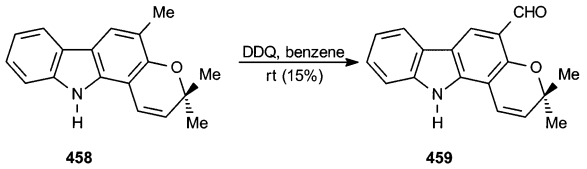
Scheme 147



Scheme 148



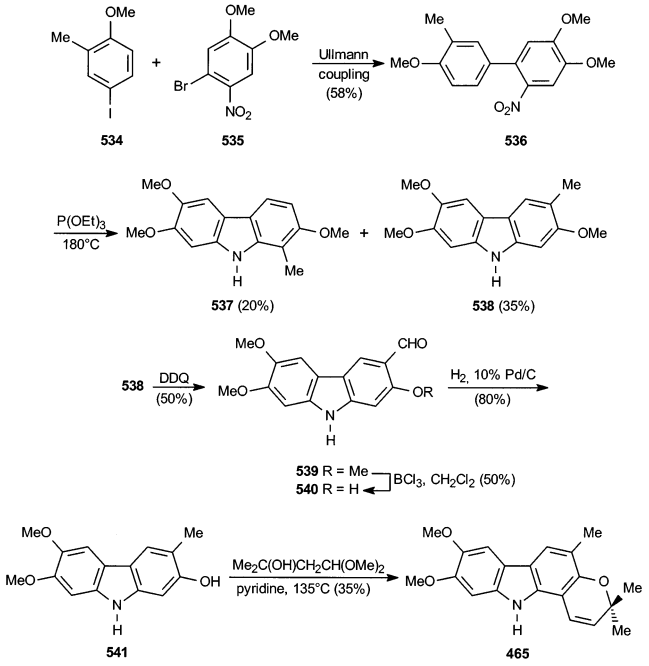
Scheme 149



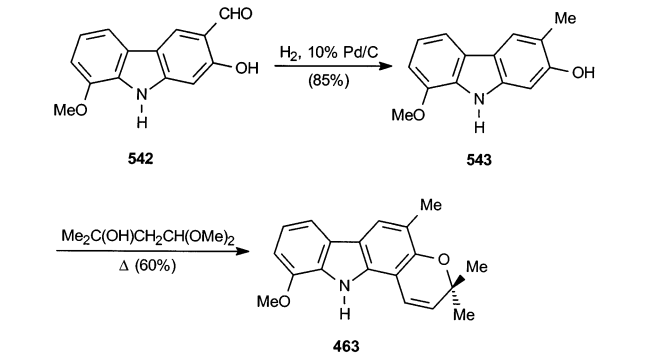
537 (20% yield). An attempt to achieve a direct regioselective transformation of 2,6,7-trimethoxy-3-methylcarbazole **538** to 2-hydroxy-6,7-dimethoxy-3-methylcarbazole **541** was unsuccessful. However, the trimethoxycarbazole **538** was transformed to 2-hydroxy-6,7-dimethoxy-3-methylcarbazole **541** by the sequence of oxidation to the 3-formyl derivative **539**, regioselective ether cleavage to **540**, and catalytic hydrogenation (Scheme 150). Condensation of the hydroxycarbazole **541** with 3-hydroxyisovaleraldehyde dimethyl acetal[119] provided directly koenigicine (**465**) in 35% yield (Scheme 150).[279]

In the following year, Kapil et al. applied the same methodology to the total synthesis of mupamine (**463**). Catalytic hydrogenation of the formylcarbazole **542** afforded 2-hydroxy-8-methoxy-3-methylcarbazole **543**.[279] Condensation of 2-hydroxy-8-methoxy-3-methylcarbazole **543** with 3-hydroxyisovaleraldehyde di-

Scheme 150



Scheme 151



methyl acetal provided mupamine (**463**) (Scheme 151).[280]

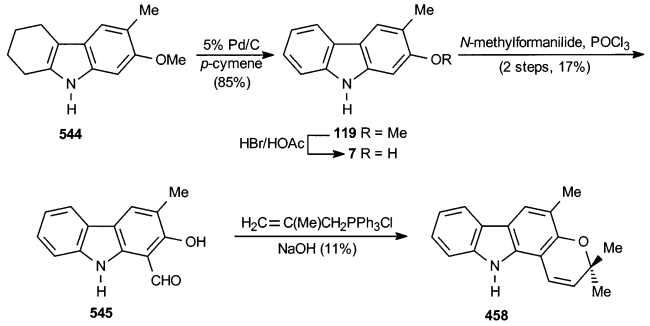
5. Total Syntheses from Tetrahydrocarbazoles

Narasimhan et al. reported the total synthesis of girinimbine (**458**), (±)-mahanimbine (**470**), and (±)-isomahanimbine (**471**) from 2-hydroxy-3-methylcarbazole (**7**) and 2-hydroxy-6-methylcarbazole **549**, respectively. 2-Hydroxy-3-methylcarbazole (**7**) was obtained from the tetrahydrocarbazole **544**[281] via a sequence of dehydrogenation and ether cleavage. Formylation of 2-hydroxy-3-methylcarbazole (**7**) to 1-formyl-2-hydroxy-3-methylcarbazole (**545**) followed by Wittig reaction with methallyltriphenylphosphonium chloride and cyclization afforded girinimbine (**458**) (Scheme 152).[282,283]

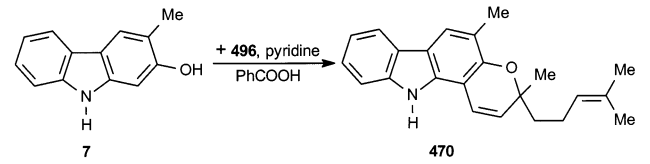
In a further synthesis, 2-hydroxy-3-methylcarbazole (**7**) was transformed to (±)-mahanimbine (**470**) by condensation with citral (**496**) in the presence of benzoic acid and pyridine (Scheme 153).[282,283]

The same methodology was also applied to the total synthesis of (±)-isomahanimbine (**471**). Condensation of 3-methoxyaniline **38c** with 2-chloro-4-methylcyclohexanone **546** gave the tetrahydrocarbazole **547** in 46% yield. Dehydrogenation of compound **547** with

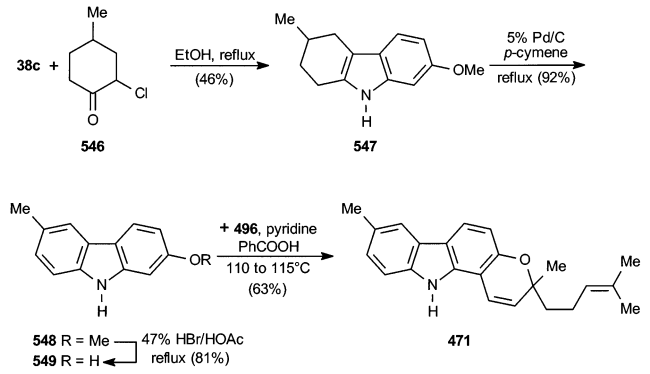
Scheme 152



Scheme 153



Scheme 154

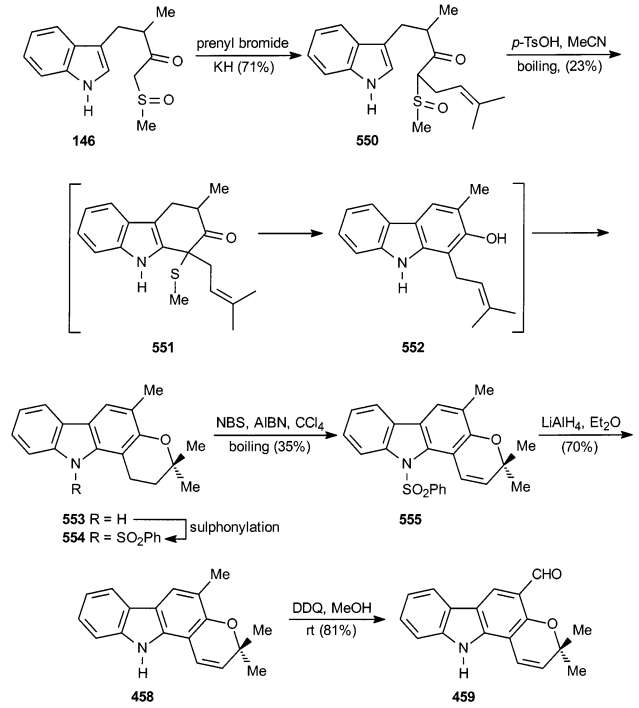


5% Pd/C gave 2-methoxy-6-methylcarbazole **548**, which on ether cleavage with HBr/HOAc afforded the corresponding hydroxy derivative **549**. Finally, condensation of **549** with citral (**496**) provided (±)-isomahanimbine (**471**) in 63% yield (Scheme 154).[283]

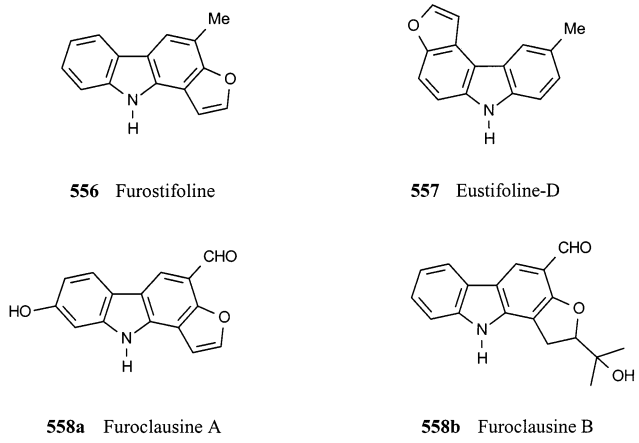
6. Total Syntheses via Acid-Catalyzed Cyclization of a β-Keto Sulfoxide

Yonemitsu et al. reported a total synthesis of girinimbine (**458**) and murrayacine (**459**) via dihydrogirinimbine (**553**). The β-keto sulfoxide **146** served previously as a precursor for the synthesis of 2-hydroxy-3-methylcarbazole (**7**) (see Scheme 37).[115] Alkylation of the β-keto sulfoxide **146** with prenyl bromide and potassium hydride gave 1-indol-3-yl-2,7-dimethyl-4-(methylsulfinyl)oct-6-en-3-one **550** in 71% yield. Compound **550** was transformed directly to dihydrogirinimbine (**553**) in the presence of *p*-toluenesulfonic acid by three consecutive acid-catalyzed reactions (cyclization to the tetrahydrocarbazole **551**, aromatization to **552**, and cyclization of the pyran ring). All attempts to achieve a direct dehydrogenation of dihydrogirinimbine (**553**) to girinimbine (**458**) were unsuccessful. However, the *N*-protected dihydrogirinimbine **554** was smoothly dehydrogenated with *N*-bromosuccinimide in the presence of azoisobutyronitrile (AIBN) to give the *N*-protected girinimbine **555**. Deprotection of **555** then afforded girinimbine (**458**) in 70% yield. Oxidation of girinimbine (**458**) with

Scheme 155



Scheme 156



556 Furostifoline **557** Eustifoline-D

558a Furoclausine A **558b** Furoclausine B

DDQ in methanol gave murraycine (**459**) in 81% yield (Scheme 155).[262,284]

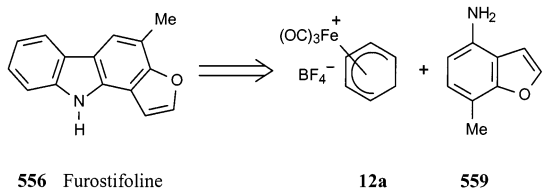
V. Furocarbazole Alkaloids

In 1990, Ito and Furukawa isolated from *M. euchrestifolia* Hayata two new members of tetracyclic carbazole alkaloids, furostifoline (**556**) and the isomeric eustifoline-D (**557**) (Scheme 156).[259] They were the first furocarbazole alkaloids obtained from natural sources. In the late 1990s, Wu et al. described the isolation and structural elucidation of two further furocarbazole alkaloids, furoclausine A (**558a**) and B (**558b**) from the root bark of *C. excavata* (Scheme 156).[285] The absolute stereochemistry of the optically active furoclausine B (**558b**) is still not known.[285]

1. Iron-Mediated Total Synthesis of Furostifoline

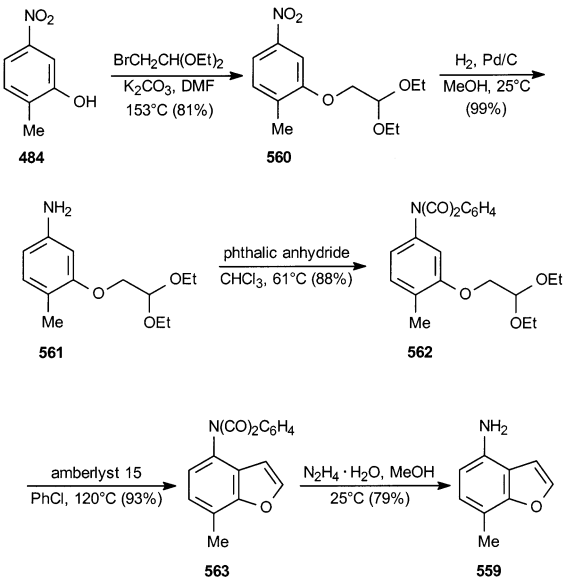
The first total synthesis of the furo[3,2-*a*]carbazole alkaloid furostifoline (**556**) was reported in 1996 based on an iron-mediated construction of

Scheme 157



556 Furostifoline **12a** **559**

Scheme 158



the carbazole nucleus using the complex salt **12a** and 4-amino-7-methylbenzofuran **559** as precursors (Scheme 157).

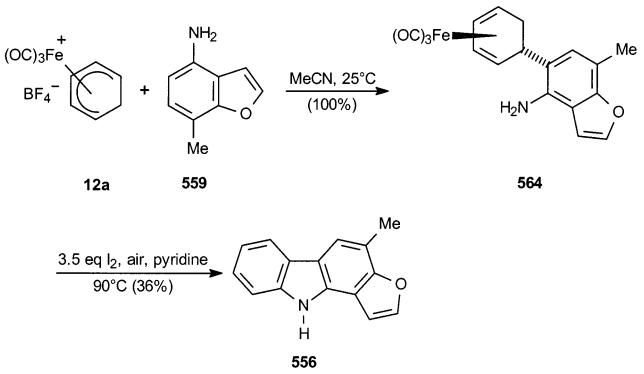
The 4-aminobenzofuran **559** was prepared from the nitrophenol **484** by annulation of the furan ring using bromoacetaldehyde diethyl acetal as C_2-building block.[286] The alkylation of the nitrophenol **484** with bromoacetaldehyde diethyl acetal afforded the ether **560**, which was hydrogenated to the arylamine **561**. After protection of the amino group to the phthalic imide **562**, an Amberlyst 15-catalyzed cyclization provided 4-(*N*-phthalimido)-7-methylbenzofuran **563**. The removal of the phthalimido group afforded the desired 4-amino-7-methylbenzofuran **559** in 79% yield (Scheme 158). This five-step sequence leads to the 4-aminobenzofuran **559** in 52% overall yield on a multigram scale.

Electrophilic aromatic substitution of the 4-aminobenzofuran **559** with the iron complex salt **12a** provided regioselectively the iron complex **564** in quantitative yield. The cyclization of complex **564** with concomitant aromatization by oxidation with an excess of iodine in pyridine in the air at 90 °C[33,39,287] afforded furostifoline (**556**) (Scheme 159).[288] An improved iron-mediated total synthesis of furostifoline is described in section XI.3.

2. Total Synthesis of Furostifoline by Benzannulation of Indoles

In 1998, Beccalli et al. reported the total synthesis of furostifoline (**556**) from ethyl 2-[1-(ethoxycarbonyl)-indol-3-yl]acetate **565**. The key step of this approach

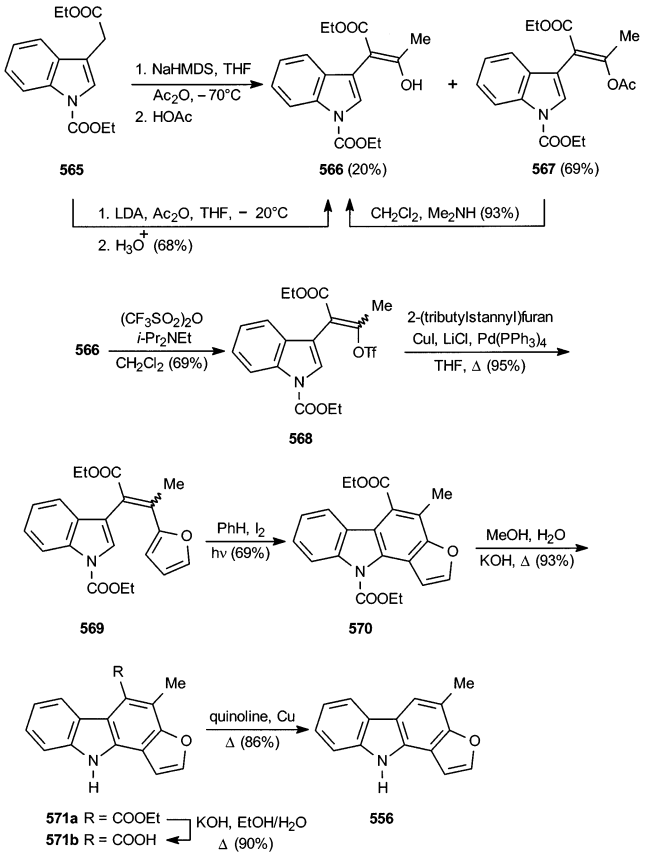
Scheme 159



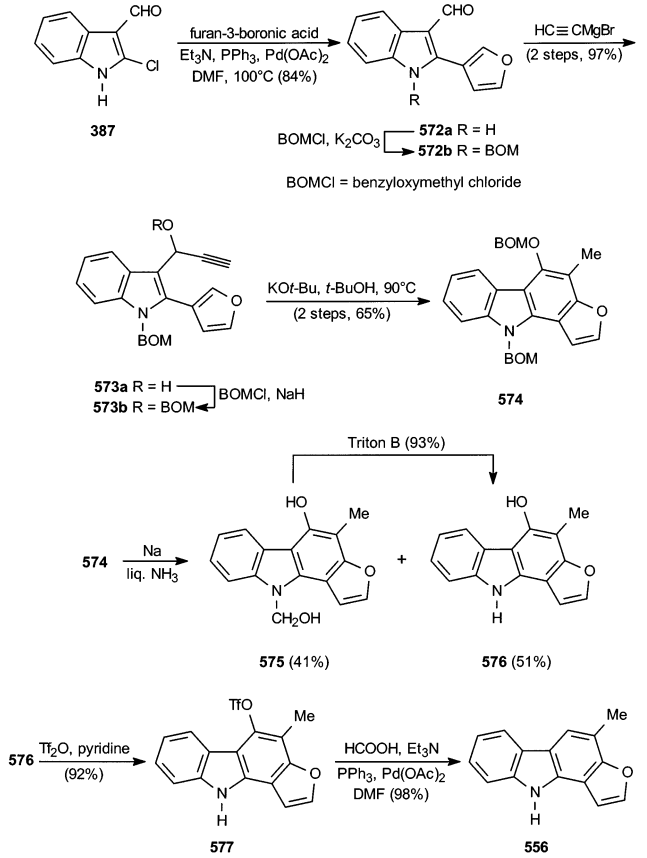
is the oxidative photocyclization of the 3-substituted indole **569**. Deprotonation of compound **565** with LDA and reaction of the corresponding anion with acetic anhydride afforded in 68% yield ethyl 2-[1-(ethoxycarbonyl)indol-3-yl]-3-hydroxybut-2-enoate **566**. Alternatively, the anion of **565** was generated using sodium bis(trimethylsilyl)amide (NaHMDS) as the base and treated with acetic anhydride to give compound **566** in a total yield of 84% (over two steps via the intermediate ethyl 3-acetoxy-2-[1-(ethoxycarbonyl)indol-3-yl]but-2-enoate **567**). The enol **566** was transformed to an inseparable diastereoisomeric 1:1 mixture of the vinyl triflate **568**. The palladium(0)-catalyzed cross-coupling[289,290] of the triflate **568** with 2-(tributylstannyl)furan afforded the vinylfuran **569** as a 1:1 mixture of the diastereoisomers. Hexatriene photocyclization of the vinylfuran **569** in the presence of iodine as the oxidizing agent provided the furo-[3,2-*a*]carbazole **570** in 69% yield. Alkaline hydrolysis of compound **570** gave the *N*-deprotected furo[3,2-*a*]-carbazole **571a**. Cleavage of the ester to the corresponding acid **571b** and decarboxylation afforded furostifoline (**556**) (Scheme 160).[291] This synthesis provides furostifoline (**556**) in nine steps and 27% overall yield based on compound **565**.

Hibino and co-workers described the total synthesis of furostifoline (**556**) from 2-chloro-3-formylindole **387** using the electrocyclic reaction of an intermediate allene with the 2,3-double bonds of indole and furan as the key step. Suzuki cross-coupling of 2-chloro-3-formylindole **387** and furan-3-boronic acid,[292] protection as the benzyloxymethyl (BOM) ether, Grignard reaction of the *N*-BOM-protected 2-(fur-3-yl)indole-3-carbaldehyde **572b** with ethynylmagnesium bromide, and again BOM-protection of the propargylic alcohol provided in four steps the 2-(fur-3-yl)-3-propargylindole **573b**. Using thermal reaction conditions the 2-(fur-3-yl)-3-propargylindole **573b** was transformed to the 4-oxygenated furo[3,2-*a*]carbazole **574**. Deprotection of compound **574** under Birch conditions led to an separable mixture of the *N*-(hydroxymethyl)furo[3,2-*a*]carbazole **575** (41%) and the furo[3,2-*a*]carbazole **576** (51%). Compound **575** was converted to **576** by treatment with Triton B (93% yield). For the final transformation of the furocarbazole **576** to furostifoline (**556**), the hydroxy group was removed via reductive elimination[293] of the intermediate triflate **577** (Scheme 161).[204] This route affords

Scheme 160

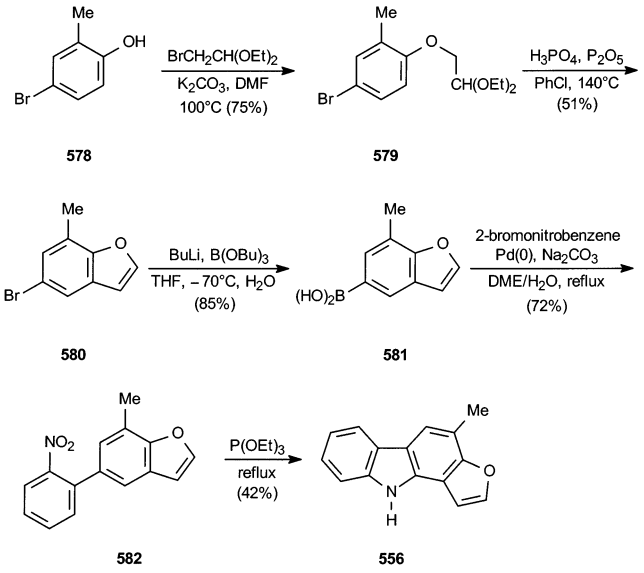


Scheme 161



furostifoline (**556**) in nine steps and 43% overall yield based on compound **387**.

Scheme 162



3. Total Synthesis of Furostifoline via Reductive Cyclization of an *o*-Nitrobiaryl

In 1999, Timári et al. reported the total synthesis of furostifoline (**556**) from the bromocresol **578**. The key steps of their approach are the Suzuki coupling to the *o*-nitrobiaryl compound **582** and the subsequent reductive cyclization via a nitrene intermediate. Annulation of the furan ring at the bromocresol **578** by reaction with bromoacetaldehyde diethyl acetal[286] afforded 5-bromo-7-methylbenzofuran **580**. A halogen/metal exchange reaction of 5-bromo-7-methylbenzofuran **580** with *n*-butyllithium and subsequent treatment with tributyl borate gave the boronic acid derivative **581**. The palladium(0)-catalyzed cross-coupling of the boronic acid derivative **581** with 2-bromonitrobenzene provided the *o*-nitrobiaryl compound **582** in 72% yield. Using Cadogan's method, by reductive cyclization with triethyl phosphite,[294] the *o*-nitrobiaryl compound **582** was transformed to furostifoline (**556**) in 42% yield (Scheme 162).[295] Thus, furostifoline (**556**) was available in five steps and 10% overall yield based on compound **578**.

For more recent total syntheses of furostifoline, see section XI.3.

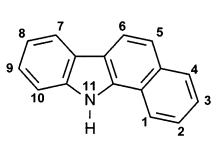
VI. Benzoannulated Carbazole Derivatives

1. Benzocarbazoles

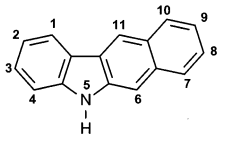
Benzo-annulated carbazole ring systems are found only rarely in natural products. They are of considerable interest, however, because of their potential as antitumor agents.[14,296−299] Moreover, many benzocarbazoles display further useful pharmacological properties.[296,297,300] The benzocarbazole frameworks are divided into the benzo[*a*]carbazoles **583**, benzo[*b*]-carbazoles **584**, and benzo[*c*]carbazoles **585**, depending on the position of the benzo ring fused at the A-ring of the 9*H*-carbazole nucleus (Scheme 163).

Among the various benzocarbazoles, a series of simple benzo[*a*]carbazoles, e.g. **586**, have been shown

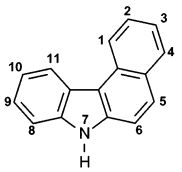
Scheme 163



583 11*H*-Benzo[*a*]carbazole

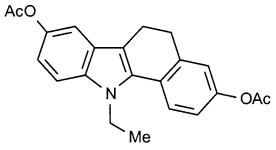


584 5*H*-Benzo[*b*]carbazole

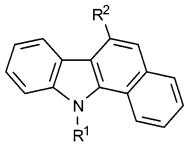


585 7*H*-Benzo[*c*]carbazole

Scheme 164

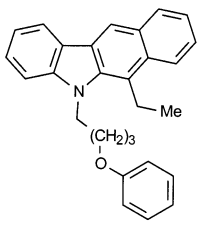


586

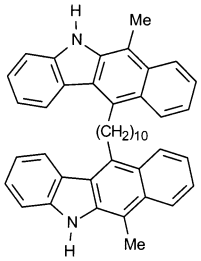


587 R^1 = SO_2Ph; R^2 = H
588 R^1, R^2 = Me

Scheme 165



589



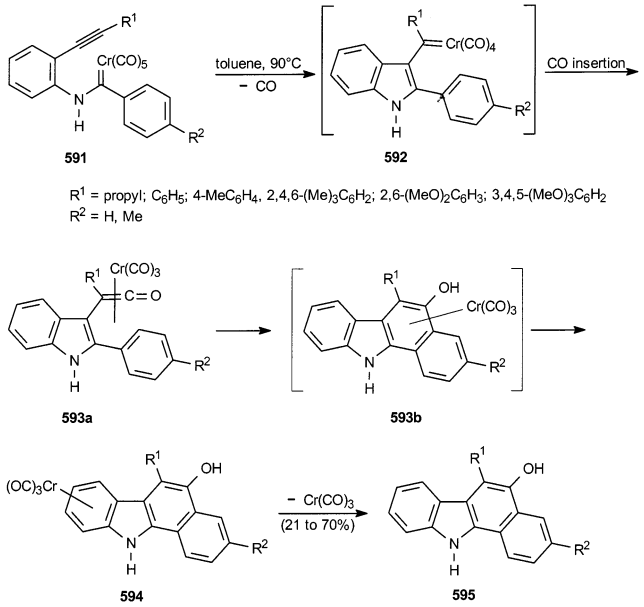
590

to bind to estrogen receptors and inhibit the growth of mammary tumors of rats.[301] Other benzo[*a*]carbazoles, such as **587** and **588**, exhibit a pronounced antitumor activity against leukemia, renal tumor, colon cancer, and malignant melanoma tumor cell lines (Scheme 164).[302] Benzo[*a*]carbazole derivatives have also found extensive application as photographic materials.[303]

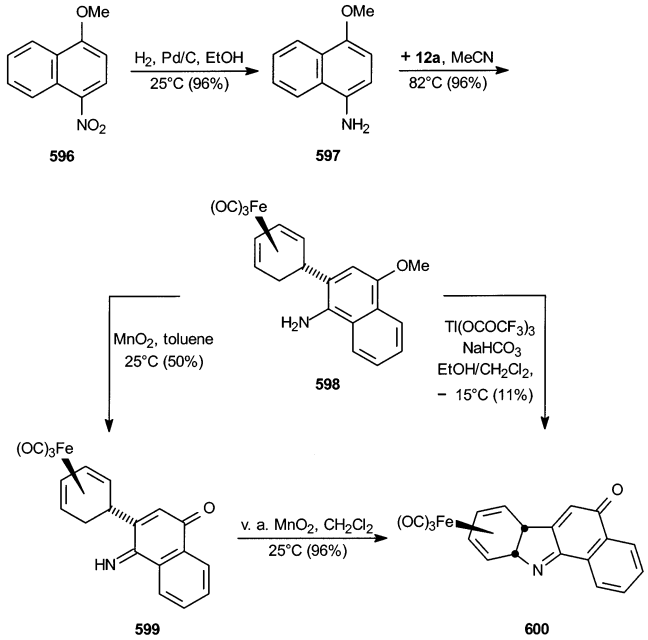
Among the different 2-deazaellipticine derivatives that were investigated, the benzo[*b*]carbazole **589** was found to have cytostatic activity against leukemia type L 1210 cell culture.[304] The 1,10-bis(6-methyl-5*H*-benzo[*b*]carbazol-11-yl)decane **590** represents a potential bifunctional nucleic acid intercalating agent (Scheme 165).[305]

A separate discussion of the synthetic approaches to the different isomeric benzocarbazoles is difficult, because many routes lead to the formation of more than a single benzocarbazole isomer. The methods that were employed for the synthesis of the various benzocarbazole derivatives range from polar (ionic) over radical to pericyclic type of reactions.[18,306−308] Complementary to these more classical synthetic strategies, various transition metal-mediated reactions have been applied as well.[19,309]

Scheme 166



Scheme 167



1.1. Benzannulations of Aminocarbene–Chromium Complexes

Dötz and co-workers reported the synthesis of the 11*H*-benzo[*a*]carbazoles **595** from the aminocarbene–chromium complexes **591**. The required complexes **591** were prepared by known methods from 2-(alkynyl)anilines and acetoxycarbene complexes. The acetoxycarbene complexes are available by reaction of tetramethylammonium pentacarbonylacyl chromate[310] with acetyl bromide.[311,312] On warming in toluene to 90 °C, the alkynylanilinocarbene complexes **591** undergo a tandem alkyne insertion/carbonylation reaction to give directly the 11*H*-benzo[*a*]carbazoles **595** via the indol-3-ylketene complexes **593a**. The formation of the 11*H*-benzo[*a*]carbazoles **595** can be rationalized by an insertion of the alkyne into the chromium–carbene bond to generate an intermediate 3-indolylcarbene complex **592**. A carbonyl insertion affords the 3-indolylketenes **593a**, which undergo an electrocyclic ring-closure to complex **593b**, followed by a haptotropic migration of the transition metal fragment to generate the chromiumtricarbonyl-coordinated benzo[*a*]carbazole **594**. Finally, demetalation provides the 11*H*-benzo[*a*]carbazoles **595** (Scheme 166).[309,313–315] The yield of the benzannulation product depends on the solvent and also on the steric demand of the substitutent at the alkyne terminus of the anilinocarbene complex.

1.2. Iron-Mediated Synthesis

The construction of the benzo[*a*]carbazole skeleton **600** was also achieved using the iron-mediated quinone imine cyclization. Electrophilic aromatic substitution of 4-methoxynaphth-1-ylamine **597**, obtained by reduction of the commercial nitro derivative **596**, with the complex salt **12a** provided the tricarbonyliron complex **598** almost quantitatively. Two alternative procedures were used for the transformation of the iron complex **598** to the benzo[*a*]carbazole skeleton **600** (Scheme 167).[38] The first procedure involves a sequential oxidation by two differently activated manganese dioxides with isolation of the intermediate noncyclized quinone imine **599**. Alternatively, complex **598** was oxidized directly to complex **600** by treatment with thallium(III) trifluoroacetate. In this one-pot transformation, the noncyclized quinone imine **599** is not isolated.

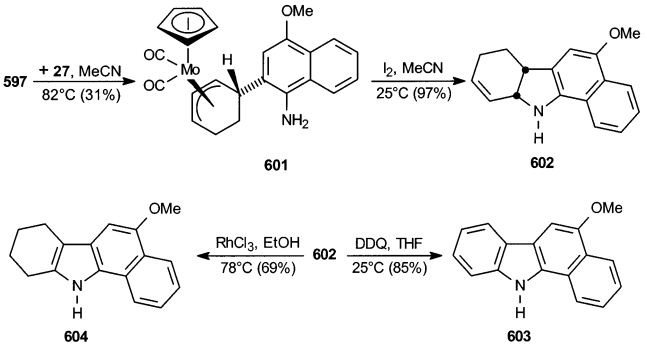
1.3. Molybdenum-Mediated Synthesis

Starting with the naphthylamine **597**, the molybdenum-mediated synthesis offers a flexible route to the benzo[*a*]carbazole **603** and different tetrahydro derivatives. The key steps of this approach are the electrophilic substitution of the arylamine by the dicarbonyl(η^5-cyclopentadienyl)molybdenum-coordinated cyclohexadiene **27** and the subsequent oxidative cyclization. Reaction of dicarbonyl(η^4-cyclohexa-1,3-diene)(η^5-cyclopentadienyl)molybdenum hexafluorophosphate **27**[40] with the naphthylamine **597** afforded regio- and stereoselectively complex **601** in 31% yield. The oxidative cyclization of complex **601** using iodine in acetonitrile at room temperature gave the 6b,7,8,-10a-tetrahydrobenzo[*a*]carbazole **602**. Aromatization of compound **602** with DDQ afforded the benzo[*a*]-carbazole **603**. An isomerization of the double bond of **602** catalyzed by rhodium(III) chloride provided the 7,8,9,10-tetrahydrobenzo[*a*]carbazole **604** (Scheme 168).[113]

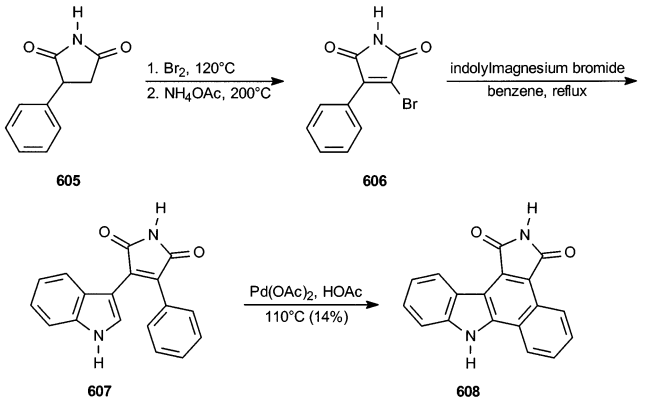
1.4. Palladium-Mediated Synthesis

Hill et al. described the synthesis of the maleimidobenzo[*a*]carbazole **608** using a palladium-mediated oxidative cyclization as the key step. Bromination of 3-phenylsuccinimide **605** and reaction of the resulting 4-bromo-3-phenylmaleimide **606** with indolylmagnesium bromide afforded 3-(indol-3-yl)-4-phenylmaleimide **607**. Finally, oxidative cyclization of compound **607** with palladium(II) acetate provided 5,6-maleimido-11*H*-benzo[*a*]carbazole **608** in 14% yield (Scheme 169).[316a] More recently, Routier and co-

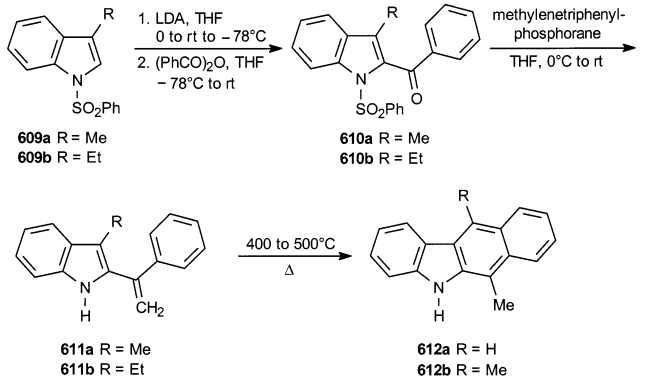
Scheme 168



Scheme 169



Scheme 170

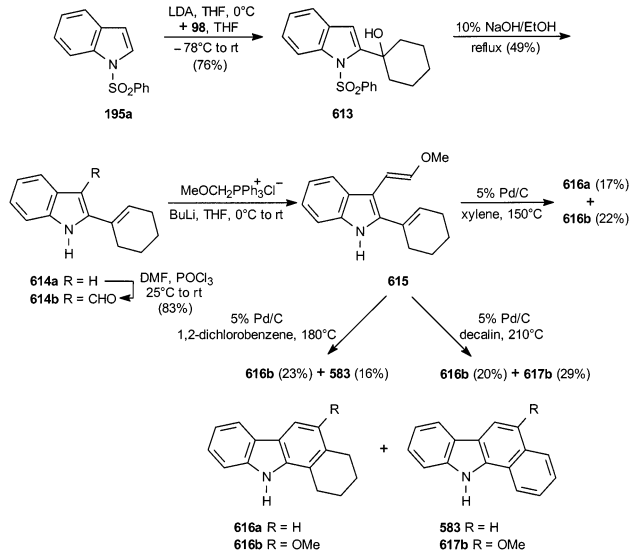


workers prepared a naphtho[2,3-*a*]pyrrolo[3,4-*c*]carbazole using a similar sequence.[316b]

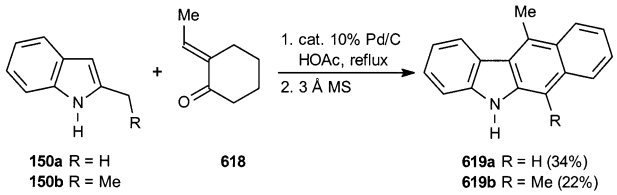
1.5. Benzannulation of Indoles

Thermal Cyclization of Indoles. Kano et al. reported the synthesis of the 6-methyl-5*H*-benzo[*b*]carbazole derivatives **612** starting from the *N*-protected-3-alkylindoles **609**. This synthesis involves as the key step a thermal electrocyclization of the 3-alkyl-2-(α-phenylvinyl)indoles **611**. Lithiation of the *N*-protected 3-alkylindoles **609** followed by acylation with benzoic anhydride afforded the 2-benzoylindoles **610**.[317] The benzoyl derivatives **610** were transformed to the methylene derivatives **611** by a Wittig olefination. A thermal electrocyclization of the compounds **611** at 400−500°C provided the 6-methyl-5*H*-benzo[*b*]carbazoles **612a** and **612b** in 26% and 25% yield, respectively (Scheme 170).[318] The thermal cyclization of the 3-ethyl derivative proceeded at a lower temperature than for the corresponding methyl compound. This reaction was extended to the synthesis of the 9-chloro derivatives by using chlorobenzoic anhydride for the acylation step.

Scheme 171



Scheme 172

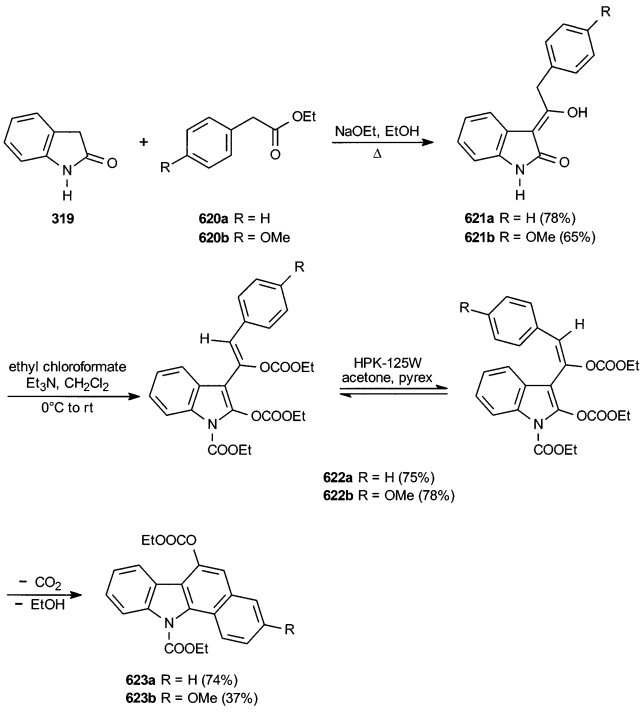


The thermal electrocyclization of the 2,3-divinylindole **615** was also applied to the synthesis of benzo[*a*]carbazole derivatives. In this approach, the intermediate dihydrocarbazoles are dehydrogenated to carbazoles with palladium on activated carbon. Lithiation of the *N*-(phenylsulfonyl)indole **195a**[317] and addition to cyclohexanone **98** gave 2-(1-hydroxycyclohex-1-yl)indole **613**. Elimination of **613** to 2-(cyclohexen-1-yl)indole **614a** followed by Vilsmeier formylation provided the indole-3-carbaldehyde **614b**. Wittig reaction of compound **614b** with (methoxymethylene)triphenylphosphorane afforded 2-(cyclohexen-1-yl)-3-(*β*-methoxyvinyl)indole **615**. With 5% palladium on activated carbon in different high boiling solvents, the 2,3-divinylindole **615** was transformed to a mixture of the tetrahydrobenzo[*a*]carbazoles **616** and the fully aromatized benzo[*a*]carbazoles **583** and **617b**, with or without removal of the methoxy group (Scheme 171).[138]

Bergman et al. reported a direct synthesis of the substituted 5*H*-benzo[*b*]carbazoles **619**. Reaction of the 2-alkylindoles **150** with 2-ethylidenecyclohexanone **618** in the presence of 10% palladium on activated carbon in refluxing acetic acid and addition of 3 Å molecular sieves (MS) afforded the 5*H*-benzo[*b*]carbazoles **619** (Scheme 172).[319]

Photoinduced Electrocyclization. In 1971, Snieckus et al. reported the photochemical cyclization of 2-styrylindoles in the presence of iodine or air for the synthesis of 7*H*-benzo[*c*]carbazoles. This method involves a double bond isomerization followed by 6π-electrocyclization and dehydrogenation.[320,321] Three

Scheme 173

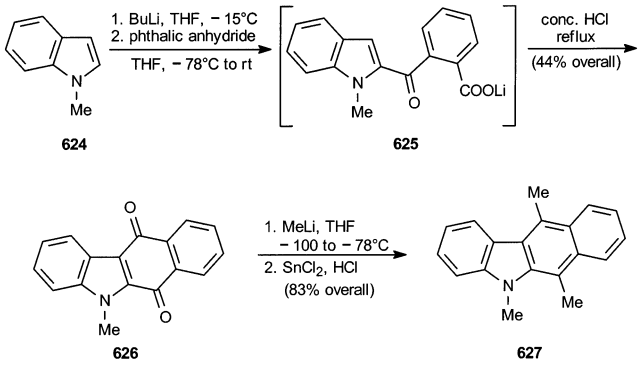


years later, Carruthers and Evans utilized the procedure for the cyclization of 3-styrylindoles to 11*H*-benzo[*a*]carbazoles.[322] In the same year a further extension was described by Mudry and Frasca, who cyclized 2,3-diphenylindoles to 9*H*-dibenzo[*a*,*c*]carbazoles.[323] All these applications of the oxidative photolytic electrocyclizations are well-covered in Sakamoto's review.[18] In 1992, Marchesini et al. reported the nonoxidative photocyclization of the 3-styrylindoles **622a,b** to the 11*H*-benzo[*a*]carbazoles **623a,b**, which involves an *E*,*Z*-isomerization followed by 6π-electrocyclization and aromatization by elimination of ethanol and carbon dioxide. Condensation of the indol-2(3*H*)-one **319** with the ethyl aryl acetates **620** afforded the 3-(arylacetyl)indol-2(3*H*)-ones **621**,[324] which were transformed to the stereoisomerically pure 3-styrylindoles **622** by reaction with an excess of ethyl chloroformate and triethylamine. By photolysis the compounds **622a,b** were cyclized to the 11*H*-benzo[*a*]carbazoles **623** (Scheme 173).[325,326] This method has the advantage over the earlier oxidative photocyclizations[320−323] that it can be applied to the cyclization of trienes, which are sensitive toward oxidation.

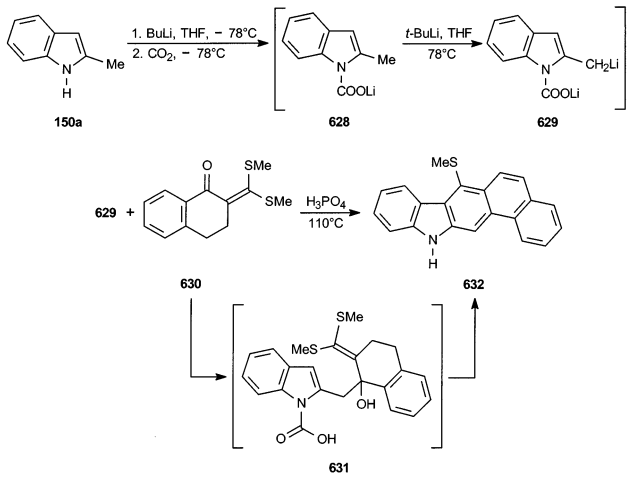
Synthesis of 5,6,11-Trimethyl-5*H*-benzo[*b*]carbazole. In 1994, Koomen and co-workers reported the synthesis of the trimethylbenzo[*b*]carbazole **627** starting from 1-methylindole **624**. Selective deprotonation of 1-methylindole **624** at C-2 with BuLi and addition of phthalic anhydride afforded the intermediate lithium salt **625**, which was cyclized to the quinone **626** using strongly acidic conditions. Double methylation of the quinone **626** with methyllithium followed in situ by reduction with tin(II) chloride provided directly 5,6,11-trimethyl-5*H*-benzo[*b*]carbazole **627** (Scheme 174).[327a]

More recently, Gribble and Fraser described the synthesis of 6,11-disubstituted benzo[*b*]carbazoles by

Scheme 174



Scheme 175



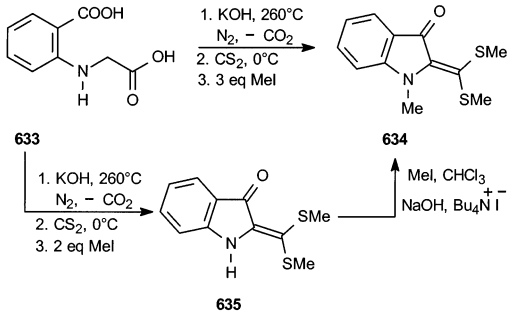
sequential regioselective addition of organolithium reagents.[327b]

Synthesis of 5*H*-Benzo[*b*]- and 7*H*-Benzo[*c*]-carbazoles. In 1998, Ila and Junjappa et al. reported the synthesis of the compound **632**, which represents a 5*H*-benzo[*b*]carbazole fused to a further benzo ring. They applied the regiospecific condensation of 2-methylindole **150a** with the tetralone derivative **630**. Reaction of the dianion **629**, generated from **150a** by using Katritzky's protocol,[328] with the oxoketene dithioacetal **630** gave the intermediate carbinol **631**, which afforded compound **632** on subsequent cycloaromatization using phosphoric acid at 110 °C (Scheme 175).[329]

In the following year, the same authors extended their heteroaromatic annulation to the synthesis of the benzo[*c*]carbazoles **638** and **641**. This approach uses *N*-methyl 2-bis(methylthio)methylene-3-oxoindole **634** as electrophilic reagent, which was prepared in 45% yield in a one-pot reaction from *N*-phenylglycine-*o*-carboxylic acid **633**. Treatment of **633** with potassium hydroxide followed by addition of carbon disulfide at 0 °C and 3 equiv of methyl iodide afforded **634**. Alternatively, *N*-methyl 2-bis(methylthio)methylene-3-oxoindole **634** was prepared via the intermediate 2-bis(methylthio)methylene-3-oxoindole **635** by sequential addition of methyl iodide (Scheme 176).[330]

The addition of the anion of phenylacetonitrile **636** to the 3-oxoindole **634** afforded compound **637** by elimination of methanethiol. Cycloaromatization of **637** was again achieved by heating in the presence of phosphoric acid and provided the benzo[*c*]carbazole

Scheme 176



638 in 59% overall yield. Using identical conditions, the reaction of 1-naphthylacetonitrile **639** with **634** afforded in 41% overall yield the benzo[*c*]carbazole **641** with an additionally annulated benzo ring (Scheme 177).[330]

Synthesis of 11*H*-Benzo[*a*]carbazoles. De Koning et al. described the synthesis of the 11*H*-benzo[*a*]carbazoles **645** from 2-bromoindole-3-carbaldehyde **642a** using the base-induced photocyclization of the 2-arylindoles **644** as the key step. Alkylation of 2-bromoindole-3-carbaldehyde **642a**[331,332] with potassium bis(trimethylsilyl)amide (KHMDS) and methyl iodide gave the *N*-methyl derivative **642b**. A palladium(0)-catalyzed Suzuki cross-coupling of **642b** with the boronic acids **643** afforded the corresponding 2-arylindoles **644**, which were transformed to the 11*H*-benzo[*a*]carbazoles **645** via a base-induced photocyclization (Scheme 178).[333,334]

1.6. Fischer Indolization of Phenylhydrazones

Synthesis of 11-Alkyl-11*H*-benzo[*a*]carbazoles. The synthesis of the 11-alkyl-11*H*-benzo[*a*]carbazoles **651** and their 5,6-dihydro derivatives **649** and **650** was reported by von Angerer and Prekajac. Condensation of the arylhydrazine hydrochlorides **646** with the tetralones **647** and subsequent Fischer indolization afforded the 5,6-dihydro-11*H*-benzo[*a*]carbazole derivatives **648**.[335] Alkylation of **648** to the corresponding *N*-alkyl derivatives **649** followed by ether cleavage and acetylation gave the acetoxy-substituted 5,6-dihydro-11-alkyl-11*H*-benzo[*a*]carbazoles **650b**. Aromatization of **650b** with 2,3-dichloro-4,6-dicyanobenzoquinone (DDQ) to **651a** and hydrolysis afforded the 11-alkyl-11*H*-benzo[*a*]carbazoles **651b** (Scheme 179).[301]

Synthesis of 8,10-Disubstituted 11*H*-Benzo[*a*]carbazoles and 7*H*-Benzo[*c*]carbazole. Katritzky et al. applied the Fischer indolization to the synthesis of the substituted 11*H*-benzo[*a*]carbazoles **583**, **656**, and **657**. Condensation of the phenyl hydrazines **652** with α-tetralone **647a** followed by Fischer indolization[336] afforded the dihydrocarbazoles **653**−**655**. Dehydrogenation of the compounds **653**−**655** using 5% palladium on activated carbon provided the corresponding 11*H*-benzo[*a*]carbazoles **583**, **656**, and **657**. Starting from *β*-tetralone **658** and using the same reaction conditions, the 7*H*-benzo[*c*]carbazole **585** was obtained via the intermediate dihydrocarbazole **659** (Scheme 180).[337]

This methodology was also extended to the synthesis of dihydro-7*H*-dibenzo[*c*,*g*]carbazoles and 13*H*-dibenzo[*a*,*i*]carbazoles by using 1 equiv of the hydrazine and 2 equiv of α-tetralone or *β*-tetralone, respectively.[337]

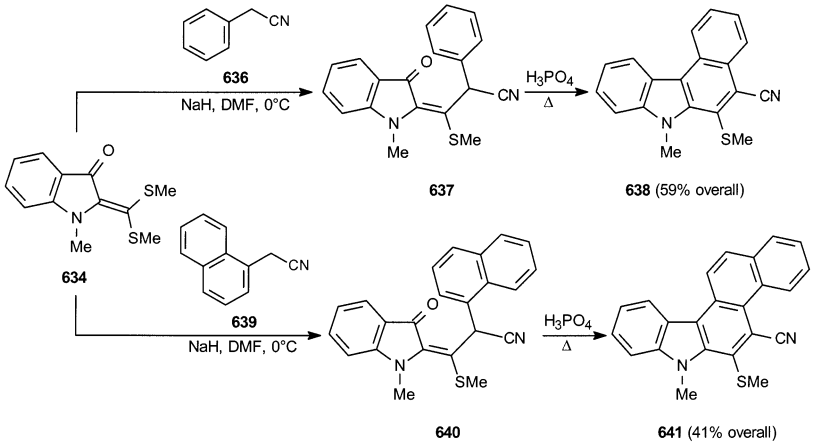
Synthesis of Trisubstituted Dihydrobenzo[*a*]carbazoles. Using von Angerer's method and the precursors **646b** and **647b** (cf. Scheme 179),[301] Pizzorno et al. reported in 1995 the synthesis of a new series of *N*-substituted 5,6-dihydro-11-alkyl-11*H*-benzo[*a*]carbazoles **661** with an alkyl side chain containing a second nitrogen atom (Scheme 181).[338]

These molecules were designed to study the estradiol receptor binding affinity at the rabbit uterus[339] and showed binding affinities similar to tamoxifen.[340] Moreover, they were tested for their potential inhibitory activity against mammary carcinomas in rats induced by *N*-nitroso-*N*-methylurea (NMU).[341]

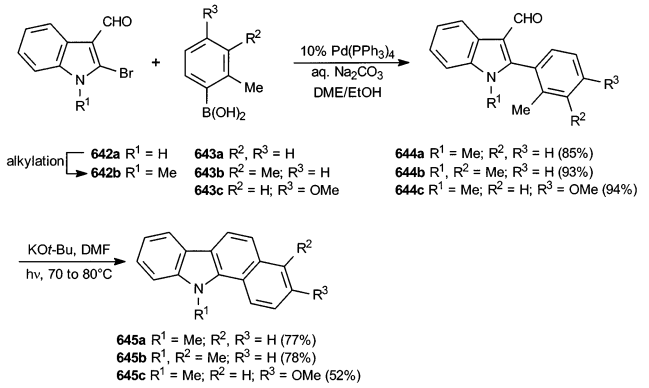
Synthesis of 11*H*-Benzo[*a*]- and 5*H*-Benzo[*b*]carbazoles. On the basis of the Fischer indole synthesis described by Rogers and Corson,[342] Kirsch et al. reported in 1996 the synthesis of the 11*H*-benzo[*a*]carbazoles **583** and **662** from α-tetralone **647a** and the arylhydrazine hydrochlorides **646a** and **646b** via the intermediate 5,6-dihydro-11*H*-benzo[*a*]carbazoles **653** and **648e**. The dehydrogenation of the dihydrobenzocarbazoles **653** and **648e** with DDQ in refluxing benzene provided the 11*H*-benzo[*a*]carbazoles **583** and **662** (Scheme 182).

The same authors reported the synthesis of 6-hydroxy-2-methoxy-5*H*-benzo[*b*]carbazole **665**. Condensation of α-tetralone **647a** with ethyl formate to *β*-hydroxymethylene-α-tetralone **663** followed by

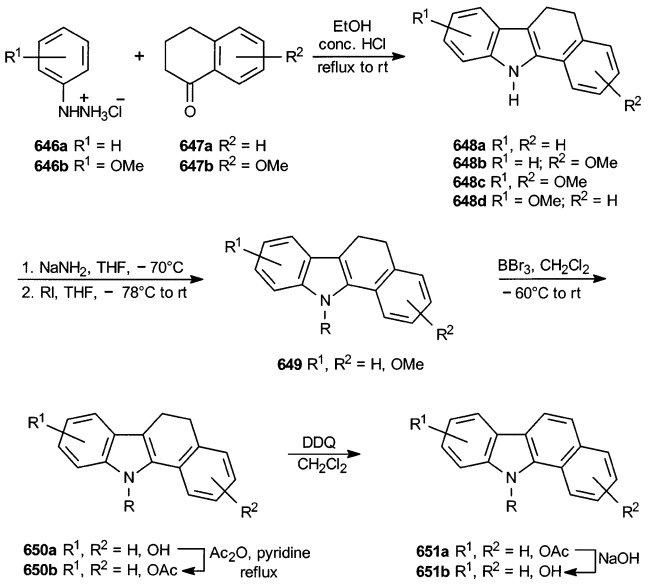
Scheme 177



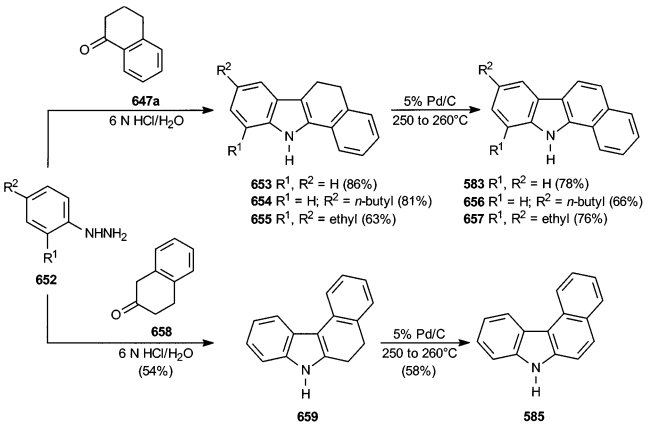
Scheme 178



Scheme 179

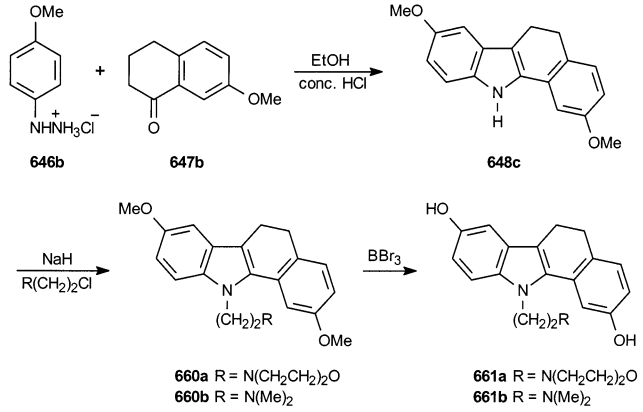


Scheme 180

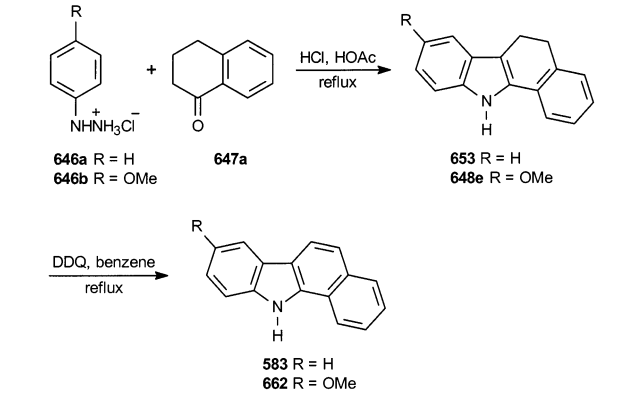


Japp−Klingemann reaction with 4-methoxyphenyldiazonium chloride **100c** afforded the hydrazone **664**. Under acidic reaction conditions,[343] compound **664** was cyclized directly to 6-hydroxy-2-methoxy-5*H*-benzo[*b*]carbazole **665** (Scheme 183).[344] However, when a similar reaction was carried out with phenyldiazonium chloride, the corresponding azo derivative was formed as a result of aromatization without cyclization.[344] The presence of the methoxy group in the para-position of the phenyl ring in **664** appears to favor the cyclization over the aromatization.

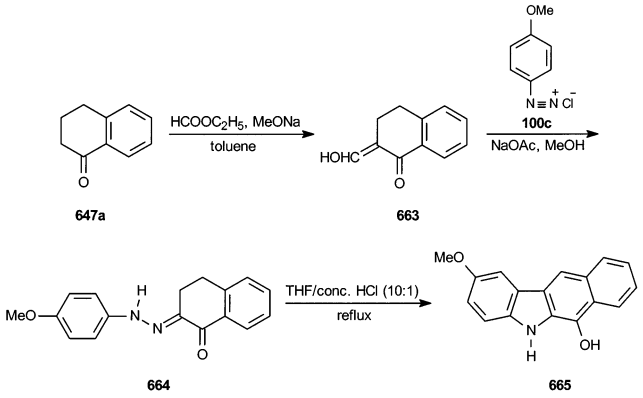
Scheme 181



Scheme 182



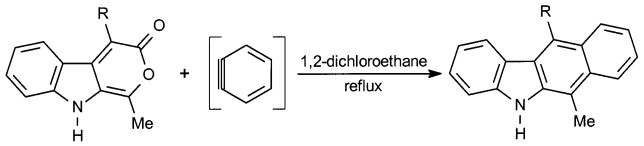
Scheme 183



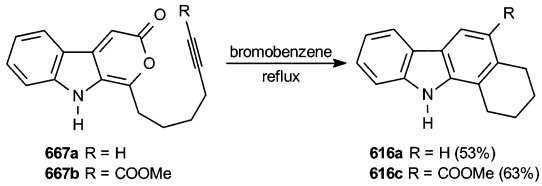
1.7. Diels–Alder Reaction of Pyrano[3,4-b]indol-3-ones

Synthesis of Substituted 5*H*-Benzo[*b*]carbazoles. In 1984, Moody reported the synthesis of the 5*H*-benzo[*b*]carbazoles **612** using the pyrano[3,4-*b*]-indol-3-ones **211** without protection of the indole nitrogen as stable equivalents for indole-2,3-quinodimethanes in Diels−Alder reactions. The pyrano-[3,4-*b*]indol-3-ones **211a**,**d** were prepared following literature procedures by reaction of acetic anhydride either with indole-3-acetic acid[145] or with α-methylindole-3-acetic acid (obtained by reaction of indole with lactic acid).[345] The Diels−Alder cycloaddition of the pyranoindolones **211** with benzyne **666** (obtained from benzenediazonium 2-carboxylate)[142,143] in boiling 1,2-dichloroethane generated in a one-pot process the 5*H*-benzo[*b*]carbazoles **612a**,**b**. Using the commercially available 2-(3,3-dimethyltriazene-1-yl)-

Scheme 184



Scheme 185



benzoic acid as benzyne precursor,[346] the 5*H*-benzocarbazoles **612** were obtained in lower yields (Scheme 184). This method represents the shortest route to the 5*H*-benzo[*b*]carbazoles (three steps from indole).[142,143]

In an extension of Moody's method, Pindur and coworkers reported the synthesis of substituted benzo[*b*]carbazole derivatives starting from different pyranoindolones. The same authors also described the synthesis of nitrobenzocarbazoles as a result of nitration by isoamyl nitrite/trichloroacetic acid during the generation of benzyne.[347−349]

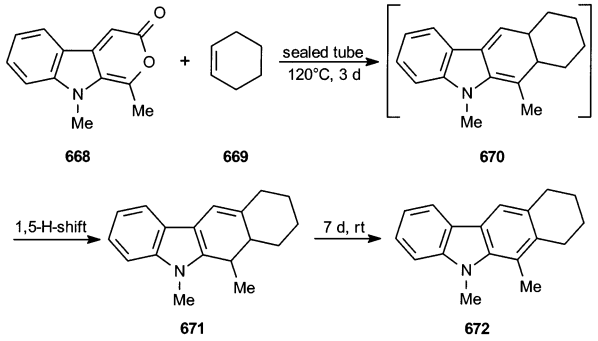
Synthesis of Tetrahydro-11*H*-benzo[*a*]carbazoles. In 1988, Moody et al. developed an intramolecular version of their pyrano[3,4-*b*]indol-3-one cycloaddition methodology using 1-alkynylpyrano[3,4-*b*]indol-3-ones for the synthesis of cycloalka[*a*]carbazoles. The 1-hexynylpyrano[3,4-*b*]indol-3-ones **667** were obtained from the corresponding alkynoic acids[350] by conversion into the anhydride, followed by reaction with indole-3-acetic acid in the presence of boron trifluoride.[143,144] Heating of the compounds **667** in refluxing bromobenzene resulted in intramolecular Diels−Alder reaction with concomitant extrusion of carbon dioxide to the tetrahydro-11*H*-benzo[*a*]carbazoles **616a**,**c** (Scheme 185).[351]

Synthesis of a Tetrahydro-5*H*-benzo[*b*]carbazole. Hoornaert and co-workers reported the synthesis of the tetrahydro-5*H*-benzo[*b*]carbazole **672** from 1,9-dimethylpyrano[3,4-*b*]indol-3-one **668**. In this reaction the pyranoindolone **668** was heated with neat cyclohexene **669** in a sealed tube to give 5,6-dimethyl-6,6a,7,8,9,10-hexahydro-5*H*-benzo[*b*]carbazole **671** as the result of a 1,5-sigmatropic hydrogen shift at the stage of the intermediate **670**. Dehydrogenation of compound **671** provided 5,6-dimethyl-7,8,9,10-tetrahydro-5*H*-benzo[*b*]carbazole **672** (Scheme 186).[352]

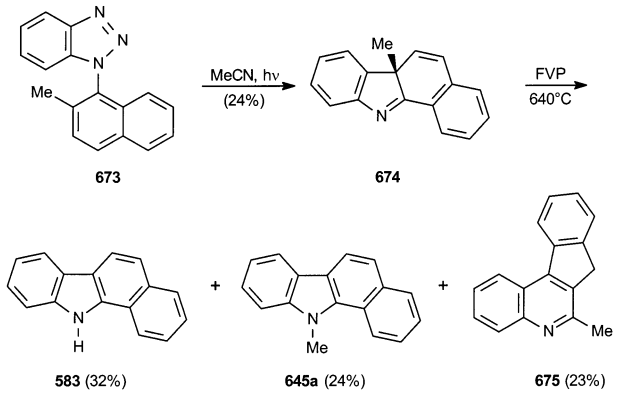
1.8. Synthesis of 11H-Benzo[a]carbazoles and 7H-Benzo[c]carbazoles by FVP

In 1985, Moody et al. reported a new method for the synthesis of 11*H*-benzo[*a*]carbazoles and 7*H*-benzo[*c*]carbazoles by flash vacuum pyrolysis of 6a-methyl-6a*H*-benzo[*a*]carbazole **674** and 11b-methyl-

Scheme 186



Scheme 187



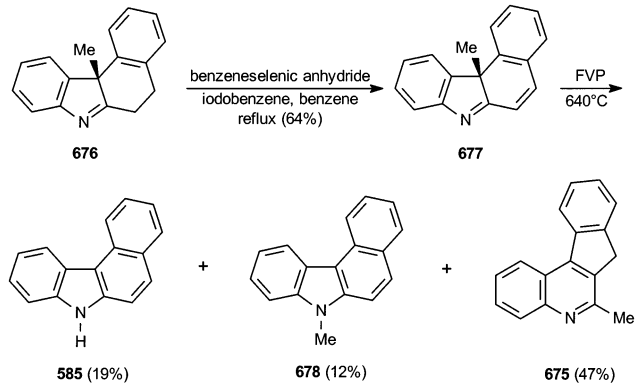
11b*H*-benzo[*c*]carbazole **677**, respectively. The 6a*H*-benzo[*a*]carbazole **674** was prepared by irradiation of the benzotriazole **673** (Graebe−Ullmann synthesis). Alternatively, compound **674** can be obtained from the corresponding dihydro compound[353] by radical bromination with NBS and subsequent dehydrobromination using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base. Compound **674** was subjected to a flash vacuum pyrolysis (FVP) at 640 °C and 0.03 mmHg to give the 11*H*-benzo[*a*]carbazoles **583** and **645a**, along with the angular indenoquinoline **675** (Scheme 187).[354,355]

Dehydrogenation of the dihydro-11b*H*-benzo[*c*]carbazole **676** with benzeneselenic anhydride and iodobenzene[356] in refluxing benzene afforded 11b-methyl-11b*H*-benzo[*c*]carbazole **677**. Flash vacuum pyrolysis of **677** using the same reaction conditions as described above provided the 7*H*-benzo[*c*]carbazoles **585** and **678** along with the same indenoquinoline **675** (Scheme 188).[354,355]

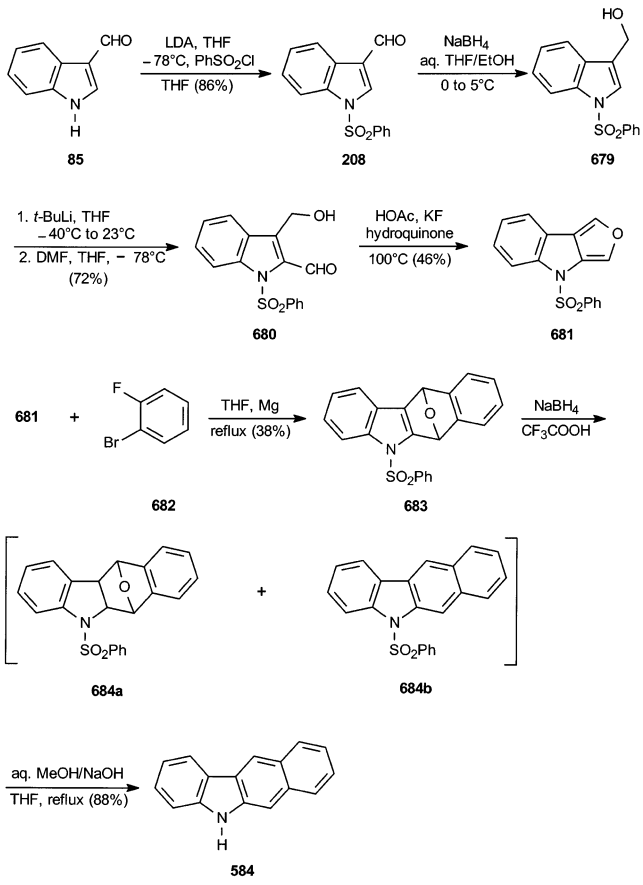
1.9. Diels–Alder Reaction of 4H-Furo[3,4-b]indoles

Synthesis of 5*H*-Benzo[*b*]carbazoles. In 1983, Gribble et al. reported the synthesis of 5*H*-benzo[*b*]carbazole **584** using a 4*H*-furo[3,4-*b*]indole cycloaddition methodology. The key step is a Diels−Alder reaction of 4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole **681** with in situ generated benzyne followed by removal of the oxygen bridge. The furo[3,4-*b*]indole **681** was prepared from commercially available 3-formylindole **85** in four steps and 28% overall yield. Protection of 3-formylindole **85** to the *N*-phenylsulfonyl derivative **208** and subsequent reduction with sodium borohydride gave the alcohol **679**. Dilithiation of **679** using *tert*-butyllithium and reaction with

Scheme 188



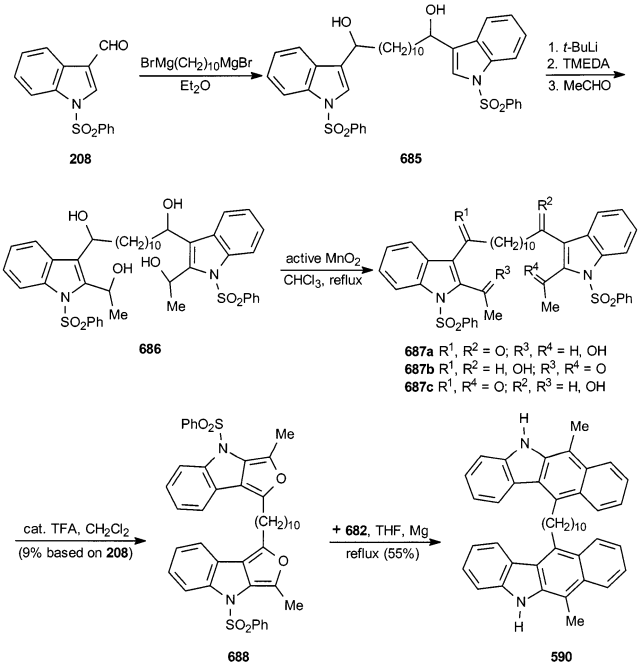
Scheme 189



dimethylformamide afforded regioselectively the indole-2-carbaldehyde **680**. Ring closure of **680** by heating with glacial acetic acid in the presence of potassium fluoride and hydroquinone provided the furo[3,4-*b*]indole **681** in 46% yield. Reaction of **681** with benzyne (generated from 1-bromo-2-fluorobenzene **682** and magnesium)[357] afforded the corresponding Diels−Alder adduct **683** in 38% yield. Reduction of **683** with sodium borohydride in trifluoroacetic acid gave a mixture of the products **684a** and **684b**. Finally, treatment of this mixture with base led to 5*H*-benzo[*b*]carbazole **584** (Scheme 189).[358]

The intramolecular Diels−Alder reaction of 4*H*-furo[3,4-*b*]indoles was used for the synthesis of benzo[*a*]carbazoles and benzo[*c*]carbazoles.[359] Further applications of this methodology include the synthesis of 6,11-dialkyl-5*H*-benzo[*b*]carbazoles using 1,3-di-

Scheme 190



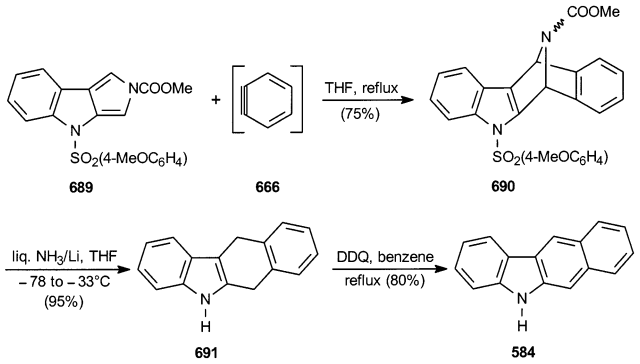
alkyl-substituted derivatives of **681** as indole-2,3-quinodimethane equivalents.[360] In 1992, Gribble and co-workers developed a new benzannulation methodology for the synthesis of 5*H*-benzo[*b*]carbazoles that proceeds via an indole keto lactam intermediate.[361]

Synthesis of 1,10-Bis(6-methyl-5*H*-benzo[*b*]carbazol-11-yl)decane. In 1984, Gribble et al. extended the 4*H*-furo[3,4-*b*]indole cycloaddition methodology to the synthesis of 1,10-bis(6-methyl-5*H*-benzo[*b*]carbazol-11-yl)decane **590**, a potential DNA bis-intercalating agent. This approach features the bis-4*H*-furo[3,4-*b*]indole **688** as a double indole-2,3-quinodimethane equivalent for a double Diels−Alder reaction with benzyne. Addition of the bis-Grignard reagent 1,10-dibromodecane to 1-phenylsulfonylindole-3-carbaldehyde **208** gave the diol **685** as a mixture of diastereoisomers in 93% yield. Lithiation of the diol **685** followed by regioselective quenching with acetaldehyde afforded a diastereoisomeric mixture of the tetraol **686**, which on oxidation with activated manganese dioxide provided a mixture of the regio- and diastereoisomeric hydroxy ketones **687a**−**c**. The hydroxy ketones **687a**−**c** were converted into the single bis-4*H*-furo[3,4-*b*]indole **688** by refluxing in dichloromethane containing catalytic amounts of trifluoroacetic acid. The reaction of the bis-4*H*-furo[3,4-*b*]indole **688** with benzyne gave two isomeric Diels−Alder adducts, which were subjected to deoxygenation and desulfonation without isolation to provide 1,10-bis(6-methyl-5*H*-benzo[*b*]carbazol-11-yl)decane **590** in 5% overall yield based on **208** (Scheme 190).[305]

1.10. Diels–Alder Reaction of a 2,4-Dihydropyrrolo[3,4-b]-indole

Sha and co-workers reported the synthesis of 5*H*-benzo[*b*]carbazole **584** using the *N*-arylsulfonyl-2,4-dihydropyrrolo[3,4-*b*]indole **689** as an indole-2,3-

Scheme 191



quinodimethane equivalent. The key step is the Diels−Alder reaction of **689** with benzyne **666**, followed by removal of the nitrogen bridge. Starting from 2-methylindole-3-carbaldehyde, the 2,4-dihydropyrrolo[3,4-*b*]indole **689** was prepared in six steps via an intramolecular 1,3-dipolar cycloaddition[362] and cycloreversion pathway.[363] The cycloaddition of **689** with benzyne **666** provided compound **690**, which was transformed to 6,11-dihydro-5*H*-benzo[*b*]carbazole **691** using Birch reduction conditions by reductive extrusion of the nitrogen bridge and *N*-deprotection. Finally, dehydrogenation of **691** with DDQ afforded 5*H*-benzo[*b*]carbazole **584** in 57% overall yield (Scheme 191).[364] Starting from 1,3-substituted 2,4-dihydropyrrolo[3,4-*b*]indoles, Kreher and Dyker reported the synthesis of substituted 5*H*-benzo[*b*]carbazoles by the same method.[365]

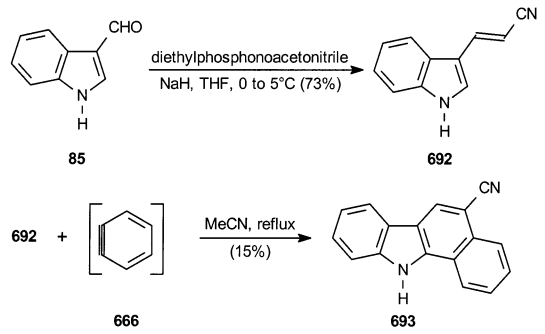
Further cycloaddition strategies leading to benzo[*b*]carbazole derivatives have been reported: Markgraf and Patterson described the synthesis of 5-methyl-5*H*-benzo[*b*]carbazole by Diels−Alder reaction of *N*-methylindole with 1,3-dihydrobenzo[*c*]thiophene-2,2-oxide as synthetic equivalent of *o*-xylylene (24% yield).[366] Vollhardt and co-workers obtained 5-phenylsulfonyl-5*H*-7,8,9,10-tetrahydrobenzo[*b*]carbazole via a cobalt-mediated [2 + 2 + 2]-cycloaddition of *N*-phenylsulfonylindole and 1,7-octadiyne (21% overall yield).[367]

1.11. Synthesis of 11H-Benzo[a]carbazoles by Diels–Alder Reaction of 3-Vinylindoles

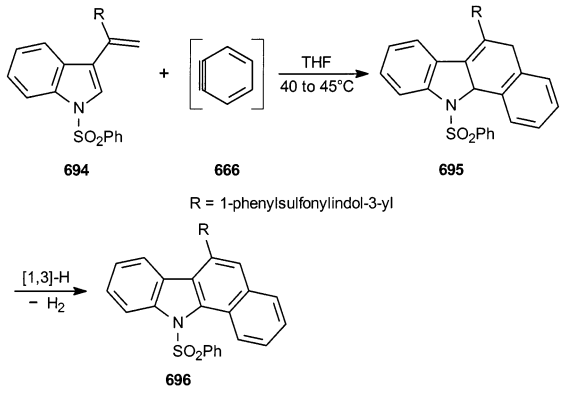
In 1982, Sainsbury et al. described the synthesis of 5-cyano-11*H*-benzo[*a*]carbazole **693** by Diels−Alder reaction of the 3-vinylindole **692** and benzyne **666**. The reaction of the ylide of diethylphosphonoacetonitrile with 3-formylindole **85** provided the 3-vinylindole **692**, which was transformed to 5-cyano-11*H*-benzo[*a*]carbazole **693** by heating with an excess of benzyne **666** (Scheme 192).[368a] An alternative synthesis of 5-cyano-11*H*-benzo[*a*]carbazole **693** as well as 5-methoxycarbonyl-11*H*-benzo[*a*]carbazole was reported by Galvez and co-workers using a photoinduced cyclization of 3*H*-indolespirocyclopropanes.[368b]

In an extension of Sainsbury's method, Pindur and co-workers reported in 1986 the synthesis of the 6-substituted 11*H*-benzo[*a*]carbazole **696** using the 1,1-bis(indol-3-yl)ethene **694** as diene. A Diels−Alder reaction of the *N*-protected 1,1-bis(indol-3-yl)ethene **694** with benzyne **666** afforded the cycloadduct **695**, which was dehydrogenated to the 11*H*-benzo[*a*]carbazole **696** (Scheme 193).[369,370] In 1996, Pindur et al. described the cycloaddition of donor- and acceptor-substituted 3-vinylindoles with benzyne to provide a variety of [*a*]annulated carbazoles.[302,371]

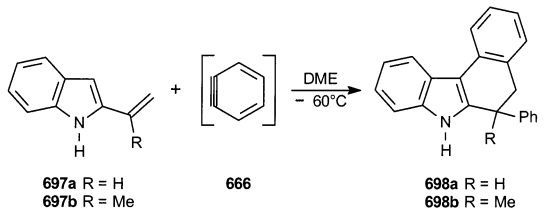
Scheme 192



Scheme 193



Scheme 194



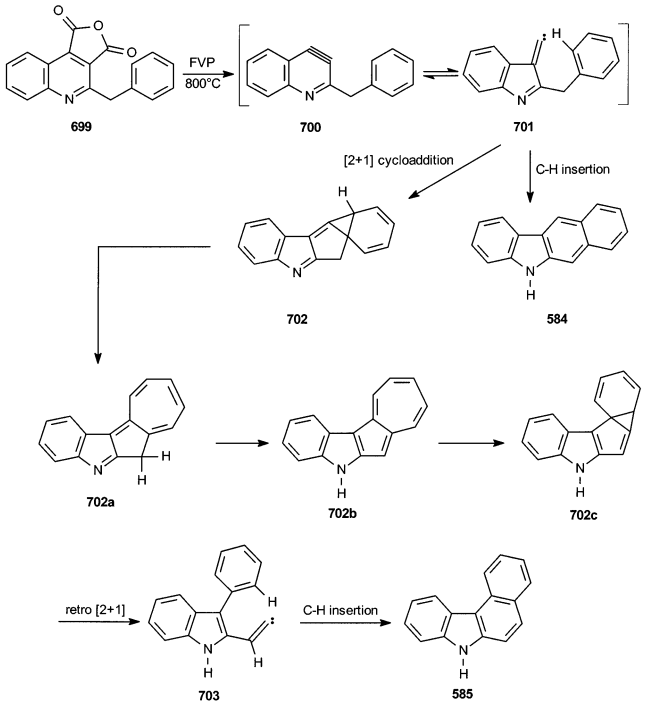
1.12. Synthesis of 7H-Benzo[c]carbazoles by Diels–Alder Reaction of 2-Vinylindoles

In 1991, Pindur and co-workers described the synthesis of 7*H*-benzo[*c*]carbazoles by using 2-vinylindoles for the Diels−Alder reaction with benzyne. The 2-vinylindoles **697** were added to in situ generated benzyne **666** in dimethoxyethane (DME) at −60 °C to give the 5,6-dihydro-7*H*-benzo[*c*]carbazoles **698** with a phenyl group in the 6-position. These products are believed to be the result of an ene reaction of the initially formed cycloadduct with a second molecule of benzyne (Scheme 194).[372]

1.13. FVP of 2-Benzylquinoline-3,4-dicarboxylic Anhydride

Brown et al. reported the synthesis of 5*H*-benzo[*b*]carbazole **584** and 7*H*-benzo[*c*]carbazole **585** by flash vacuum pyrolysis (FVP) of 2-benzylquinoline-3,4-dicarboxylic anhydride **699**. The synthesis of the dicarboxylic acid precursor for the anhydride **699** was prepared by Pfitzinger condensation of isatin with methyl 4-phenyl-3-oxobutanoate in 30% aqueous

Scheme 195



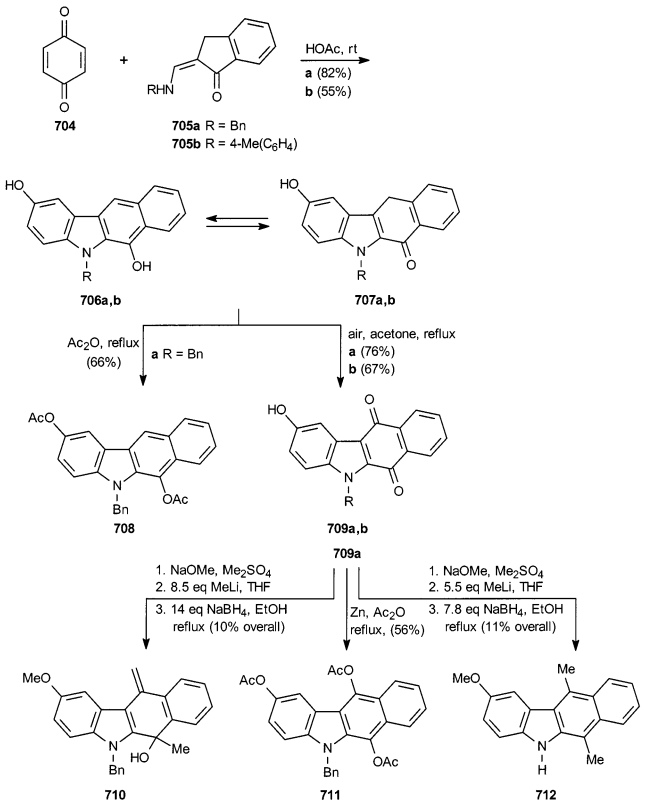
potassium hydroxide. Treatment of this diacid with acetic anhydride at 100 °C afforded 2-benzylquinoline-3,4-dicarboxylic anhydride **699**. Flash vacuum pyrolysis (FVP) of the anhydride **699** at 800 °C afforded 5*H*-benzo[*b*]carbazole **584** and 7*H*-benzo[*c*]carbazole **585** in a 1:2 ratio (Scheme 195).[373]

The FVP reaction leads to an equilibration of the aryne **700** and the exocyclic vinylcarbene **701**. An insertion of the carbene into a neighboring phenyl C−H bond generates the 5*H*-benzo[*b*]carbazole **584**. The formation of the 7*H*-benzo[*c*]carbazole **585** involves an initial [2 + 1]-cycloaddition of the carbene and a double bond of the phenyl ring to the norcaradiene **702**. An electrocyclic ring expansion of the norcaradiene **702** provides the cycloheptatriene **702a**. Tautomerization to the cycloheptatriene **702b**, followed by electrocyclic reaction to the norcaradiene **702c**, retro-[2 + 1]-cycloaddition to the vinylcarbene **703**, and insertion into a phenyl C−H bond, affords 7*H*-benzo[*c*]carbazole **585**. The condensation of 3-phenylindole-2-carbaldehyde with Meldrum's acid and subsequent FVP reaction at 900 °C provide a more direct way to the 3-phenylindol-2-ylvinyl carbene intermediate **703**, which leads to the exclusive formation of 7*H*-benzo[*c*]carbazole **585**, albeit in low yield (Scheme 195).[374]

1.14. Reaction of 2-Aminomethylene-1-indanones with 1,4-Benzoquinone

Kuckländer and co-workers reported the synthesis of different oxygenated benzo[*b*]carbazole derivatives **710**−**712** by condensation of 1,4-benzoquinone **704** with the 2-aminomethylene-1-indanones **705**. The indanones **705** were prepared from 2-(hydroxymethylene)indanone.[375] The acid-promoted enamine quinone condensation of the enaminones **705** with 1,4-benzoquinone **704** led in a one-pot process to the tautomeric benzo[*b*]carbazoles **706** and **707**. By acetylation or oxidation these carbazoles are transformed to the corresponding acetate **708** or quinones **709**, respectively. The 5*H*-benzo[*b*]carbazolequinone **709a** was subsequently converted to the different benzo[*b*]carbazole derivatives **710**−**712** (Scheme 196).[298]

Scheme 196



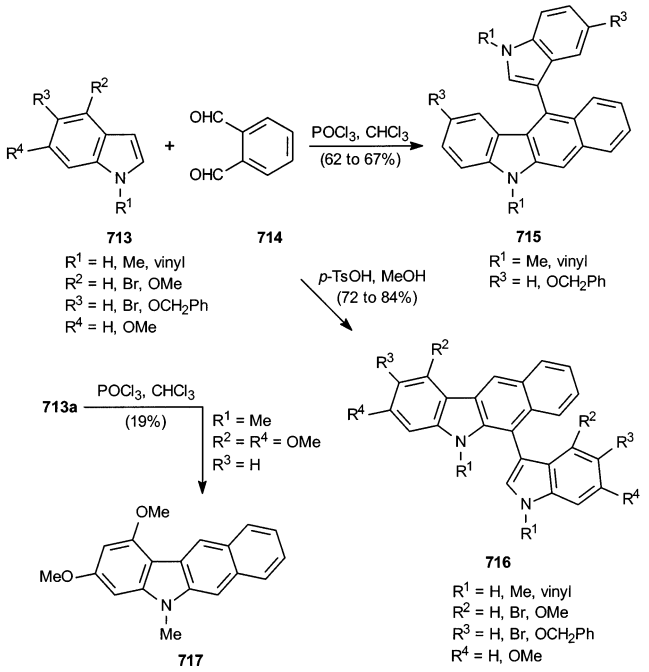
1.15. Reaction of Indoles with Phthalaldehyde

In 1999, Black et al. reported the regioselective synthesis of the 11-(indol-3-yl)-5*H*-benzo[*b*]carbazoles **715** and the 6-(indol-3-yl)-5*H*-benzo[*b*]carbazoles **716** by the acid-catalyzed reaction of the indoles **713** with phthalaldehyde **714**. Reaction of **713** with **714** in anhydrous chloroform in the presence of phosphoryl chloride afforded the 11-(indol-3-yl)-5*H*-benzo[*b*]carbazoles **715** in 62% to 67% overall yield. This reaction is believed to proceed via a bis(indol-3-yl)methane, which undergoes cyclization and aromatization to **715**. Using the same conditions, 4,6-dimethoxy-1-methylindole **713a** provided 1,3-dimethoxy-5*H*-benzo[*b*]carbazole **717** in 19% yield. The presence of *p*-toluenesulfonic acid (*p*-TsOH) led to the isomeric 6-(indol-3-yl)-5*H*-benzo[*b*]carbazoles **716** in good yields (72−84%). The mechanism proposed for this reaction involves an attack of one indole at each aldehyde function to a dicarbinol followed by cyclization and dehydration to **716** (Scheme 197).[376a] The same group described the synthesis of benzofuran-fused benzo[*c*]carbazoles by modified Vilsmeier reactions of activated benzofurans with indolin-2-ones.[376b]

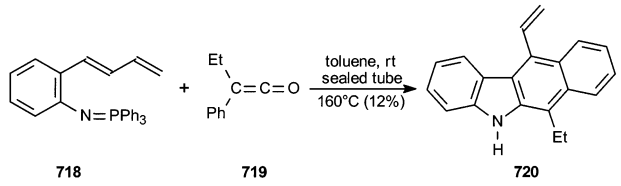
1.16. Reaction of an Aryliminophosphorane with a Ketene

Molina and co-workers reported the synthesis of 6-ethyl-11-vinyl-5*H*-benzo[*b*]carbazole **720** from the iminophosphorane **718** and the ketene **719**. This

Scheme 197



Scheme 198

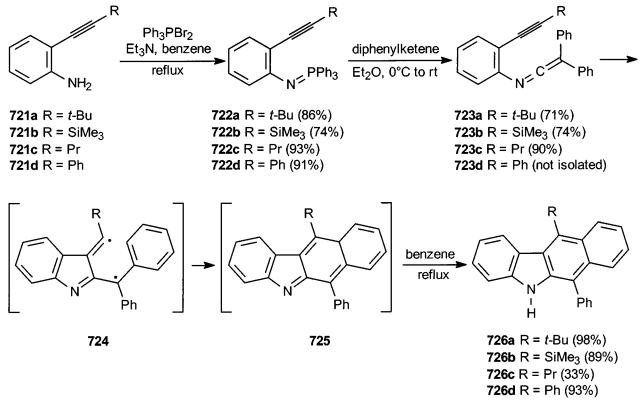


novel annulation is based on the initial generation of an *N*-(aryl)ketenimine with an unsaturated side chain in the ortho-position, followed by an intramolecular Diels−Alder cycloaddition and aromatization. The iminophosphorane **718** was prepared in 47% overall yield from 1-(*o*-nitrophenyl)buta-1,3-diene.[377] An aza-Wittig reaction of the iminophosphorane **718** and the ketene **719** in dry toluene at room temperature gave the corresponding ketenimine, which on heating at 160 °C in a sealed tube afforded 6-ethyl-11-vinyl-5*H*-benzo[*b*]carbazole **720** (Scheme 198).[378]

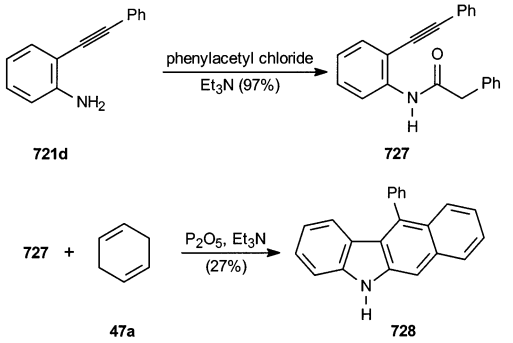
1.17. Cycloaromatization of N-[2-(1-Alkynyl)phenyl]-ketenimines

Shi and Wang reported the synthesis of the 11-substituted 6-phenyl-5*H*-benzo[*b*]carbazoles **726a**−**d** from the 2-alkynylanilines **721a**−**d**. This reaction involves the trapping of the diradicals **724** generated by cycloaromatization of the *N*-[2-(1-alkynyl)phenyl]-ketenimines **723**. Using known palladium-catalyzed cross-coupling reactions, the 2-alkynylanilines **721a**−**d** were prepared in almost quantitative yield from 2-iodoaniline and the corresponding 1-alkynes.[379−381] Treatment of **721** with Ph_3PBr_2 afforded the iminophosphoranes **722**. Under aza-Wittig conditions, the reaction of the iminophosphorane **722d** with diphenylketene provided exclusively the benzo[*b*]carbazole **726d**, presumably because the phenyl substituent leads to an additional stabilization of the vinyl radical in **724**, which gives rise to a thermally labile ketenimine **723d**. Under identical aza-Wittig conditions,

Scheme 199



Scheme 200



the iminophosphoranes **722a**−**c** were transformed to the ketenimines **723a**−**c**,[378] which in benzene at reflux provided the benzo[*b*]carbazoles **726a**−**c**. This reaction sequence involves an initial formation of the five-membered ring to the diradical **724**, followed by an intramolecular radical combination to form **725** and tautomerization to the benzo[*b*]carbazole **726** (Scheme 199).[382]

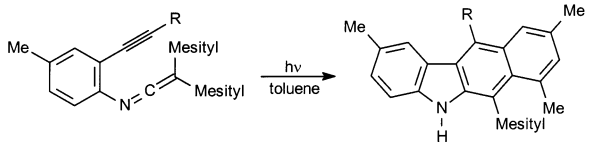
Alternatively, 11-phenyl-5*H*-benzo[*b*]carbazole **728** was prepared from the *N*-(phenylacetyl)aniline **727**, obtained by acylation of **721d** with phenylacetyl chloride. This reaction proceeds via a similar ketenimine intermediate, which was generated in situ by dehydration of **727** with P_2O_5 in refluxing triethylamine in the presence of cyclohexa-1,4-diene **47a** to provide 11-phenyl-5*H*-benzo[*b*]carbazole **728** in 27% yield. (Scheme 200).[382]

In 2000, Schmittel et al. reported the photochemical cyclization of the enyne ketenimines **729** to the 5*H*-benzo[*b*]carbazoles **730**. This photolytic reaction proceeds via the triplet analogues to the thermal diradical cyclization. The photolysis of the enyne ketenimines **729** in degassed toluene in a Rayonet RPR-100 photochemical reactor at 254 nm afforded the 5*H*-benzo[*b*]carbazoles **730** (Scheme 201).[383] The low yield of the 5*H*-benzo[*b*]carbazoles **730** was ascribed to the formation of polymeric material.

2. 5*H*-Benzo[*b*]carbazole-6,11-diones

In 1970, the first isolation of the kinamycin antibiotics from *Streptomyces murayamaensis* was reported.[384] On the basis of chemical, spectroscopic, and X-ray crystallographic data, they were originally assigned as 5*H*-benzo[*b*]carbazole-6,11-diones with a

Scheme 201

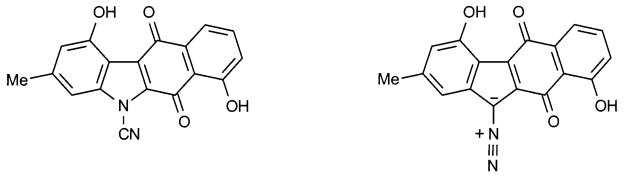


729a R = TMS
729b R = *t*-Bu

730a R = TMS (50%)
730b R = *t*-Bu (62%)

Mesityl = 2,4,6-(Me)$_3$C$_6$H$_2$

Scheme 202



731 **732**

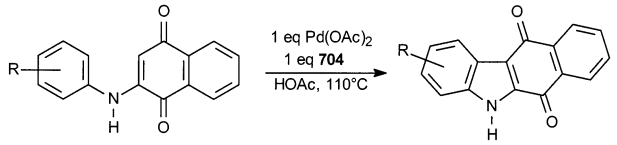
highly oxygenated D-ring.[385−388] Subsequently, the kinamycins were also isolated from other actinomycetes.[389,390] The kinamycin antibiotics exhibit potent activity against Gram-positive organisms and modest antitumor properties.[387,388] Extensive biogenetic studies performed by Gould et al. demonstrated that they derive from a single-chain decaketide.[391−398] The key intermediate in the biosynthesis of the kinamycins, which differ in the oxygen-substituents, was shown to be prekinamycin. In 1979, Gould et al. isolated prekinamycin from *S. murayamaensis* and assigned the structure as 5-cyano-1,7-dihydroxy-3-methyl-5*H*-benzo[*b*]carbazole-6,11-dione **731**.[399,400] However, synthetic **731**[401−404] was shown to be different from the natural product. This fact led to a reinvestigation of these antibiotics, and on the basis of a more accurate X-ray crystal structure determination, the kinamycins were reassigned as 5-diazobenzo[*b*]fluorenes.[405−409] Therefore, prekinamycin was assigned structure **732**.[405] However, two parallel synthetic efforts have demonstrated that the metabolite isolated in 1979 was not **732**,[410,411] although a search on the extracts of *S. murayamaensis* revealed that **732** is indeed a natural product (Scheme 202).[410] On the basis of the original structural assignment for the kinamycins and prekinamycin until 1994, several approaches were developed directed toward the synthesis of substituted 5*H*-benzo[*b*]carbazole-6,11-diones.

2.1. Palladium-Catalyzed Syntheses

5*H*-Benzo[*b*]carbazole-6,11-diones. Bittner and co-workers reported the synthesis of the 5*H*-benzo-[*b*]carbazole-6,11-diones **734** by oxidative cyclization of the corresponding 2-arylamino-1,4-naphthoquinones **733** with palladium(II) acetate in boiling acetic acid (Scheme 203).[412a] Even when reoxidants, e.g. 1,4-benzoquinone **704** or chloranil, were present, the cyclization required stoichiometric amounts of palladium(II) acetate. Cheng et al. used the same synthetic approach to 5*H*-benzo[*b*]carbazole-6,11-diones.[412b]

Hydroxy-Substituted 5-Cyano-5*H*-benzo[*b*]carbazole-6,11-diones. Using a palladium-promoted cyclization of the 2-arylamino-1,4-naphthoquinones

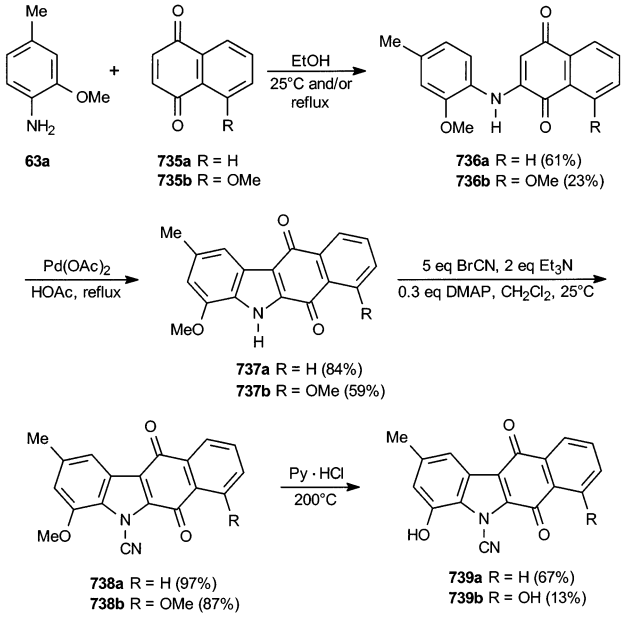
Scheme 203



733a R = OMe
733b R = Br

734a R = OMe (54%)
734b R = Br (40%)

Scheme 204



63a

735a R = H
735b R = OMe

736a R = H (61%)
736b R = OMe (23%)

737a R = H (84%)
737b R = OMe (59%)

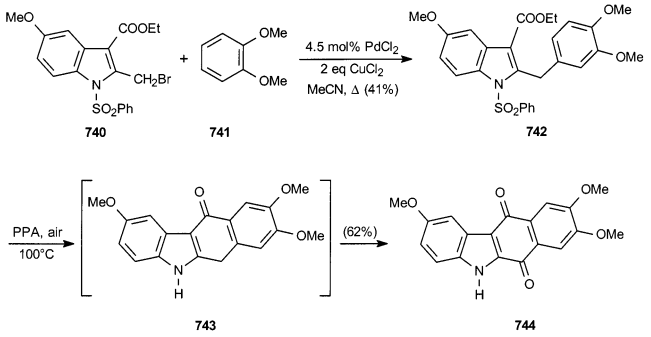
738a R = H (97%)
738b R = OMe (87%)

739a R = H (67%)
739b R = OH (13%)

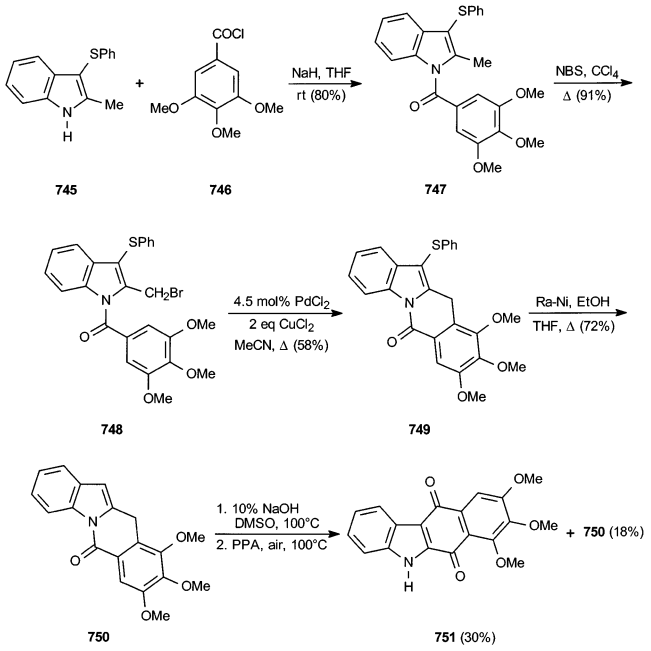
736, we developed a four-step synthesis of the hydroxy-substituted 5-cyano-5*H*-benzo[*b*]carbazole-6,11-diones **739** (Scheme 204). The arylamine **63a** was previously used as a starting material for the iron-mediated total synthesis of the cytotoxic carbazole alkaloid koenoline **3** (see Scheme 18).[85,86] Addition of **63a** to naphthoquinone **735a** provided the 2-arylamino-1,4-naphthoquinone **736a** in 61% yield. Treatment of **736a** with stoichiometric amounts of palladium(II) acetate in refluxing glacial acetic acid provided the 5*H*-benzo[*b*]carbazole-6,11-dione **737a** in 84% yield. When the reaction was carried out with catalytic amounts of palladium(II) acetate in the presence of equimolar amounts of copper(II) acetate under argon, the cyclized product **737a** was obtained in 34% yield. This result indicated for the first time that palladium(II)-catalyzed oxidative cyclizations are feasible in the synthesis of carbazolequinones. Reaction of **737a** with an excess of cyanogen bromide and triethylamine in the presence of DMAP afforded the cyanamide **738a** in 97% yield. A selective cleavage of the methyl ether in the presence of the *N*-cyano moiety was achieved with pyridine hydrochloride[413,414] and provided 5-cyano-4-hydroxy-2-methyl-5*H*-benzo-[*b*]carbazole-6,11-dione **739a**.[415,416] Starting from *O*-methyljuglone (5-methoxy-1,4-naphthoquinone) **735b**, this method was applied to the synthesis of 5-cyano-4,7-dihydroxy-2-methyl-5*H*-benzo[*b*]carbazole-6,11-dione **739b** (Scheme 204).[416]

Synthesis of 5*H*-Benzo[*b*]carbazole-6,11-diones via Palladium-Catalyzed Arylations. Rajeswaren and Srinivasan reported the synthesis of 2,8,9-trimethoxy-5*H*-benzo[*b*]carbazole-6,11-dione **744**

Scheme 205



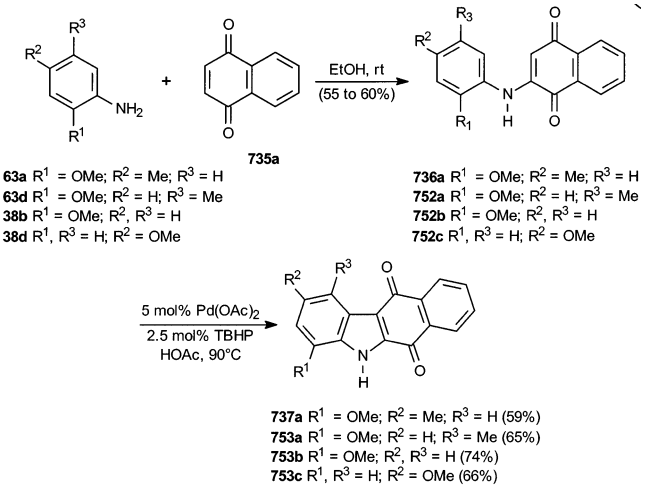
Scheme 206



using a palladium-catalyzed intermolecular arylation followed by polyphosphoric acid-promoted cyclization of the intermediate 2-substituted indole **742**. A palladium-catalyzed arylation[417] of the bromoindole **740**[418] with veratrole **741** afforded ethyl 1-phenylsulfonyl-5-methoxy-2-veratrylindole-3-carboxylate **742** in 41% yield. Cyclization of compound **742** with polyphosphoric acid (PPA) in the presence of air provided the 5*H*-benzo[*b*]carbazole-6,11-dione **744** in 62% yield (Scheme 205).[419] The presence of the methoxy group in the indole ring is essential for this cyclization.

Using an alternative method, the same authors described the synthesis of 7,8,9-trimethoxy-5*H*-benzo[*b*]carbazole-6,11-dione **751**. The *N*-aroylation of 2-methyl-3-phenylthioindole **745** with 3,4,5-trimethoxybenzoyl chloride **746** in the presence of sodium hydride afforded the indole derivative **747**, which on bromination with NBS led to the bromo derivative **748**. A palladium(II)-catalyzed intramolecular arylation of **748** afforded the isoquinolonoindole **749**. Removal of the phenylthio group with Raney nickel gave compound **750**. Amide cleavage of **750** followed by treatment with polyphosphoric acid in the presence of air provided the 5*H*-benzo[*b*]carbazole-6,11-dione **751** (Scheme 206).[419]

Scheme 207

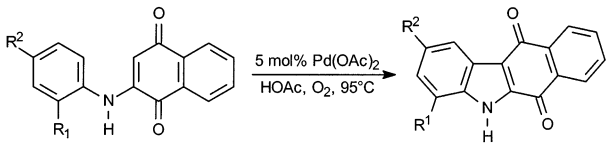


63a R^1 = OMe; R^2 = Me; R^3 = H
63d R^1 = OMe; R^2 = H; R^3 = Me
38b R^1 = OMe; R^2, R^3 = H
38d R^1, R^3 = H; R^2 = OMe

736a R^1 = OMe; R^2 = Me; R^3 = H
752a R^1 = OMe; R^2 = H; R^3 = Me
752b R^1 = OMe; R^2, R^3 = H
752c R^1, R^3 = H; R^2 = OMe

737a R^1 = OMe; R^2 = Me; R^3 = H (59%)
753a R^1 = OMe; R^2 = H; R^3 = Me (65%)
753b R^1 = OMe; R^2, R^3 = H (74%)
753c R^1, R^3 = H; R^2 = OMe (66%)

Scheme 208



752b R^1 = OMe; R^2 = H
752c R^1 = H; R^2 = OMe

753b R^1 = OMe; R^2 = H (89%)
753c R^1 = H; R^2 = OMe (87%)

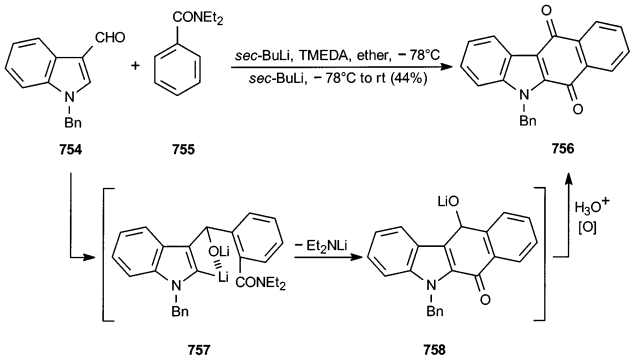
Synthesis of 5*H*-Benzo[*b*]carbazole-6,11-diones by Palladium-Catalyzed Cyclization. Åkermark et al. reported the synthesis of various oxygenated 5*H*-benzo[*b*]carbazole-6,11-diones **737a** and **753a**−**c,** starting from the 2-arylamino-1,4-naphthoquinones **736a** and **752a**−**c**. In this oxidative cyclization, *tert*-butyl hydroperoxide (TBHP) was used for the reoxidation of palladium. The addition of the arylamines **63a**,**d** and **38b**,**d** to naphthoquinone **735a** afforded the 2-arylamino-1,4-quinones **736a** and **752a**−**c**. The subsequent oxidative cyclization by reaction with 5 mol % palladium(II) acetate in the presence of an excess of TBHP provided the 5*H*-benzo[*b*]carbazole-6,11-diones **737a** and **753a**−**c** (Scheme 207).[193]

Also, oxygen was used as an oxidant for the reoxidation of palladium in this cyclization. Reaction of the 2-arylamino-1,4-naphthoquinones **752b**,**c** with 5 mol % palladium(II) acetate and molecular oxygen at atmospheric pressure gave the 5*H*-benzo[*b*]carbazole-6,11-diones **753b**,**c** (Scheme 208).[194]

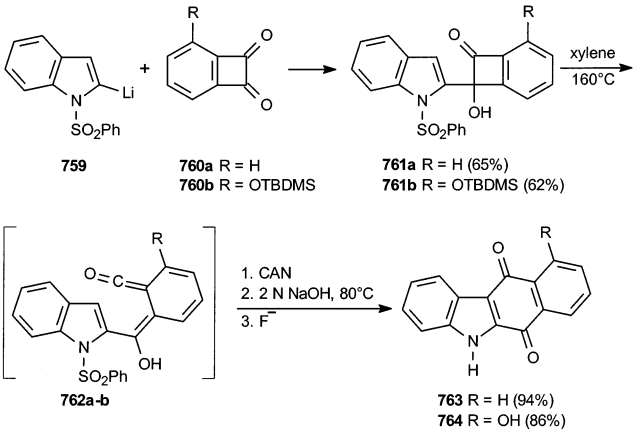
2.2. Tandem-Directed Metalation of Tertiary Benzamides

Watanabe and Snieckus reported a one-pot construction of 5-benzyl-5*H*-benzo[*b*]carbazole-6,11-dione **756** from 1-benzylindole-3-carbaldehyde **754** and *N*,*N*-diethylbenzamide **755**. They used the concept of tandem-directed metalation via an ortho-lithiation of the tertiary benzamide **755**. The reaction of *N*,*N*-diethylbenzamide **755** with *s*-BuLi and TMEDA generated an ortho-lithiated tertiary benzamide, which on sequential treatment with 1-benzylindole-3-carbaldehyde **754** and *s*-BuLi afforded directly 5-benzyl-5*H*-benzo[*b*]carbazole-6,11-dione **756** (Scheme 209).[420] The mechanism proposed for this reaction involves the formation of the dianion **757**, which on

Scheme 209



Scheme 210



subsequent elimination of lithium diethylamide cyclizes to the corresponding lithium alkoxide **758**. A final oxidation of **758** in the air leads to the 5*H*-benzo[*b*]carbazole-6,11-dione **756**. This reaction can also be applied to the synthesis of 7,8-annulated 5*H*-benzo[*b*]carbazole-6,11-diones by using ortho-lithiated 1-naphthamides.[420]

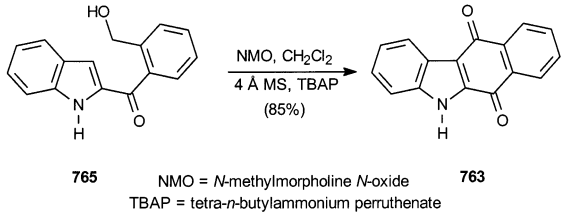
2.3. Annulation of Lithiated Indoles

Liebeskind and co-workers described the synthesis of the 5*H*-benzo[*b*]carbazole-6,11-diones **763** and **764** from the precursors **759** and **760** by a novel annulation involving a tandem pericyclic reaction.[421a] A 4π-electrocyclic ring opening of the indolylbenzocyclobutenones **761** is followed by a 6π-electrocyclization of the intermediate ketenes **762**.

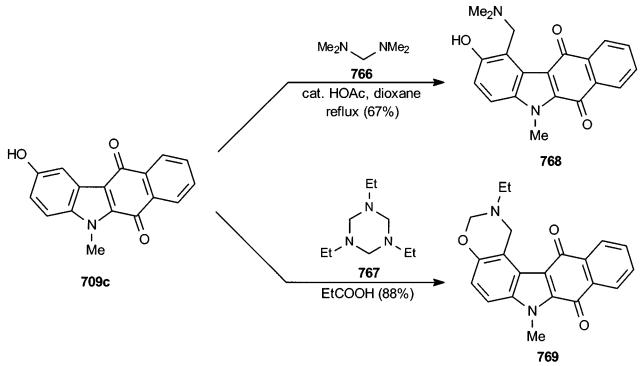
The regioselective addition of 2-lithio-1-(phenylsulfonyl)indole **759** to the benzocyclobutenediones **760** afforded the indolylbenzocyclobutenones **761**. Thermolysis of **761** followed by oxidation of the intermediate hydroquinone with ceric ammonium nitrate (CAN) provided the 5*H*-benzo[*b*]carbazole-6,11-diones **763** and **764** in high yields (Scheme 210).[421a]

In 1994, Koomen et al. extended this method to a one-pot synthesis of 5-methyl-5*H*-benzo[*b*]carbazole-6,11-dione **626** by reaction of 2-lithio-1-methylindole with phthalic anhydride (44% yield, cf. Scheme 174).[327a] More recently, Gribble and Liu described the annulation of indoles using 2,3-dilithiated indole derivatives. A double halogen/metal exchange reaction of 2,3-diiodo-1-methylindole using *tert*-butyllithium afforded 2,3-dilithio-1-methylindole, which on

Scheme 211



Scheme 212



addition of phthalic anhydride provided 5-methyl-5*H*-benzo[*b*]carbazole-6,11-dione **626** in 41% yield.[421b]

2.4. Cyclization of Benzylic Alcohols under Oxidative Reaction Conditions

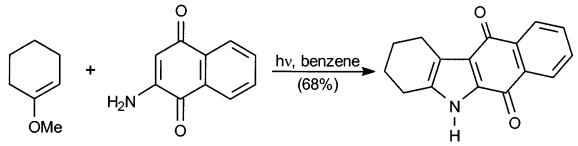
Ley et al. developed tetra-*n*-butylammonium perruthenate (TBAP) and tetra-*n*-propylammonium perruthenate (TPAP) as mild catalytic oxidants for the oxidation of alcohols to aldehydes using *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant. This catalytic system was efficiently used for the synthesis of 5*H*-benzo[*b*]carbazole-6,11-dione **763** from 2-(*o*-hydroxymethylbenzoyl)indole **765**.[422] The reaction of the indole **765** with NMO, TBAP, and 4 Å molecular sieves (MS) in dichloromethane at room temperature afforded 5*H*-benzo[*b*]carbazole-6,11-dione **763** in 85% yield (Scheme 211).[423] The synthesis of compound **763** involves oxidation of the benzylic alcohol, cyclization of the intermediate aldehyde, and oxidation to the quinone.

In 1975, Thomson and co-workers reported that persulfate oxidation of 2-alkylamino-3-phenyl-1,4-naphthoquinones provided 5-alkyl-5*H*-benzo[*b*]carbazole-6,11-diones via cyclization onto the adjacent phenyl group.[424] This reaction can be used only for the synthesis of 5-substituted 5*H*-benzo[*b*]carbazole-6,11-diones.

2.5. Synthesis of 5H-Benzo[b]carbazole-6,11-diones from 2-Aminomethylene-1-indanones

Using an acid-promoted condensation of 1,4-benzoquinone **704** with the aminomethylene indanone **705c** (R = Me), Kuckländer et al. obtained 2-hydroxy-5-methyl-5*H*-benzo[*b*]carbazole-6,11-dione **709c** (cf. Scheme 196).[298] Aminomethylation at the 1-position of **709c** led to the compounds **768** and **769** (Scheme 212).[298] The aminomethylated derivatives **768** and **769** showed a strong cytotoxic activity against colon and pulmonary carcinom cells.

Scheme 213



770 **771** **772**

In 1972, Grinev and co-workers reported the synthesis of 2-methoxy-5-methyl-5*H*-benzo[*b*]carbazole-6,11-dione, the corresponding methyl ether of **709c**. The key steps of this approach were a Fischer indolization of the *N*-methyl-*N*-phenylhydrazone of methyl γ-phenylacetoacetate and a subsequent polyphosphoric acid-promoted cyclization (cf. Scheme 205).[425]

2.6. Photoaddition of 2-Amino-1,4-naphthoquinone and 1-Methoxycyclohexene

Suginome and co-workers reported a one-step synthesis of 1,2,3,4-tetrahydro-5*H*-benzo[*b*]carbazole-6,11-dione **772** by photoaddition of 1-methoxycyclohexene **770** and 2-amino-1,4-naphthoquinone **771**. The regioselective [2 + 3]-photoaddition leads to an intermediate adduct, which provides **772** by spontaneous elimination of methanol. Irradiation of a solution of **770** and **771** in benzene under nitrogen with a 500-W high-pressure Hg arc lamp using a Pyrex filter afforded 1,2,3,4-tetrahydro-5*H*-benzo[*b*]carbazole-6,11-dione **772** in 68% yield (Scheme 213).[426,427] However, this method failed using electron-deficient olefins or *N*-substituted-1,4-naphthoquinones.[428]

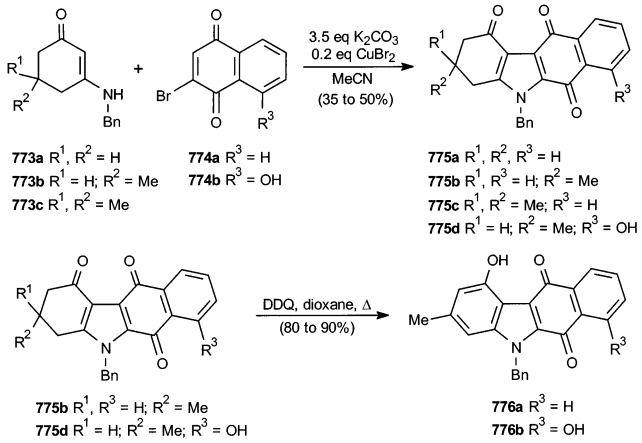
2.7. Addition of 2-Bromonaphthoquinone and 3-Amino-2-cyclohexenones

Murphy et al. developed a bromoquinone enaminone annulation for the synthesis of the 5*H*-benzo[*b*]carbazole-6,11-diones **776**. The reaction of the *N*-benzyl enamino ketones **773** with the 2-bromo-1,4-naphthoquinones **774**[429,430] in the presence of copper(II) bromide and potassium carbonate in acetonitrile afforded the tetrahydrobenzo[*b*]carbazole-1,6,11-triones **775**. Heating of **775** with DDQ in dioxane at reflux resulted in smooth aromatization to the 5*H*-benzo[*b*]carbazoles **776** (Scheme 214).[431]

2.8. Intramolecular Claisen Condensation

Castedo and co-workers reported a simple synthesis of 2,3,8,9-tetramethoxy-5*H*-benzo[*b*]carbazole-6,11-dione **780** from the nitro keto ester **778a** using a Claisen condensation as the key step. The nitro keto acid **777a** was prepared by nitration of the corresponding keto acid.[432] Esterification of **777a** led to the nitro keto ester **778a**. Treatment of the nitro keto ester **778a** with sodium hydroxide in refluxing methanol afforded the nitroquinone **779** via a Claisen condensation and subsequent oxidation in the air. The reduction of the nitro group in compound **779** with sodium borohydride in 2-propanol was followed by a cyclization to afford 2,3,8,9-tetramethoxy-5*H*-benzo[*b*]carbazole-6,11-dione **780** in 92% yield (Scheme 215).[433a] More recently, Estévez et al. described further applications of the same approach.[433b,c] An

Scheme 214



773a R^1, R^2 = H
773b R^1 = H; R^2 = Me
773c R^1, R^2 = Me

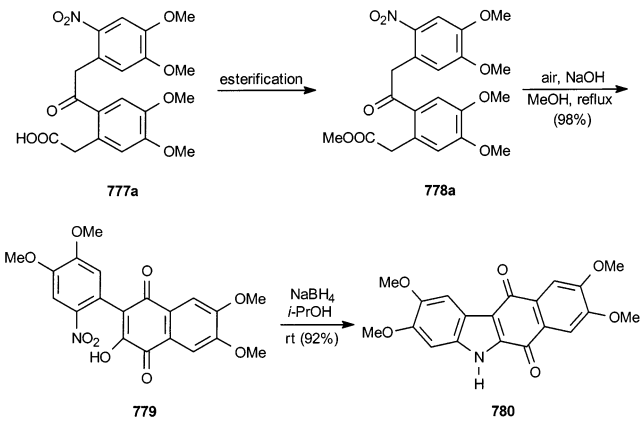
774a R^3 = H
774b R^3 = OH

775a R^1, R^2, R^3 = H
775b R^1, R^3 = H; R^2 = Me
775c R^1, R^2 = Me; R^3 = H
775d R^1 = H; R^2 = Me; R^3 = OH

775b R^1, R^3 = H; R^2 = Me
775d R^1 = H; R^2 = Me; R^3 = OH

776a R^3 = H
776b R^3 = OH

Scheme 215



777a **778a** **779** **780**

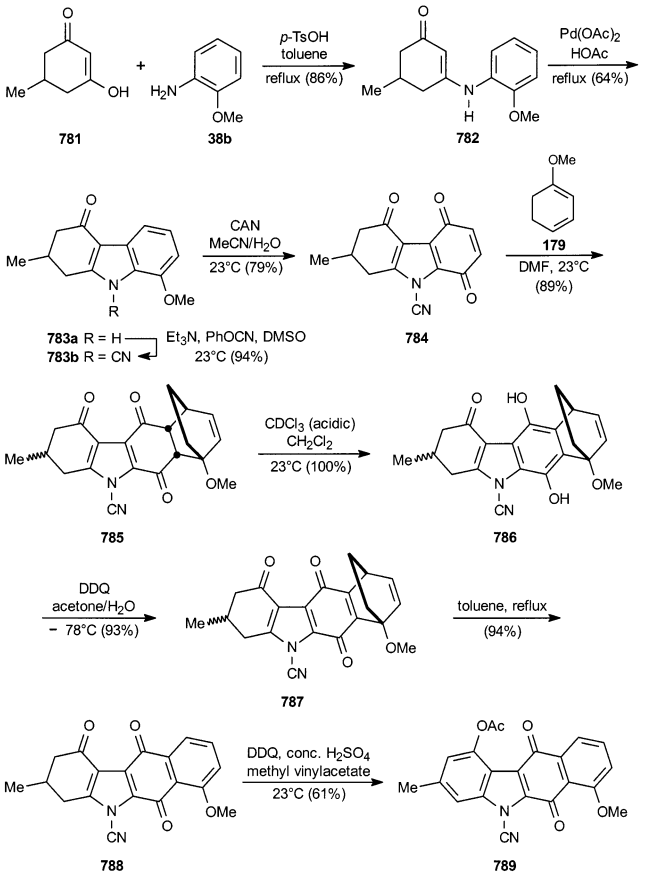
application of the same precursor to the synthesis of benzo[*a*]carbazoles is described in section XI.4.

2.9. Diels–Alder Reaction of 1-Methoxycyclohexa-1,3-diene with an N-Cyanocarbazoletrione

On the basis of previous model studies,[402,403] Dmitrienko and co-workers reported the synthesis of 1-acetoxy-7-methoxy-3-methyl-5-cyano-5*H*-benzo[*b*]-carbazole-6,11-dione **789** from 2-methoxyaniline **38b** and 3-hydroxy-5-methylcyclohex-2-enone **781**. The two key steps of this approach are the palladium-mediated cyclization to the 1,2,3,4-tetrahydrocarbazol-4-one **783** and the regioselective Diels−Alder reaction of the *N*-cyanocarbazoletrione **784** with 1-methoxy-1,3-cyclohexadiene **179**.

The *N*-arylenaminone **782** was easily prepared by proton-catalyzed addition of 2-methoxyaniline **38b** to 3-hydroxy-5-methylcyclohex-2-enone **781**. A palladium-mediated oxidative cyclization of **782** afforded 1,2,3,4-tetrahydrocarbazol-4-one **783**. Reaction with phenyl cyanate in the presence of a base led to the corresponding *N*-cyano derivative **783b**, which was oxidized with ceric ammonium nitrate (CAN) to the *N*-cyanocarbazoletrione **784**. A regioselective Diels−Alder reaction of the *N*-cyanocarbazoletrione **784** with 1-methoxycyclohexa-1,3-diene **179**[434,435] led to the diastereomeric mixture of the hydroquinone **786** via the intermediate dihydro derivative **785**. The oxidation of the hydroquinone **786** with DDQ to the quinone **787** was followed by a thermal retro-Diels−

Scheme 216

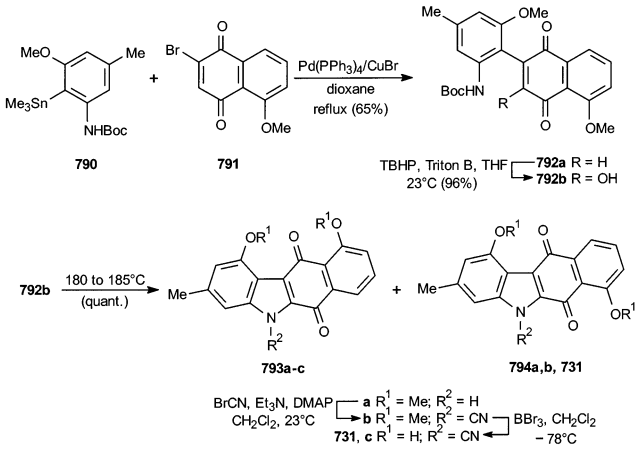


Alder extrusion of ethylene to give compound **788**. Aromatization of **788** followed by acetylation provided 1-acetoxy-7-methoxy-3-methyl-5-cyano-5*H*-benzo[*b*]-carbazole-6,11-dione **789** (Scheme 216).[404] This synthesis afforded the 5*H*-benzo[*b*]carbazole-6,11-dione **789** in nine steps and 21% overall yield from 2-methoxyaniline **38b**.

2.10. Stille Coupling of a 2-Bromonaphthoquinone with an Arylstannane

Echavarren et al. reported the synthesis of the 5-cyano-5*H*-benzo[*b*]carbazole-6,11-diones **793c** and **731** by Stille coupling of the arylstannane **790** with 2-bromo-5-methoxy-1,4-naphthoquinone **791**, followed by ring closure, *N*-cyanation, and cleavage of the methyl ether. The coupling of the arylstannane **790**[436] with the 2-bromo-1,4-naphthoquinone **791**[437] in the presence of $Pd(PPh_3)_4$ and cuprous bromide (5 mol % each) in dioxane at reflux provided compound **792a** in 65% yield. Hydroxylation of compound **792a** with *tert*-butyl hydroperoxide (TBHP) and Triton B in tetrahydrofuran led to the corresponding hydroxy derivative **792b**. Cyclization of **792b** with catalytic amounts of sulfuric acid in methanol under reflux gave a 1:1.4 mixture of the 5*H*-benzo[*b*]carbazolequinones **793a** and **794a** in 82% yield. However, thermolysis of **792b** at 180−185 °C afforded the 5*H*-benzo[*b*]carbazolequinones **793a** and **794a** quantitatively in a ratio of 3:1. The formation of the rearranged product **793a** was explained by attack of the amino group at C-2 of the quinone leading to an azetidine, followed by migration of the aryl ring to

Scheme 217



C-3. The 5*H*-benzo[*b*]carbazolequinones **793a** and **794a** were transformed quantitatively to the corresponding *N*-cyano derivatives **793b** and **794b** by reaction with cyanogen bromide in the presence of triethylamine and DMAP. Ether cleavage of **793b** and **794b** with BBr_3 provided corresponding hydroxy derivatives **793c** and **731** (Scheme 217).[401]

In 1997, the same group described a further application of this method by using different substituted arylstannanes for the synthesis of various 5*H*-benzo-[*b*]carbazole-6,11-diones.[438]

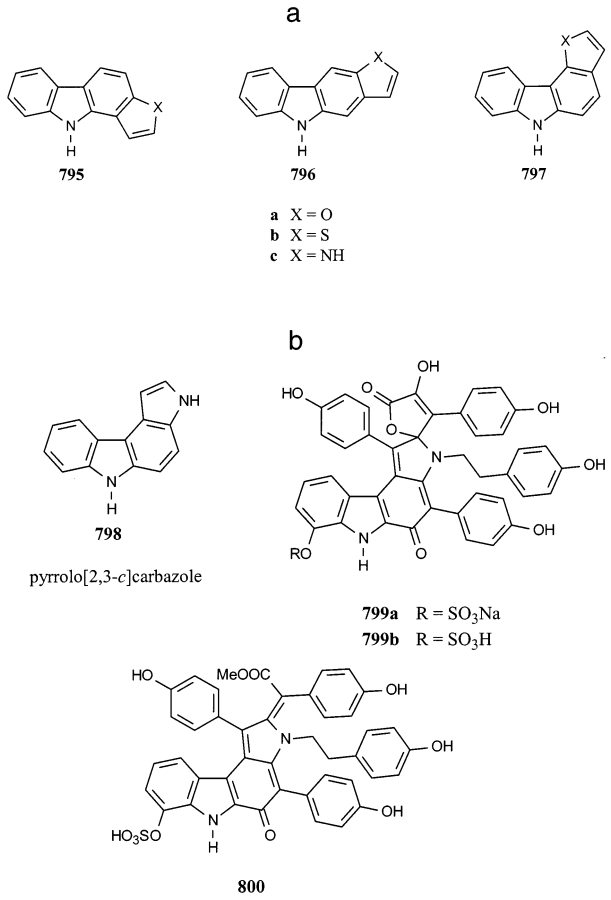
3. Heteroarylcarbazoles

Over the past years, the rapidly growing class of heteroaryl-condensed carbazoles began to attract increasing interest because of their broad spectrum of useful biological activities.[439] To provide an overview on the hetaryl-annulated carbazole derivatives, we classified these compounds into [*a*]-annulated (**795**), [*b*]-annulated (**796**), and [*c*]-annulated (**797**) furo-, thieno-, and pyrrolocarbazoles, respectively. This classification is solely based on the position at which the heteroaromatic ring is fused to the carbazole nucleus, either at bond a, b, or c (Scheme 218, part a). In Scheme 218, part a, only the structures with a [3,2]-annulated heteroaromatic five-membered ring are shown. Moreover, the mode of fusion of the annulated heteroaromatic ring itself can vary, which leads to an even broader variety of heterocyclic ring systems.

The first alkaloid from natural sources with a furo-[3,2-*a*]carbazole skeleton **795a** (Scheme 218, part a) was furostifoline (**556**), isolated in 1990 (cf. Scheme 156).[259] The strong interest in this class of compounds is emphasized by several independent total syntheses.[204,288,291,295] Therefore, the furocarbazoles were covered separately in section V. Independent syntheses were developed for the different isomeric furo-[*b*]carbazoles.[440] The alkaloid eustifoline D (**557**) (cf. Scheme 156) has a furo[2,3-*c*]carbazole framework.[259]

Although there are no reports of natural products with a thienocarbazole framework, the synthesis of isomeric thieno[*a*]-, -[*b*]-, and -[*c*]carbazoles **795b**−**797b** (Scheme 218, part a) was reported by various groups in the 1990s.[325,330,344,440b] These syntheses were mostly developed to study the biological activities of the thieno-fused carbazoles.[304,441]

Scheme 218



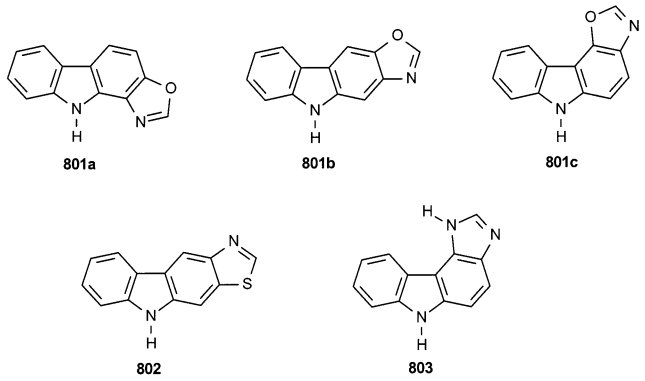
Since the early 1980s, the pyrrolocarbazoles **795c**−**797c** (Scheme 218, part a) have received attention due to their pharmacologocal activities, e.g. anticancer,[442,443] antidiabetic,[444] neurotropic,[445] and inhibitory properties against protein kinase C.[446] Only the pyrrolo[2,3-*c*]carbazole skeleton **798** (Scheme 218, part b) has been found in nature so far. All other different isomeric pyrrolocarbazoles are of synthetic origin. The pyrrolo[2,3-*c*]carbazole alkaloids **799a**,**b** and **800** were isolated from the marine sponge *Dictyodendrilla* sp (Scheme 218, part b).[444] They show a potent aldose reductase inhibitory activity.

The various synthetic methodologies led to a broad structural variety of the different isomeric pyrrolocarbazoles.[370,447] In addition to new synthetic routes,[330,448−451] the general methods that were applied to the synthesis of isomeric pyrrolocarbazoles are as follows: Borsche cyclization of appropriate indolylhydrazones,[452] Fischer indolization starting from aminocarbazoles,[453−455] thermally and photolytically induced electrocyclization of hexatriene systems,[18,325,456] Diels−Alder cycloaddition of 2- and 3-vinylindoles,[307,370,446,457−467] Diels−Alder cycloaddition of indole-2,3-quinodimethane equivalents,[348,349,440a,468−472] and intramolecular Diels−Alder reaction of appropriately substituted indoles.[473]

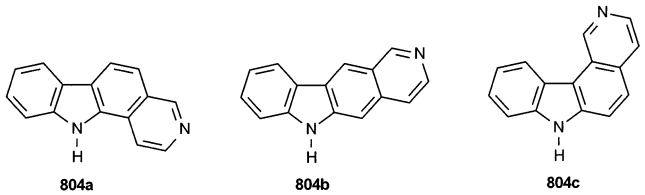
The indolocarbazoles are described separately because of their importance, which results primarily from the pharmacological potential of the indolo[2,3-*a*]carbazoles (see section VIII).

So far there are no reports of natural products containing an oxazolocarbazole **801** or an isoxazolocarbazole framework (Scheme 219). In 1985, Das and co-workers reported the synthesis of oxazolo[5,4-*c*]-carbazole derivatives to study the in vivo mechanism of action and the structure−activity relationship of *N*-2-methyl-9-hydroxyelliptinium acetate (elliptinium).[474] Elliptinium, a derivative of the pyrido[4,3-*b*]-carbazole alkaloid ellipticine, is used for the treatment of osteolytic metastases of breast cancer.[475] In an investigation of the antioxidant carazostatin, Moody et al. prepared an oxazolo[5,4-*c*]carbazole.[149] Hibino et al. reported the synthesis of oxazolo[4,5-*c*]-carbazoles **801c** and oxazolo[5,4-*c*]carbazoles by electrocyclization of the corresponding 3-oxazolyl-2-propargylindoles.[476] In 1999, Shanmugasundaram and Prasad reported the synthesis of isoxazolo-[3,4-*a*]carbazoles.[477] Besson and co-workers recently described a simple synthesis of thiazolo[5,4-*b*]carbazoles **802** from the corresponding 3-aminocarbazoles (Scheme 219).[478a] Achab et al. obtained imidazo[4,5-*c*]carbazoles **803** by electrocyclization of an appropriate 3-(imidazol-5-yl)-2-vinylindole.[478b]

Scheme 219



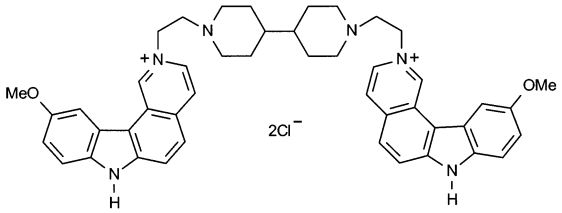
Scheme 220



It is well-established that the pyridocarbazole ring system is an appropriate skeleton to design DNA-intercalating drugs.[441,479] For this reason, there has been a strong synthetic activity in this area. Examples of potential annulation modes are the pyrido-[4,3-*a*]carbazoles **804a**, the pyrido[4,3-*b*]carbazoles **804b**, and the pyrido[4,3-*c*]carbazoles **804c** (Scheme 220).[479] Among the different isomeric pyridocarbazole frameworks, the pyrido[4,3-*b*]carbazole **804b** has attracted most of the interest because ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) and its 9-hydroxy and 9-methoxy derivatives show significant anticancer activity.[480−485] Therefore, various methods have been developed for the synthesis of the pyrido-[4,3-*b*]carbazoles,[486−491] which are described separately (section VII).

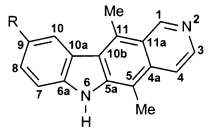
Compared to the synthetic efforts and structure−activity studies focused on the pyrido[4,3-*b*]carbazoles **804b**, little attention has been directed toward the isomeric pyridocarbazoles. Ditercalinium (**805**), a

Scheme 221

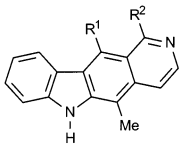


805

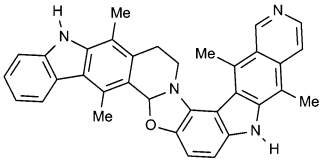
Scheme 222



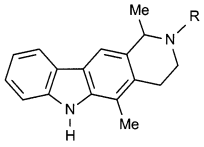
806 Ellipticine
R = H
807 9-Methoxyellipticine
R = OMe
808 9-Hydroxyellipticine
R = OH



809 Olivacine
R^1 = H; R^2 = Me
810 5-methyl-6*H*-pyrido[4,3-*b*]-carbazole-11-methanol
R^1 = CH_2OH, R^2 = H



811 Strellidimine



812 Guatambuine
R = Me
813 Janetine
R = H

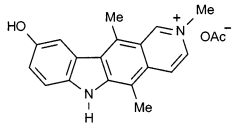
dimeric pyrido[4,3-*c*]carbazole, is under clinical trial for the treatment of cancer (Scheme 221).[492,493]

The methods that were used for the synthesis of various isomeric pyrido[*a*]carbazoles and pyrido[*c*]-carbazoles involve the photocyclization of indole derivatives,[320,321,334,479,494−498] the functionalization of carbazole derivatives,[499−503] the Fischer indolization of hydrazone derivatives,[504−506] the base-induced cyclization of indole derivatives,[507] the Diels−Alder cycloaddition of indole-2,3-quinodimethane equivalents,[318,360,508] the intramolecular Diels−Alder reaction of substituted indoles,[473] the tandem reaction of 2-cyano-Δ^3-piperidines,[509] the cyclization of aminoquinolines and azidoquinolines,[510] and the thermal cyclization of azidocarbazole derivatives.[451]

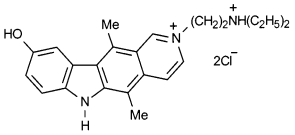
VII. Pyrido[4,3-b]carbazole Alkaloids

In 1959, Goodwin et al. isolated ellipticine (**806**), a pyrido[4,3-*b*]carbazole, from the leaves of *Ochrosia elliptica* Labill.[511] In the same year Woodward et al. assigned this plant alkaloid as 5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole, confirmed by the first total synthesis.[512] In the following years, ellipticine (**806**) and its derivatives **807**−**813** were isolated from various other species of the genera *Aspidosperma*, *Tabernaemontana*, *Strychnos*, and *Peschiera Buchtieni* (Scheme 222).[513−521] The isolation of additional pyrido[4,3-*b*]carbazole alkaloids is described in section XI.5.5.

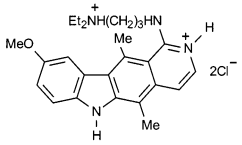
Scheme 223



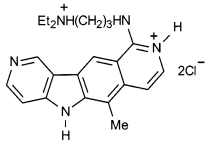
814 Elliptinium



815 Datelliptium



816 Retellipticine (BD-84)



817 Pazellipticine (BD-40)

In 1967, Australian scientists disclosed the antitumor activity of ellipticine (**806**) and 9-methoxyellipticine (**807**) toward various animal tumors.[480,481] This discovery stimulated a strong interest in the synthesis of ellipticine and its analogues. A derivative of 9-hydroxyellipticine (**808**), *N*-2-methyl-9-hydroxyellipticinium acetate (**814**) (elliptinium), was commercialized for clinical use in the treatment of myeloblastic leukemia, advanced breast cancer, and other solid tumors.[522−525] In the late 1980s, a second-generation of ellipticine-derived antitumor agents was developed, including the new clinical candidates datelliptium (**815**),[297,526] retellipticine (BD-84) (**816**),[297,527] and pazellipticine (PZE or BD-40) (**817**)[297,528] (Scheme 223). These findings initiated further extensive activities directed toward the synthesis of pyrido[4,3-*b*]carbazole derivatives for biological evaluation.

In 1985, Suffness and Cordell reviewed comprehensively the synthesis and biological profile of the ellipticine alkaloids covering the literature until 1984.[529] In 1990, Gribble gave a detailed overview on the syntheses and biological properties of pyrido[4,3-*b*]carbazole alkaloids covering the literature up to 1989.[297,530] In addition to these comprehensive reviews, Sainsbury published in 1977 an extensive review on 15 different synthetic routes based on the formation of the final ring for the pyrido[4,3-*b*]-carbazole framework.[486] In 1981, Barone and Chanon reported a review focusing on computer-generated strategies for the construction of the ellipticine ring system.[487] The computer program suggested 253 conceivable routes to ellipticine, which derive from the retrosynthetic cleavage of two bonds. Shannon et al. published an update of Sainsbury's review by describing syntheses of pyrido[4,3-*b*]carbazoles and their analogues from 1977 to 1982.[488] In 1985, Gribble and Saulnier published a review on ellipticine and related pyridocarbazoles covering the literature from 1977 to 1984. In this review synthetic strategies have been classified on the basis of the key bond formation.[489] In 1986, Kansal and Potier reported a review with the main emphasis on biogenesis, antitumor activity, and mechanism of action of ellipticine along with a few important synthetic methods based on Sainsbury's classification.[490] In 1992, Potier described the antitumor activity of ellipticine and its con-

geners.[531a] More recently, Álvarez and Joule provided an overview on the chemistry and the synthesis of some classes of indole alkaloids, including ellipticine and related alkaloids.[531b] In addition to all these comprehensive reviews on different aspects of ellipticine alkaloids, Gribble[491] in 1991 and Moody[17] in 1994 gave personal accounts on the synthesis of antitumor pyridocarbazole alkaloids. Pindur et al. reported a series of articles on the intercalating properties of pyrido[4,3-*b*]carbazoles.[304,441,532]

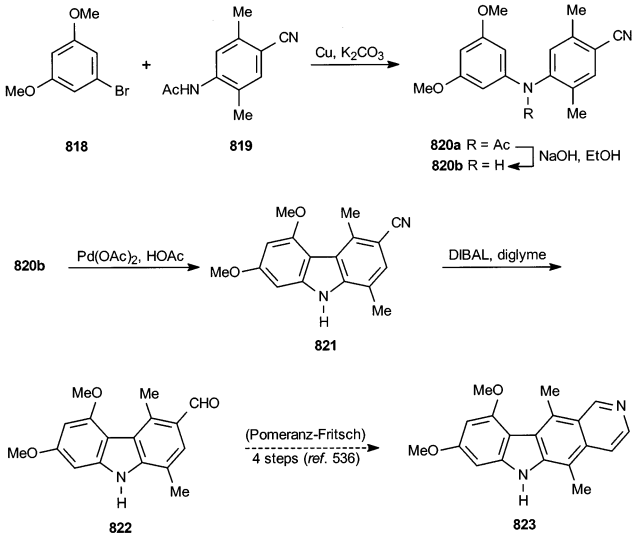
Herein, we summarize some novel syntheses of the pyrido[4,3-*b*]carbazole alkaloids developed since 1990. The approaches are classified on the basis of the applied synthetic methodologies.

1. Syntheses via Palladium-Promoted Reactions

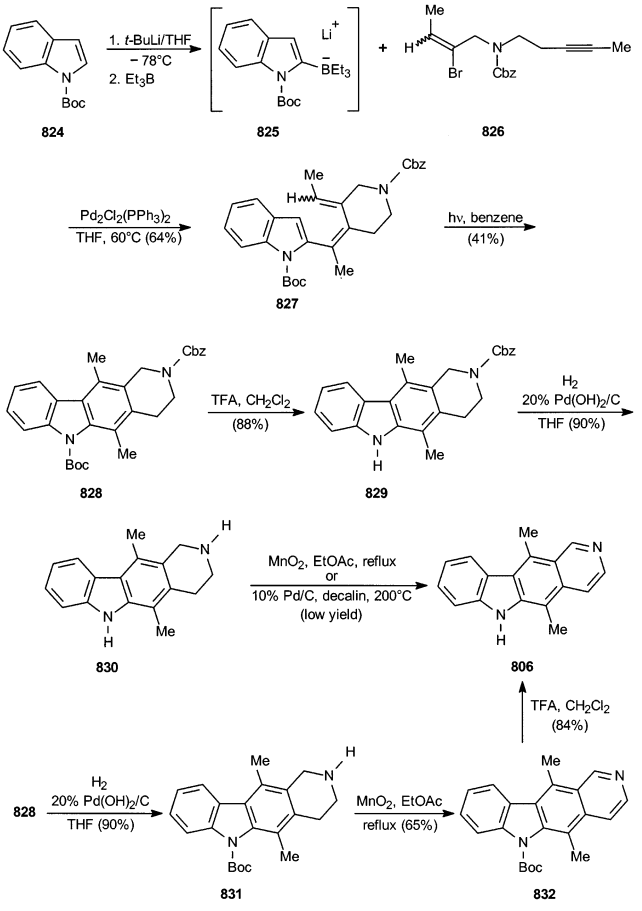
1.1. Palladium-Promoted Synthesis of 8,10-Dimethoxyellipticine

Shannon et al. reported the synthesis of 8,10-dimethoxyellipticine (**823**) using an annulation of ring D by a modified Pomeranz−Fritsch cyclization of the 3-formylcarbazole **822**.[533] The key-step for the synthesis of the 3-formylcarbazole **822** was the palladium(II)-mediated oxidative cyclization of the diarylamine **820b**. The reaction of the bromide **818**[534] with the nitrile **819**[535] by using the Goldberg conditions of the Ullmann coupling afforded the diarylamide **820a**. Cleavage of the amide led to the corresponding diarylamine **820b**. Oxidative cyclization of the diarylamine **820b** with palladium(II) acetate in acetic acid provided 3-cyano-5,7-dimethoxy-1,4-dimethyl-9*H*-carbazole **821**. Alternatively, the 3-cyanocarbazole **821** was obtained via a photochemical cyclization of the sulfonamide derivative of the diarylamine **820b**. The direct photochemical reaction of the diarylamide **820a** led to photo-Fries products along with only minor amounts of the desired 3-cyanocarbazole **821**. Reduction of the 3-cyanocarbazole **821** with diisobutylaluminum hydride (DIBAL) in diglyme provided the 3-formylcarbazole **822**. Using a modified Pomeranz−Fritsch cyclization,[536] the 3-formylcarbazole **822** was transformed to 8,10-dimethoxyellipticine (**823**) in four steps (Scheme 224).[537] This method was previously applied to syntheses of ellipticines and olivacines.[538]

Scheme 224



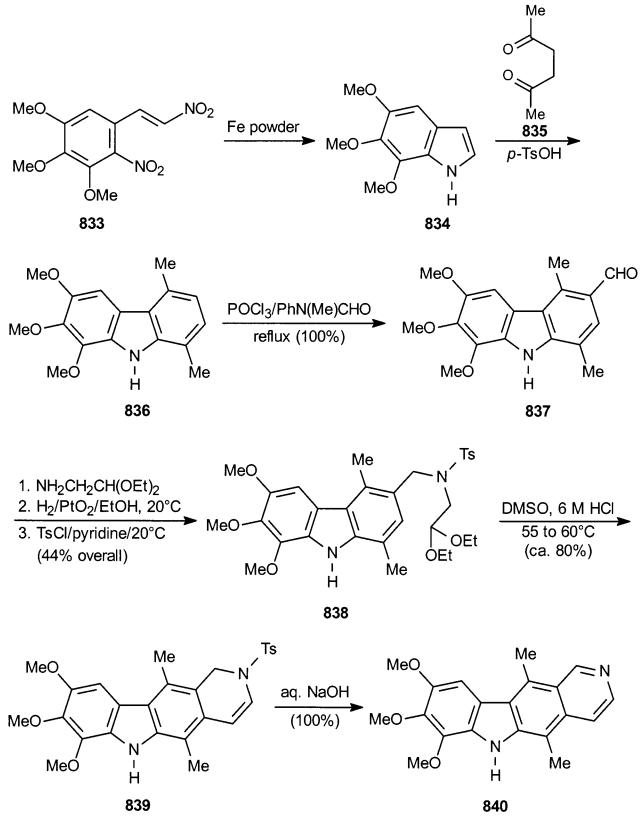
Scheme 225



1.2. Palladium-Catalyzed Total Synthesis of Ellipticine

Ishikura and co-workers reported the total synthesis of ellipticine **806** by a palladium-catalyzed tandem cyclization−cross-coupling reaction of the indolyl borate **825** with the vinyl bromide **826** as the key step. The vinyl bromide **826** was prepared as an *E*/*Z* mixture starting from *cis*- and *trans*-crotyl alcohol.[539−542] The indolyl borate **825** was generated in situ from *N*-Boc indole **824** and *tert*-butyllithium, followed by treatment with triethylborane.[543] A palladium-catalyzed tandem cyclization−cross-coupling reaction by heating of compound **825** with the vinyl bromide **826** in the presence of catalytic amounts of bis(triphenylphosphine)palladium(II) chloride provided the hexatriene **827** in 64% yield. Photolytic electrocyclization of the hexatriene **827** led to the tetrahydropyridocarbazole **828**. Deprotection of **828** by sequential removal of the *tert*-butoxycarbonyl (Boc) and benzyloxycarbonyl (Cbz) groups and subsequent dehydrogenation of **830** afforded ellipticine (**806**) in low yield. The low yield of this step was ascribed to the presence of the free indole N−H. Thus, chemoselective removal of the Cbz group of **828**, dehydrogenation of **831**, and deprotection of compound **832** were shown to give an improved yield of ellipticine **806** over three steps (Scheme 225).[544] This methodology was also applied to the synthesis

Scheme 226



of 6-methylellipticine derivatives starting from 1-methylindole.[545]

2. Syntheses by Condensation Reactions

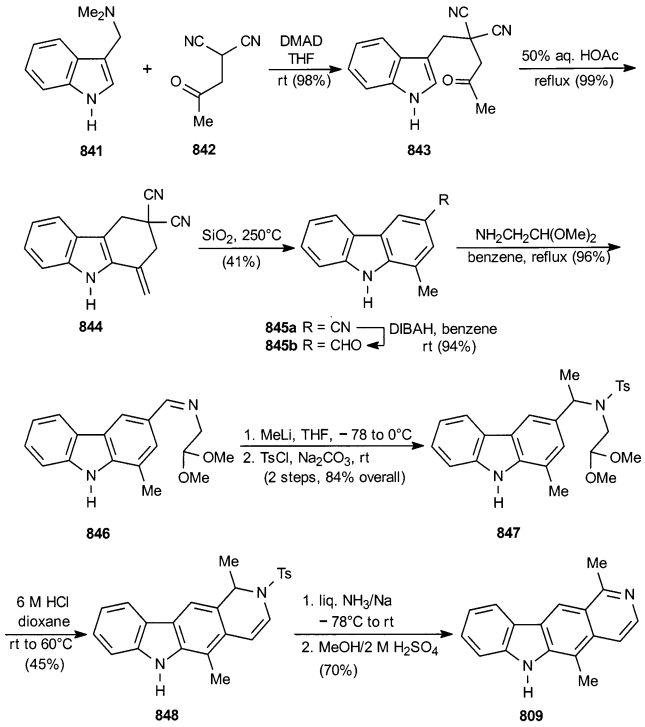
2.1. Condensation of Indoles with Hexa-2,5-dione

Shannon et al. modified[533] the Cranwell and Saxton method[546] for the synthesis of 7,8,9-trimethoxyellipticine (**840**). This approach involves the condensation of 5,6,7-trimethoxyindole **834** with hexane-2,5-dione **835** to 1,2,3-trimethoxy-5,8-dimethylcarbazole **836**. After introduction of a formyl group at C-6, the pyridine annulation was achieved by a modified Pomeranz−Fritsch procedure.[533]

The indole **834** was obtained by reduction of the corresponding dinitrostyrene **833** (Nenitzescu indole synthesis).[547] Condensation of the indole **834** with hexane-2,5-dione **835** in the presence of *p*-toluenesulfonic acid (*p*-TsOH) afforded the carbazole **836**. Vilsmeier formylation of **836** provided the formylcarbazole **837**. Reaction of **837** with aminoacetaldehyde diethyl acetal afforded an unstable imine, which without isolation was subjected to hydrogenation followed by tosylation to give the stable sulfonamide **838** in 44% overall yield. Treatment of the sulfonamide **838** with dilute hydrochloric acid in hot dimethyl sulfoxide led to 7,8,9-trimethoxy-2-tosyl-1,2-dihydroellipticine **839**. Alkaline hydrolysis of **839** afforded quantitatively 7,8,9-trimethoxyellipticine (**840**) (Scheme 226).[548,549]

This method was subsequently applied to the synthesis of dimethoxyellipticine[536] and hydroxyellipticine derivatives.[550] It was demonstrated that the condensation is limited to the synthesis of carbazoles with the same substituents at C-1 and C-4 (or at C-5 and C-8 following alternative numbering). This substitution pattern is required for the synthesis of ellipticine derivatives. The condensation of indoles with unsymmetrical 1,4-dicarbonyl compounds resulted only in a mixture of regiosiomeric products. Groundwater and Lewis used the same method for the synthesis of 7-fluoroellipticine.[551]

Scheme 227



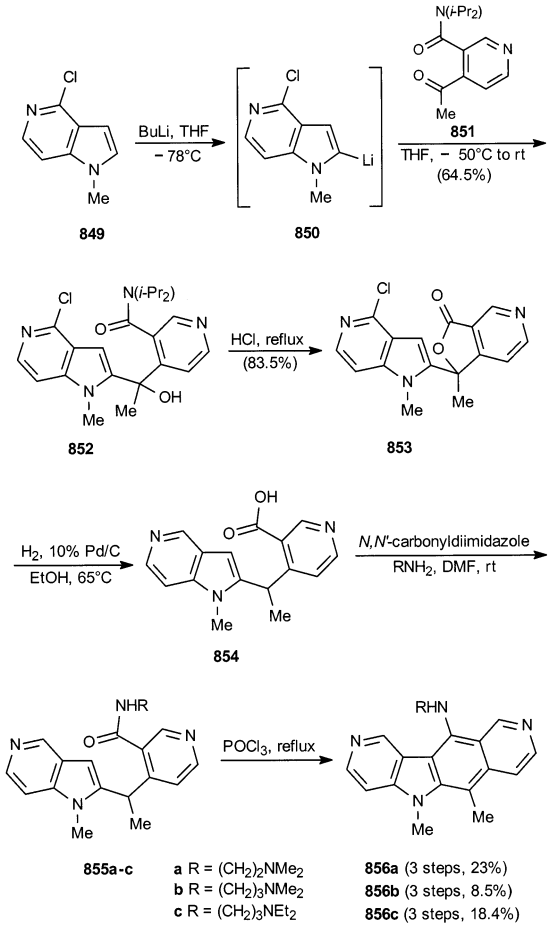
2.2. Total Synthesis of Olivacine by Condensation of Gramine

To overcome the limitation of Shannon's method, Sainsbury and co-workers reported a new procedure for the synthesis of olivacine starting from gramine and 2-cyano-4-oxopentanonitrile. The reaction of gramine (**841**) with 2-cyano-4-oxopentanonitrile **842** in the presence of dimethylacetylene dicarboxylate (DMAD) afforded the indole derivative **843**, which on treatment with hot 50% acetic acid cyclizes to the *exo*-methylene compound **844**. By thermal reaction with silica, compound **844** was transformed to the 3-cyanocarbazole **845a**. The reduction to the 3-formylcarbazole **845b** was followed by a modified Pomeranz−Fritsch reaction[533] using aminoacetaldehyde dimethyl acetal. The 3-acetyl derivative corresponding to **845**[552] failed to give olivacine (**809**) in good yield under modified Pomeranz−Fritsch conditions. Therefore, the methyl group at C-1 was introduced by addition of methyllithium to the imine **846**. Subsequent cyclization and aromatization provided olivacine (**809**) (Scheme 227).[553,554] This synthesis leads to olivacine (**809**) in nine steps and 9.5% overall yield starting from gramine (**841**).[554]

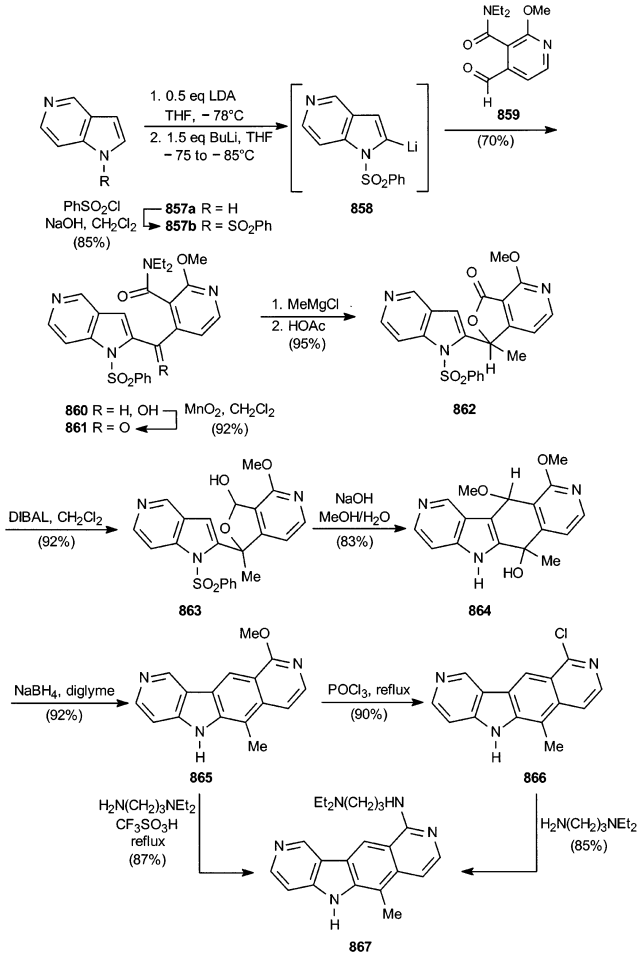
2.3. Synthesis of 11-Aminoazaellipticines by Condensation of a Nicotinamide

Bisagni et al. reported the synthesis of the 11-aminoazaellipticine derivatives **856a**−**c** to study the structure−activity relationship. This synthesis in-

Scheme 228



Scheme 229



volves the condensation of 4-chloro-2-lithio-1-methyl-1*H*-pyrrolo[3,2-*c*]pyridine **850** with 4-acetyl-*N*,*N*-diisopropylnicotinamide **851**. The reaction of the lithio derivative **850**[555,556] with the keto amide **851** led to the hydroxyamide **852**, which on hydrolysis afforded the lactone **853**. Catalytic hydrogenation of the lactone **853** provided, with concomitant chlorine elimination, the acid **854**. The reaction of various amines with the acid **854** in the presence of *N*,*N*′-carbonyldiimidazole led to the corresponding amides **855a**−**c**, which were directly cyclized to the 11-aminoazaellipticine derivatives **856a**−**c** by refluxing with phosphorus oxychloride (Scheme 228).[557] Using lithioindole and the same keto amide, this method was also applied to the synthesis of 11-amino substituted 6*H*-pyrido[4,3-*b*]carbazoles.[558]

2.4. Synthesis of Pazelliptine by Condensation of a Nicotinamide

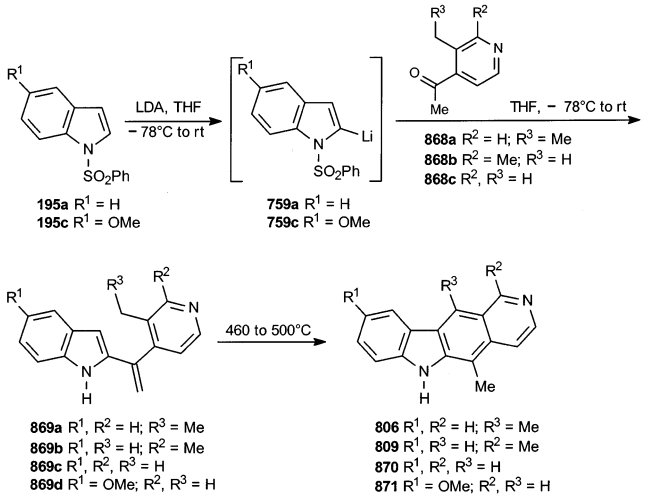
On the basis of Bisagni's method,[557,558] Dormoy and Heymes reported the industrial synthesis of pazelliptine (**867**) by condensation of the 2-lithio-5-azaindole **858** with the 3-pyridinecarboxamide **859**. The required 5-azaindole **857a**[559−561] and the 3-pyridinecarboxamide **859**[561,562] were prepared using literature procedures from 3-methylpyridine *N*-oxide and 2-chloronicotinic acid, respectively. Reaction of the 5-azaindole **857a** with phenylsulfonyl chloride under phase transfer conditions afforded the 1-phenylsulfonyl-5-azaindole **857b**. Deprotonation of **857b** to the intermediate 2-lithio derivative **858**[563] and condensation with the 3-pyridinecarboxamide **859** gave the carbinol **860** in 70% yield. Oxidation with manganese dioxide to the ketone **861** and addition of methylmagnesium chloride followed by heating in acetic acid under reflux provided the lactone **862**. Reduction of the lactone **862** with DIBAL to the lactol **863** and subsequent reaction with methanolic sodium hydroxide afforded by concomitant removal of the phenylsulfonyl group the tetracyclic compound **864**. Reduction of compound **864** with sodium borohydride in diglyme provided the 9-azaolivacine analogue **865**. The reaction of compound **865** with trifluoromethanesulfonic acid and 3-(*N*,*N*-diethylamino)propylamine led directly to pazelliptine (**867**) in 87% yield. Alternatively, compound **865** was transformed to pazelliptine (**867**) in 76.5% overall yield by a two-step procedure via the intermediate chloro derivative **866** (Scheme 229).[564]

This method was also used for the industrial synthesis of retelliptine (for the corresponding hydrochloride **816**, see Scheme 223).[564] In 1997, Mérour and co-workers reported the synthesis of 7-azaolivacine analogues from 7-azaindole and the same 3-pyridinecarboxamide as starting materials.[565]

2.5. Total Synthesis of Ellipticine and Olivacine by Condensation of 4-Acetylpyridines

Hibino and Sugino reported a total synthesis of ellipticine (**806**) and olivacine (**809**) by thermal electrocyclization of the 2-alkenylindoles **869a,b**. The

Scheme 230



electrocyclization proceeds via an intermediate hexatriene system, which is formed by a [1,5]-sigmatropic reaction of the 2-alkenylindoles. The 2-alkenylindoles **869a,b** were obtained by condensation of 2-lithio-1-phenylsulfonylindole **759a** with the substituted 4-acetylpyridines **868a,b**. Thermal reaction of the 2-alkenylindoles **869a,b** at 460−500 °C afforded directly ellipticine (**806**) and olivacine (**809**) in 30% and 57% yield. This method was extended to the synthesis of the 11-demethylellipticines **870** and **871** by condensation of the 2-lithioindoles **759a,c** with 3-methyl-4-acetylpyridine **868c** (Scheme 230).[566]

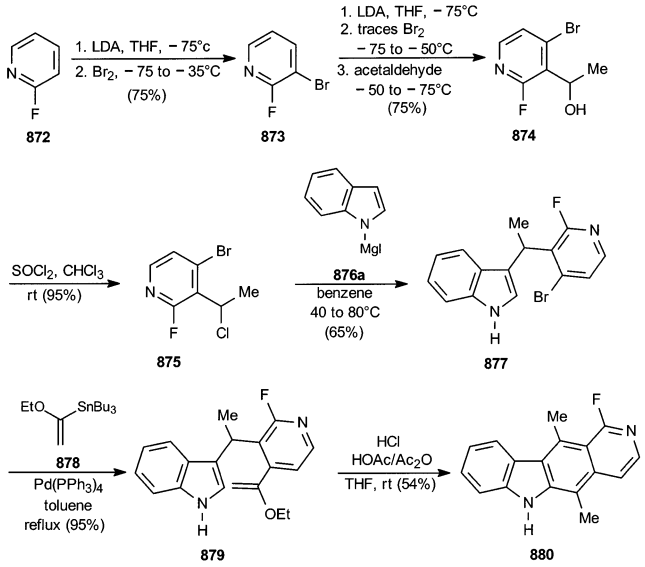
2.6. Synthesis of 1-Fluoroellipticine from 2-Fluoropyridine

Queguiner and co-workers reported the synthesis of 1-fluoroellipticine (**880**) from 1-indolylmagnesium iodide **876a** and 4-bromo-3-(1-chloroethyl)-2-fluoropyridine **875**. Transformation of 2-fluoropyridine **872**[567] to 3-bromo-2-fluoropyridine **873** followed by quenching of the intermediate 4-bromo-2-fluoro-3-lithiopyridine with acetaldehyde afforded the fluoro alcohol **874** in two steps and 56% overall yield. Compound **874** was converted to the corresponding chloro derivative **875**. Addition of 1-indolylmagnesium iodide **876a** to the chloro derivative **875** following DeGraw's procedure[568] gave the 3-substituted indole **877** in 65% yield. A Stille cross-coupling at C-4 of the pyridine ring in compound **877** afforded the vinylpyridine **879**. Finally, the acid-promoted cyclization of **879** provided 1-fluoroellipticine (**880**) (Scheme 231).[569]

2.7. Synthesis of 6H-Pyrido[4,3-b]carbazoles by Condensation of Indoles with 3-Acylpyridines

Archer and co-workers reported the synthesis of 5-hydroxymethyl-9-methoxy-11-methyl-6*H*-pyrido-[4,3-*b*]carbazole *N*-methylcarbamate **888** by an acid-promoted condensation of methyl 5-methoxyindol-2-yl acetate **884** with 3-acetylpyridine. Reaction of commercially available 3-methyl-4-nitroanisole **881** with ethyl oxalate and sodium methoxide gave an intermediate pyruvate which on oxidation with alkaline hydrogen peroxide and acidification afforded the acid **882a**.[570] Treatment of the acid **882a** with thionyl chloride followed by condensation of the

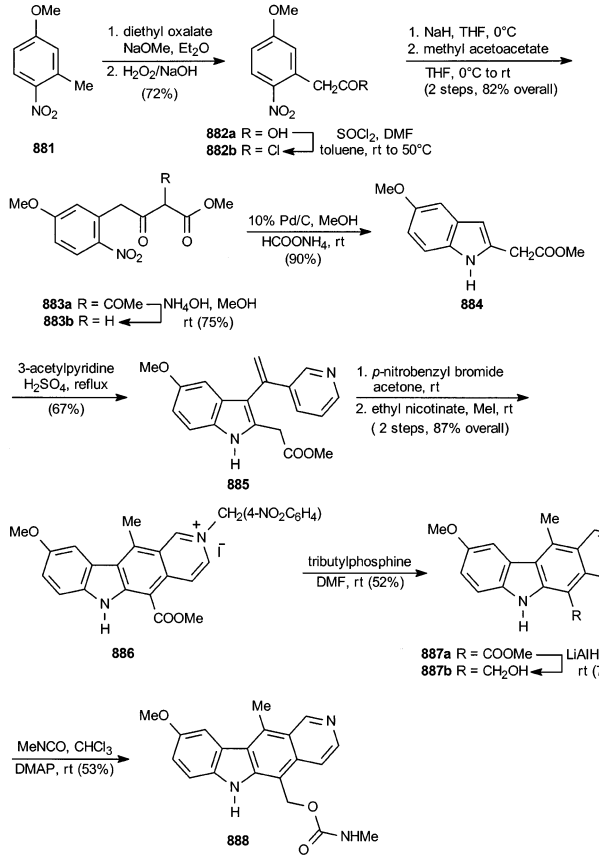
Scheme 231



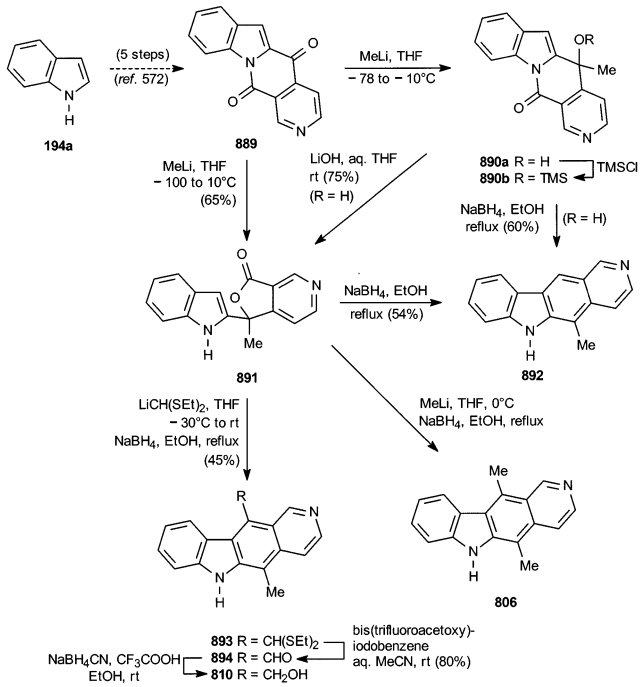
intermediate acid chloride **882b** with the anion of methyl acetoacetate provided in 82% yield the keto ester **883a**. Cleavage of **883a** to the ester **883b** and reduction with Pd/C and ammonium formate afforded methyl 5-methoxyindol-2-yl acetate **884**. Condensation of the ester **884** with 3-acetylpyridine in the presence of sulfuric acid led to the vinylindole **885**. Quaternization of the vinylindole **885** with *p*-nitrobenzyl bromide followed by cyclization and aromatization with ethyl nicotinate and methyl iodide gave the quaternary salt **886**. Dequaternization of **886** using tributylphosphine gave the 6*H*-pyrido[4,3-*b*]carbazole derivative **887a**. Reduction of **887a** to the alcohol **887b** and subsequent reaction with methyl isocyanate in the presence of 4-(dimethylamino)-pyridine (DMAP) provided 5-hydroxymethyl-9-methoxy-11-methyl-6*H*-pyrido[4,3-*b*]carbazole *N*-methylcarbamate **888** (Scheme 232).[571]

The same group reported the total synthesis of 5-methyl-6*H*-pyrido[4,3-*b*]carbazole-11-methanol **810** starting from Gribble's keto lactam intermediate **889**.[572] The keto lactam **889** was obtained in five steps from indole **194a** via a regioselective acylation of 2-lithio-1-(phenylsulfonyl)indole with 3,4-pyridinedicarboxylic anhydride.[572] Treatment of the keto lactam **889** with 1 equiv of methyllithium followed by quenching with solid ammonium chloride gave the lactam carbinol **890a** as the major product. However, when the same reaction was quenched with water, the lactone **891** was formed in 65% yield due to reaction of the lactam carbinol **890a** with LiOH generated in situ. The lactone **891** was used as an intermediate for the introduction of different substituents at C-11. Reduction of the lactone **891** with sodium borohydride in refluxing ethanol provided 11-demethylellipiticine **892**. Addition of methyllithium to the lactone **891** followed by reduction with sodium borohydride in refluxing ethanol afforded almost quantitatively ellipticine (**806**). Reaction of the compound **891** with the lithio derivative of formaldehyde diethylmercaptal[573] and reduction with sodium borohydride in refluxing ethanol led to the mercaptal **893**.

Scheme 232



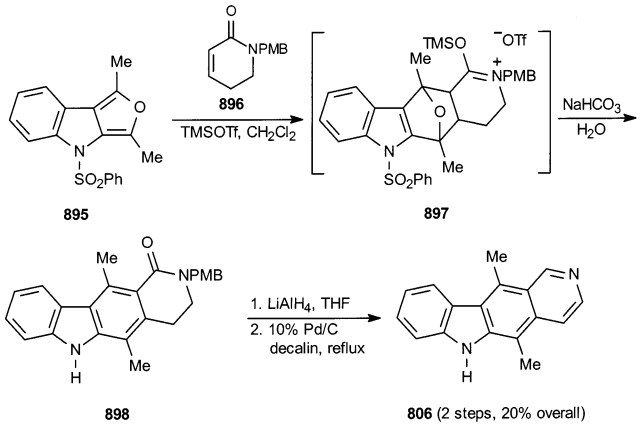
Scheme 233



Cleavage of the mercaptal **893** with bis(trifluoroacetoxy)iodobenzene[574] in aqueous acetonitrile gave the 11-formyl derivative **894**, which was reduced to 5-methyl-6*H*-pyrido[4,3-*b*]carbazole-11-methanol **810** (Scheme 233).[575,576]

Gribble and co-workers used the keto lactam **889** and its methoxy derivative for the total syntheses of

Scheme 234



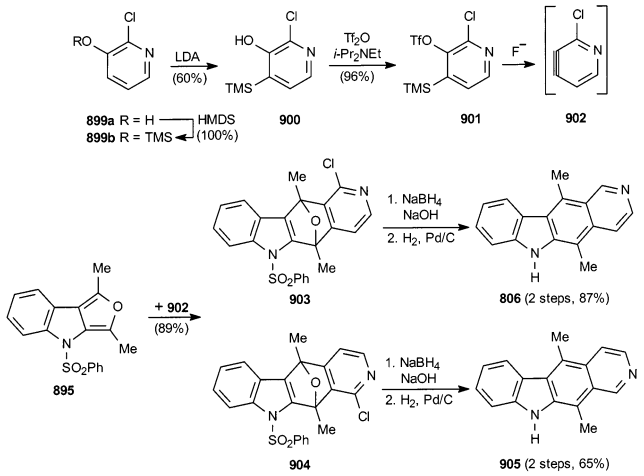
ellipticine (**806**), olivacine (**809**), 9-methoxyellipticine (**807**), and 9-hydroxyellipticine (**808**).[361]

3. Total Synthesis of Ellipticine by Diels–Alder Reaction of a 4*H*-Furo[3,4-*b*]indole

In 1990, Gribble et al. reported an improved version of their earlier synthesis[360] of ellipticine by using the 1-(*p*-methoxybenzyl)-5,6-dihydropyridone **896** as a synthetic equivalent for 3,4-pyridyne. The 5,6-dihydropyridone **896** was prepared in three steps from commercial *δ*-valerolactam analogous to the method of Zoretic.[577] The trimethylsilyl trifluoromethanesulfonate (TMSOTf)-accelerated[578] Diels–Alder reaction of 1,3-dimethyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole **895**[360] and 5,6-dihydropyridone **896** afforded in 40% yield the carbazole **898**. The low yield is presumably a consequence of decomposition of the lactam **897** during the reaction. Reduction of the carbonyl group with lithium aluminum hydride followed by aromatization with concomitant debenzylation converted the carbazole **898** to ellipticine (**806**) in 20% yield over two steps (Scheme 234).[358b,579]

In 1998, Guitián and co-workers described a modification of Gribble's approaches[360,579] for the total synthesis of ellipticine (**806**). They applied 2-chloro-3,4-pyridyne **902** as a synthetic equivalent for 3,4-pyridyne and used the polar effect of the chlorine atom for the regiocontrol of the cycloaddition with the indolofuran **895**.[580] Silylation of 2-chloro-3-hydroxypyridine **899a** followed by treatment of **899b** with LDA afforded the 4-trimethylsilylpyridine **900**. This reaction probably involves proton abstraction at C-4 and subsequent migration of the TMS group.[581] After transformation to the triflate **901**, the 2-chloro-3,4-pyridyne **902** is easily formed using Kobayashi's method by treatment with fluoride.[582] The reaction of in situ generated 2-chloro-3,4-pyridyne **902** with the indolofuran **895** provided the two regioisomers **903** and **904** in a ratio of 2.4:1 (89% yield). Reductive cleavage of the ether bridge of the major product **903** with sodium borohydride and sodium hydroxide followed by hydrogenolysis to remove the chlorine substituent provided ellipticine (**806**) in 87% overall yield. The minor adduct **904** was transformed to isoellipticine (**905**) in 65% overall yield by the same sequence of steps (Scheme 235).[583]

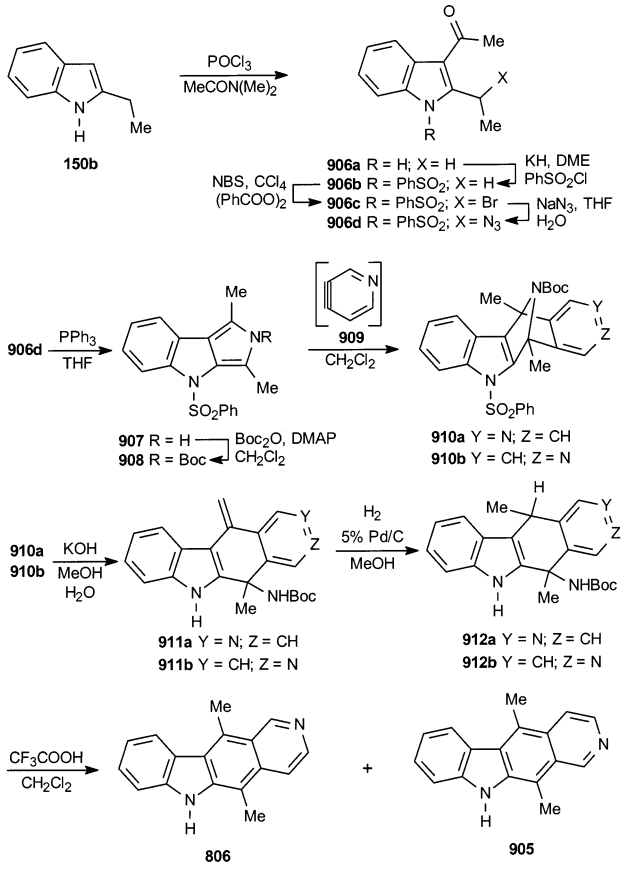
Scheme 235



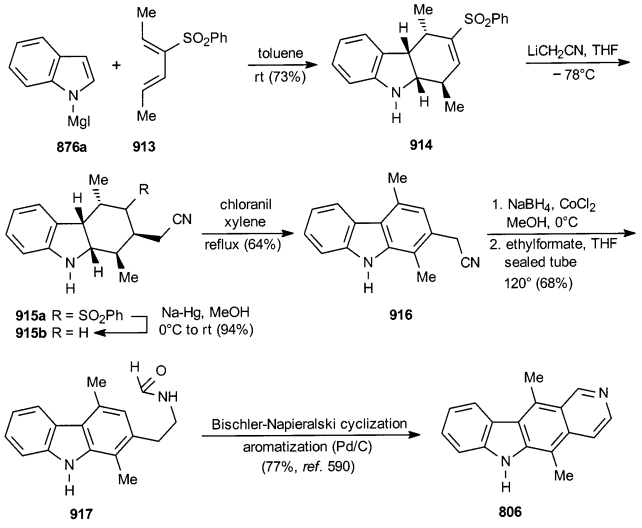
4. Total Synthesis of Ellipticine by Diels–Alder Reaction of a 2,4-Dihydropyrrolo[3,4-*b*]indole

Sha and Yang reported the total synthesis of ellipticine (**806**) using the 2,4-dihydropyrrolo[3,4-*b*]-indole **908** as a synthetic equivalent of indole-2,3-quinodimethane[363,364] in a Diels–Alder reaction with 3,4-pyridyne **909**. The acetylation of 2-ethylindole **150b** with *N*,*N*-dimethylacetamide and phosphorus oxychloride afforded the 3-acetylindole **906a** in 90% yield. After protection of the indole as the corresponding phenylsulfonyl derivative, compound **906b** was transformed to the bromide **906c** and then to the azido compound **906d**. The Staudinger reaction[584] of the azido compound **906d** with triphenylphosphine gave the 2,4-dihydropyrrolo[3,4-*b*]indole **907** in 94% yield. Protection of the pyrrolo nitrogen of the 2,4-dihydropyrrolo[3,4-*b*]indole **907** was achieved by transformation to the *N*-Boc derivative **908**. The Diels–Alder cycloaddition of **908** with 3,4-pyridyne **909**, generated by reaction of 1-aminotriazolo[4,5-*c*]-pyridine with lead tetraacetate,[585] provided the regioisomeric cycloadducts **910a** and **910b** in a ratio of 55:45 (62% yield). Hydrolysis of the cycloadducts **910a**,**b** afforded the tetracyclic carbazoles **911a**,**b** in 35 and 39% yield, respectively. Separate catalytic hydrogenation to the carbazole derivatives **912a**,**b** (80% and 83% yield, respectively) followed by treatment with trifluoroacetic acid provided ellipticine (**806**) (85% yield) and isoellipticine (**905**) (78% yield) (Scheme 236).[586] This method was also applied to the synthesis of amino analogues of ellipticine.[586]

Scheme 236



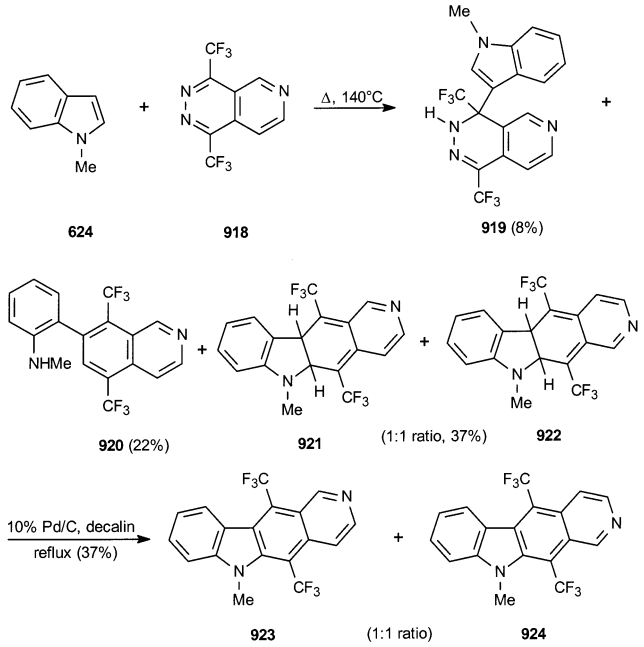
Scheme 237



5. Formal Synthesis of Ellipticine and Olivacine by Cycloaddition of a 2-Phenylsulfonyl-1,3-diene

Bäckvall and Plobeck reported a formal synthesis of ellipticine (**806**) starting from indole. The [4 + 2] cycloaddition of 1-indolylmagnesium iodide **876a**[587] with 3-(phenylsulfonyl)-2,4-hexadiene **913**[588] afforded the tetrahydrocarbazole **914** as the major diastereoisomer. Michael addition of lithio acetonitrile to the tetrahydrocarbazole **914** gave the hexahydrocarbazole **915a**. Reductive desulfonation of **915a** with sodium amalgam in buffered methanol to **915b** followed by aromatization with chloranil provided the carbazole **916**. Reduction of compound **916** using $CoCl_2/NaBH_4$ to the amine and subsequent formylation with ethylformate led to the formamide **917**. The known formamide **917**[589,590] was previously reported to provide ellipticine (**806**) in 77% overall yield[590] by Bischler–Napieralski cyclization to dihydroellipticine and subsequent aromatization (Scheme 237).[591] Based on the cycloaddition of (*E*)-2-(phenylsulfonyl)-1,3-pentadiene with 1-indolylmagnesium iodide **876a** (84% yield), a similar reaction sequence was used for a formal synthesis of olivacine.[591]

Scheme 238



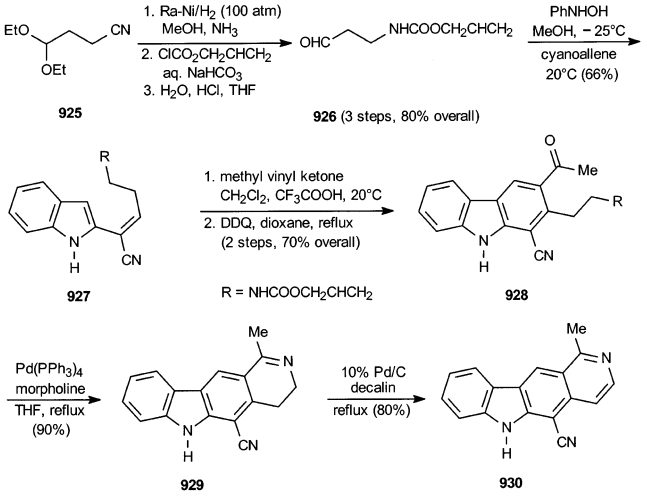
6. Synthesis of *N*-Methylhexafluoroellipticine

Haider et al. reported the synthesis of 5,11-bis(trifluoromethyl)-6-methyl-6*H*-pyrido[4,3-*b*]carbazole **923** starting from *N*-methylindole **624**. Heating of 1,4-bis(trifluoromethyl)pyrido[3,4-*d*]pyridazine **918**[592] with *N*-methylindole **624** at 140°C afforded the four products **919**−**922**. The inverse-electron-demand Diels−Alder cycloaddition of the triazanaphthalene **918** and *N*-methylindole **624** provides the two isomeric dihydropyridocarbazoles **921** and **922** in a 1:1 ratio. A palladium-catalyzed dehydrogenation of the mixture of **921** and **922** afforded a mixture of *N*-methylhexafluoroellipticine (**923**) and *N*-methylhexafluoroisoellipticine (**924**), which was inseparable by crystallization and by preparative liquid chromatography (Scheme 238).[593]

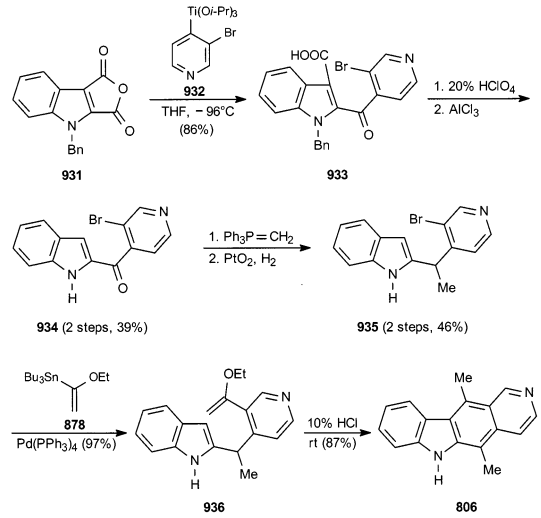
7. Synthesis of 5-Cyano-1-methyl-6*H*-pyrido[4,3-*b*]carbazole

Blechert and co-workers reported the synthesis of 5-cyano-1-methyl-6*H*-pyrido[4,3-*b*]carbazole **930**, a cyano analogue of olivacine, using an acid-promoted Diels−Alder reaction of the 2-vinylindole **927** with methyl vinyl ketone. The commercially available nitrile **925** was transformed to the aldehyde **926** in three steps and 80% overall yield. A domino reaction of the aldehyde **926** with *N*-phenylhydroxylamine and cyanoallene afforded the 2-vinylindole **927**.[594] The acid-promoted Diels−Alder reaction of the 2-vinylindole **927** with methyl vinyl ketone led to the intermediate tetrahydrocarbazole, which was dehydrogenated with DDQ to afford the cyanocarbazole **928** in 70% yield. The cyclization following the palladium-catalyzed release of the amine generated the dihydro derivative **929**. Finally, dehydrogenation of compound **929** provided the cyano analogue of olivacine (**930**) in 80% yield (Scheme 239).[595]

Scheme 239



Scheme 240

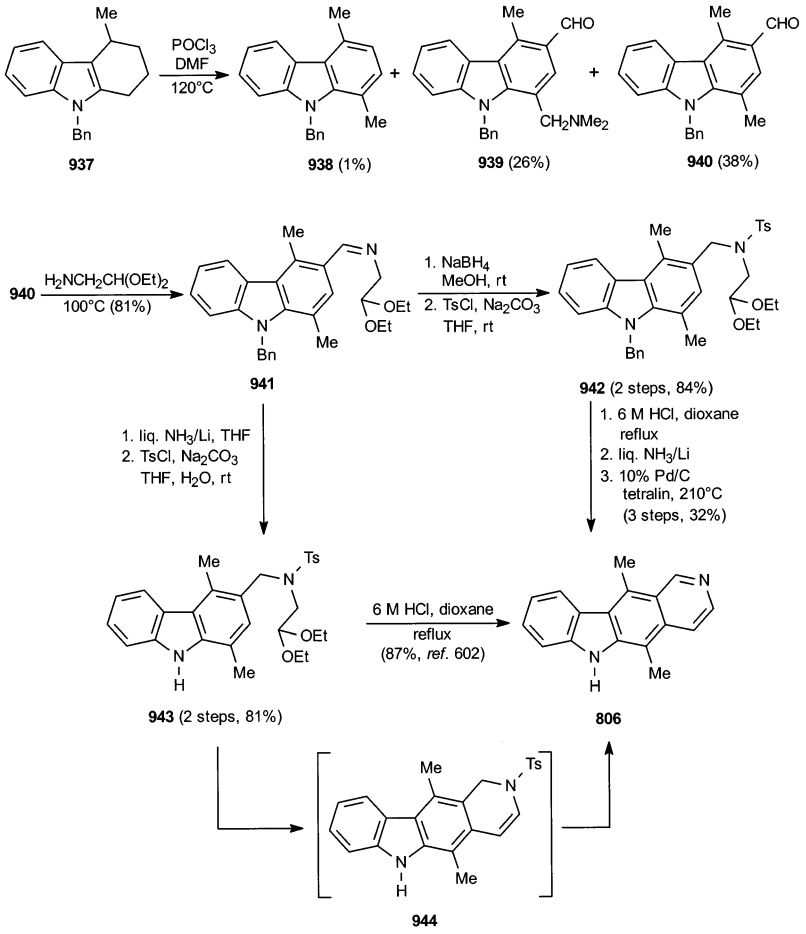


8. Total Synthesis of Ellipticine from Indole-2,3-dicarboxylic Anhydride

Miki et al. reported the synthesis of ellipticine (**806**) from *N*-benzylindole-2,3-dicarboxylic anhydride **931**.[596] The reaction of 3-bromo-4-lithiopyridine[597] and ClTi(*i*-OPr)$_3$[598] in tetrahydrofuran at −96 °C afforded the 3-bromo-4-pyridyltitanium compound **932**. Regioselective cleavage of the anhydride **931** with the titanium reagent **932** afforded in 86% yield the 2-acylindole-3-carboxylic acid **933**. Decarboxylation and debenzylation of **933** led to the ketone **934**. Wittig olefination of the ketone **934** followed by catalytic hydrogenation provided compound **935**. Palladium(0)-catalyzed cross-coupling of **935** with (1-ethoxyvinyl)tributyltin **878** afforded the ethoxyvinyl derivative **936**. Cyclization of **936** with 10% hydrochloric acid provided ellipticine (**806**) in 87% yield (Scheme 240).[599]

In 1998, Miki and his group reported a formal synthesis of ellipticine by reaction of the anhydride **931** with 3-bromo-4-lithiopyridine and subsequent transformation to the intermediate 6-benzyl-6*H*-pyrido[4,3-*b*]carbazole-5,11-quinone.[600]

Scheme 241



9. Total Synthesis of Ellipticine and Olivacine by Pomeranz–Fritsch Reaction

Murakami and co-workers described a synthesis of ellipticine (**806**) from 9-benzyl-4-methyl-1,2,3,4-tetrahydro-9*H*-carbazole **937**. Using an optimized Vilsmeier−Haack reaction, the tetrahydrocarbazole **937**[601] was transformed in 38% yield to the 3-formylcarbazole **940** along with the carbazole derivatives **938** (1% yield) and **939** (26% yield). Compound **940** was converted to the imine **941** and then to the tosyl amide **942**. The tosyl amide **942** was transformed to ellipticine **806** using a modified Pomeranz−Fritsch cyclization,[533] followed by spontaneous detosylation, aromatization, and debenzylation. However, the Birch reduction, used for the removal of the benzyl group, also reduced the pyridine ring to dihydroellipticine, which subsequently had to be rearomatized with 10% Pd/C to ellipticine (**806**). Therefore, an alternative route was developed involving removal of the benzyl group before the formation of the pyridine ring. The Birch reduction of the imine **941** removed the benzyl group with concomitant reduction of the C−N double bond. Tosylation of the resulting amine gave the acetal **943**. Cyclization of the tosylate **943** using Jackson and Shannon's conditions[602] with hydrochloric acid in dioxane provided ellipticine (**806**) along with 13% of 2-tosyl-1,2-dihydroellipticine (**944**). The compound **944** was separated and transformed to ellipticine (**806**) by heating with hydrochloric acid in dioxane (total yield 87%) (Scheme 241).[603,604] By a similar synthetic sequence starting from 9-benzyl-1,2,3,4-tetrahydro-9*H*-carbazole, Murakami et al. reported the synthesis of olivacine.[603,604]

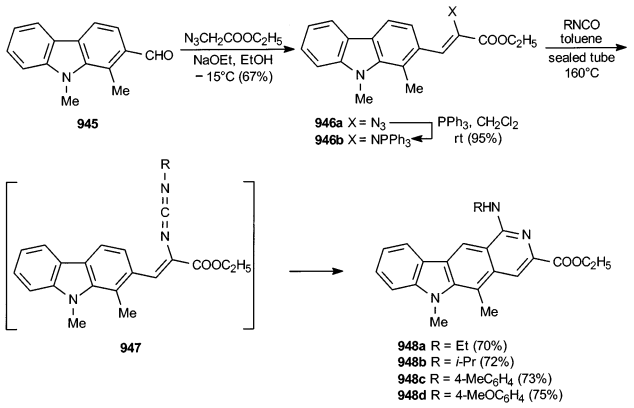
10. Synthesis of 1-Amino-6*H*-pyrido[4,3-*b*]-carbazoles

Molina and co-workers reported a series of 1-amino-6*H*-pyrido[4,3-*b*]carbazoles **948a**−**d** using the aza-Wittig reaction of an iminophosphorane with isocyanates as the key step. The condensation of 2-formyl-1,9-dimethyl-9*H*-carbazole **945**[605] with ethyl azidoacetate in the presence of sodium ethoxide afforded the azido derivative **946a**. The Staudinger reaction of compound **946a** gave the iminophosphorane **946b**. The aza-Wittig reaction of the iminophosphorane **946b** with aliphatic and aromatic isocyanates in dry toluene in a sealed tube provided the 1-amino-6*H*-pyrido[4,3-*b*]carbazoles **948a**−**d** in 70−75% yield (Scheme 242).[606]

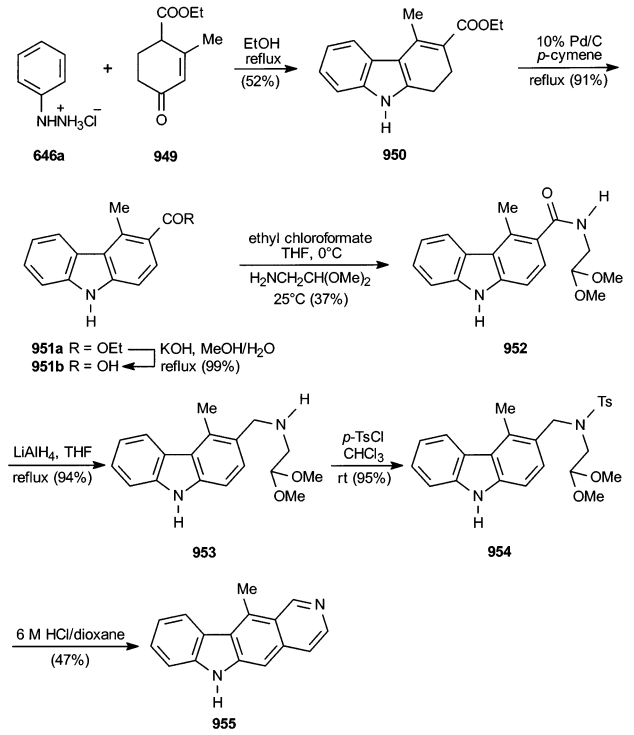
11. Synthesis of 5-Demethylellipticine from Hagemann's Ester

Okay et al. reported the synthesis of 5-demethylellipticine (**955**) from Hagemann's ester **949** using a modified Pomeranz−Fritsch cyclization as the key step. Condensation of phenylhydrazine hydrochloride **646a** with Hagemann's ester **949** in absolute ethanol under reflux provided the 1,2-dihydrocarbazole **950** in 52% yield. Aromatization to the carbazole **951a**[607]

Scheme 242



Scheme 243

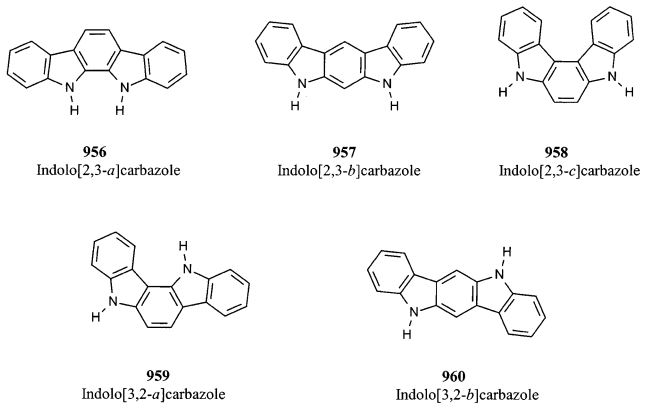


and alkaline hydrolysis afforded the acid **951b**. The reaction of the acid **951b** with aminoacetaldehyde dimethyl acetal led to the amide **952**. The amide **952** was reduced with lithium aluminum hydride to the amine **953** and then converted to the tosyl derivative **954**. Treatment of **954** with hydrochloric acid in dioxane provided 5-demethylellipticine **955** (Scheme 243).[608]

VIII. Indolo[2,3-a]carbazole Alkaloids

To the indolocarbazole family belong the five different isomeric ring systems **956**−**960** (Scheme 244). Among these, the most interesting structural class are the indolo[2,3-*a*]carbazoles **956**.[296,302,609−613] The indolo[2,3-*a*]carbazole framework **956** is found in many natural products with a broad range of potent biological activities, e.g. antifungal, antimicrobial, antitumor, and antihypertensive activity.[614−621] Their activity as potent inhibitors of protein kinase C (PKC)[622] has received special attention and was the focus of several investigations.[620,623−628] The indolo-

Scheme 244



[2,3-*b*]carbazole **957**, indolo[2,3-*c*]carbazole **958**, indolo[3,2-*a*]carbazole **959**, indolo[3,2-*b*]carbazole **960**, and their derivatives have been studied in much less detailed. This is explained by the fact that they are not present in natural products and there is a lack of knowledge of their biological activities. However, several aza analogues of indolo[3,2-*a*]carbazole **959** were shown to be powerful benzodiazepine receptor ligands.[629,630] Moreover, derivatives of the indolo[3,2-*b*]carbazole **960** recently attracted interest because of their affinity to the 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) receptor [also referred to as the aryl hydrocarbon (Ah) receptor protein],[631] which plays an important physiological role.[300,632−634]

The diverse synthetic approaches to the isomeric indolocarbazole ring systems **956**−**960** were summarized recently by Bergman and co-workers.[635] Therefore, only a few selected syntheses of the different indolocarbazole frameworks are described below.

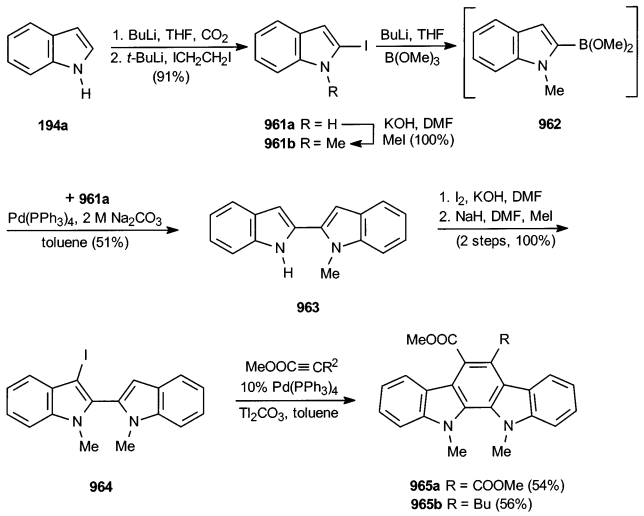
1. Construction of the Different Indolocarbazole Frameworks

1.1. Synthesis of Indolo[2,3-a]carbazole

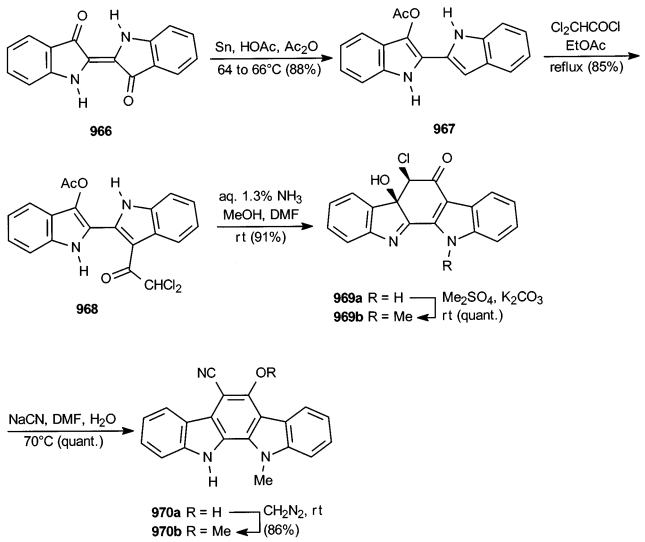
Prior to their isolation from nature and the discovery of their biological action, little attention was paid to the synthesis of indolo[2,3-*a*]carbazole derivatives. In 1956, Tomlinson and co-workers reported the first synthesis of the indolo[2,3-*a*]carbazole ring system as its *N*-methyl derivative by condensation of 8-amino-1,2,3,4-tetrahydro-9-methyl-9*H*-carbazole with 2-hydroxycyclohexanone. However, attempts to apply this synthesis to the parent indolo[2,3-*a*]-carbazole **956** were unsuccessful.[636] In the following year, Bhide et al. reported the synthesis of the parent indolo[2,3-*a*]carbazole **956** using two alternative Fischer indolizations by treatment of either 1,2,3,4-tetrahydro-9*H*-carbazol-1-one or the monophenylhydrazone of cyclohexane-1,2-dione with phenylhydrazine.[637] In 1958, Willcox and co-workers using Bhide's method reported the synthesis of indolo[2,3-*a*]carbazole **956** by Fischer indolization of 1,2,3,4-tetrahydro-9*H*-carbazol-1-one phenylhydrazone hydrochloride.[638] A further application of this method to the synthesis of indolo[2,3-*a*]carbazole **956** was described more recently by Kirsch and co-workers.[639]

In 1983, Magnus et al. reported the synthesis of *N*-substituted indolo[2,3-*a*]carbazoles by intramo-

Scheme 245



Scheme 246



lecular [4 + 2]-cycloaddition to an indole-2,3-quinodimethane. Attempts to transform the *N*-substituted indolo[2,3-*a*]carbazole to the parent indolo[2,3-*a*]carbazole **956** were unsuccessful.[640] Pindur and Kim reported the synthesis of substituted indolo[2,3-*a*]carbazole derivatives by reaction of 1,1′-dimethyl-2,2′-bisindolyl with racemic α-chloro-α-phenylacetyl chloride.[641] They also used 1,1′-dimethyl-2,2′-bisindolyl for the synthesis of indolo[2,3-*a*]carbazoles by electrophilic reaction with dimethyl acetylenedicarboxylate and subsequent photochemically induced 6π-electrocyclization of the intermediate 3-vinyl-1,1′-dimethyl-2,2′-bisindolyl.[642] In 1993, Beccalli and Marchesini reported the synthesis of a substituted indolo[2,3-*a*]carbazole from a 3-substituted indol-2(3*H*)-one by photochemical 6π-electrocyclization and subsequent aromatization.[326] The same group described the synthesis of different indolo[2,3-*a*]carbazole derivatives starting from 1-phenylsulfonyl-3-tributylstannylindole using a Stille coupling followed by electrocyclization.[643]

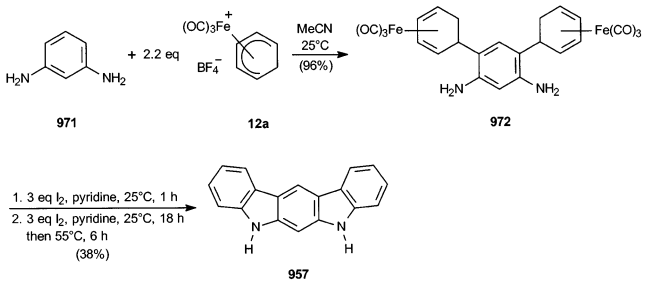
In 1997, Merlic and McInnes reported the synthesis indolo[2,3-*a*]carbazole derivatives from indole **194a** using sequential palladium-catalyzed cross-coupling reactions. Indole **194a** was iodinated at the 2-position to **961a** using the procedure of Bergman and Venemalm[644] and then *N*-methylated to give 2-iodo-1-methylindole **961b**. A Suzuki cross-coupling reaction[645,646] of **961a** with the in situ generated boronic ester **962** provided the unsymmetrical 1-methyl-2,2′-bisindolyl **963**. Iodination at the 3′-position using the procedure of Bocchi and Palla[647] followed by *N* ′-methylation afforded 3-iodo-1,1′-dimethyl-2,2′-bisindolyl **964**. The palladium-catalyzed benzannulation of compound **964** with acetylene esters afforded the indolo[2,3-*a*]carbazoles **965a** and **965b** (Scheme 245).[648] Alternatively, 3-iodo-1,1′-dimethyl-2,2′-bisindolyl **964** was transformed to indolo[2,3-*a*]carbazole derivatives by the photochemical or thermal benzannulation of the corresponding Fischer chromium carbene complexes.[649]

Somei and co-workers used 2,2′-bisindolyl as diene for the [4 + 2]-cycloaddition with dimethyl acetylenedicarboxylate or *N*-phenylmaleimide to give indolo-[2,3-*a*]carbazoles.[650] They reported the total synthesis of the cytotoxic and antiviral 5-cyano-6-methoxy-11-methylindolo[2,3-*a*]carbazole **970b**, which was isolated from the blue-green alga *Nostoc sphaericum* (strain EX-5-1) by Moore and co-workers.[651] Reduction of indigo **966** with tin in acetic acid/acetic anhydride afforded 3-acetoxy-2,2′-bisindolyl **967** in 88% yield.[652] Heating of **967** with dichloroacetyl chloride in ethyl acetate under reflux provided 3-acetoxy-3′-dichloroacetyl-2,2′-bisindolyl **968**, which was treated with aqueous ammonia in methanol/*N*,*N*-dimethylformamide at room temperature to give the indolo[2,3-*a*]carbazole derivative **969a**. *N*-Methylation to **969b** followed by reductive cyanation afforded 5-cyano-6-hydroxy-11-methylindolo[2,3-*a*]carbazole **970a**. The *O*-methylation of **970a** with diazomethane afforded 5-cyano-6-methoxy-11-methylindolo[2,3-*a*]carbazole **970b** in 86% yield (Scheme 246).[653] Starting from indigo **966**, the natural product **970b** was obtained in six steps and 59% overall yield. The two previous total syntheses of **970b** by Somei et al. started also from indigo but gave a low overall yield.[654] Further syntheses of various indolo[2,3-*a*]carbazoles from indigo were described by the same group more recently.[655]

1.2. Synthesis of Indolo[2,3-b]carbazole

In 1954, von Dobeneck and Maas claimed the synthesis of a dihydroindolo[2,3-*b*]carbazole using indole or 3,3′-bisindolylmethane and formaldehyde as synthetic precursors.[656] However, on the basis of later reports this structure assignment should be revised.[635,657,675] The first synthesis of the parent indolo[2,3-*b*]carbazole **957** was reported by Grotta and co-workers in 1961 using a catalytic dehydrogenation of *N*,*N* ′-diphenyl-*m*-phenylenediamine at 500 °C in the vapor phase. The drawback of this method is the lack of regioselectivity in the cyclodehydrogenation and the low yield of indolo[2,3-*b*]carbazole **957**.[657] In the same year, Noland et al. reported the synthesis of different dihydroindolo[2,3-*b*]carbazoles by condensation of carbonyl compounds with indole or a 3,3′-bisindolylmethane in refluxing maleic acid solution. The formation of the corresponding fully aromatic indolo[2,3-*b*]carbazoles by this method was

Scheme 247



not reported.[658] In 1992, Kistenmacher and Müllen reported the synthesis of indolo[2,3-*b*]carbazole **957** for the design of new donors for electrically conducting charge-transfer complexes. The key step of their synthesis was the reductive ring closure of 2,4-dinitro-1,5-diphenylbenzene using Cadogan's method.[659] The 2,4-dinitro-1,5-diphenylbenzene was obtained by a Suzuki coupling of phenylboronic acid and 1,5-dibromo-2,4-dinitrobenzene.[660] In 1995, Black et al. reported the synthesis of methoxy-substituted indolo[2,3-*b*]carbazole derivatives by reaction of 4,6-dimethoxyindole with arylaldehydes and phosphoryl chloride. However, unsubstituted indole under these conditions led only to 3,3′-diindolylmethanes. The 3,3′-diindolylmethanes did not provide the aromatic indolo[2,3-*b*]carbazoles but served as precursors for the formation of dihydroindolo[2,3-*b*]carbazoles.[661]

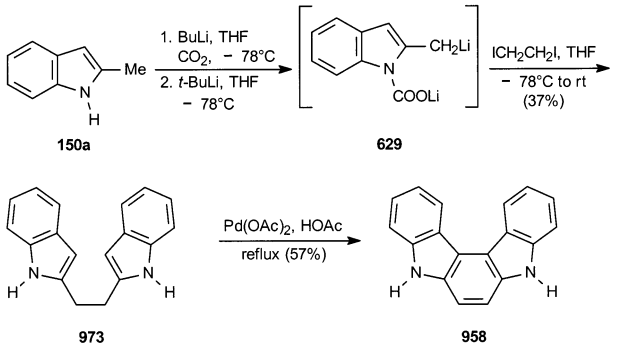
In 1998, we reported a convergent two-step synthesis of indolo[2,3-*b*]carbazole **957** in 36% overall yield from commercial *m*-phenylenediamine **971** by an iron-mediated bidirectional annulation of the two indole rings. The 2-fold electrophilic substitution of *m*-phenylenediamine **971** using the iron complex salt **12a** afforded the dinuclear iron complex **972** in 96% yield. A double iron-mediated arylamine cyclization of the iron complex **972** with iodine in pyridine provided indolo[2,3-*b*]carbazole **957** (Scheme 247).[662,663]

1.3. Synthesis of Indolo[2,3-c]carbazole

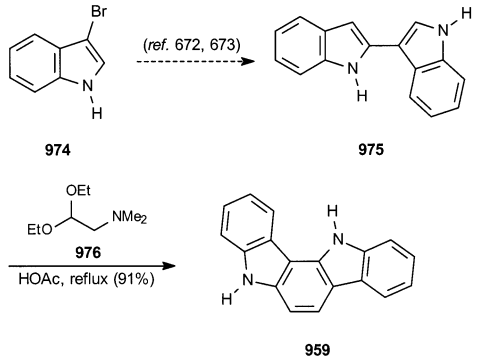
Until 1983, indolo[2,3-*c*]carbazole **958** was the only unknown isomer of the five different indolocarbazoles. In that year, Grellmann described the photoreaction of *N*,*N*′-dimethyl-*N*,*N*′-diphenyl-1,4-phenylenediamine, which gave directly *N*,*N*′-dimethylindolo[2,3-*c*]carbazole via an intermediate *N*,*N*′-dimethyl-3-anilinocarbazole.[664] Bergman and Desarbre developed in 1997 two different methods for the synthesis of indolo[2,3-*c*]carbazoles from readily available 3,3′-bisindolyl derivatives. The first method involves a thermally induced electrocyclic reaction of a 2-nitrovinyl-3,3-bisindolyl derivative. The second procedure uses 3,3′-bisindolyl as a diene for the Diels−Alder reaction with appropriate dienophiles (dimethyl acetylenedicarboxylate and ethyl propiolate) to give the corresponding indolo[2,3-*c*]carbazole derivatives.[665,666] More recently, Bergman and co-workers developed another method for the synthesis of indolo[2,3-*c*]carbazole derivatives, including the preparation of the parent indolo[2,3-*c*]carbazole **958** by oxidative cyclization of 1,2-bis(1*H*-indol-2-yl)-ethane **973**.[667]

Using Katritzky's method, 2-methylindole **150a** was transformed to the 2-lithiomethylindole derivative **629**,[328] which on reaction with 1,2-diiodoethane afforded compound **973** in 37% yield.[668] The oxidative cyclization of 1,2-bis(1*H*-indol-2-yl)ethane **973** with palladium(II) acetate in refluxing acetic acid provided indolo[2,3-*c*]carbazole **958** in 57% yield (Scheme 248).[669] Alternatively, indolo[2,3-*c*]carbazole **958** was prepared by a double Fischer indolization of the *N*,*N*′-diphenylbishydrazone of cyclohexan-1,4-dione, albeit in low yield (8%).[669]

Scheme 248



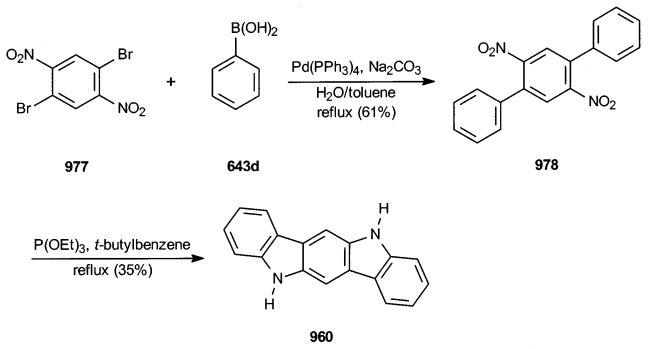
Scheme 249



1.4. Synthesis of Indolo[3,2-a]carbazole

In 1951, Tomlinson reported the first synthesis of indolo[3,2-*a*]carbazole **959** by double Fischer indolization and subsequent dehydrogenation of bis(cyclohexanone) *m*-phenylenedihydrazone.[670] Hall and Plant reported in 1953 a new method for the synthesis of indolo[3,2-*a*]carbazole **959** and its 5-methyl derivative via an intermediate octahydroindolo[3,2-*a*]carbazole by heating 5-aminotetrahydrocarbazole and 5-aminotetrahydro-8-methylcarbazole with 2-chlorocyclohexanone.[671] In 1958, Willcox and co-workers developed another method for the synthesis of indolo[3,2-*a*]carbazole **959** by Fischer indolization using 1,2,3,4-tetrahydro-9*H*-carbazol-4-one and phenylhydrazine as starting materials.[638] Starting from 1,2,3,4-tetrahydro-9*H*-carbazol-4-one and arylhydrazines, Kirsch et al. applied the Fischer indolization method of Wilcox to the synthesis of various indolo[3,2-*a*]-carbazoles.[639] Bergman and co-workers developed an elegant synthesis of indolo[3,2-*a*]carbazole **959** starting from the readily available 2,3′-bisindolyl **975**.[672,673] The reaction of 2,3′-bisindolyl **975** with dimethylaminoacetaldehyde diethyl acetal **976** in refluxing acetic acid provided indolo[3,2-*a*]carbazole **959** in 91% yield (Scheme 249).[674] Various 5,6-disubstituted indolo[3,2-*a*]carbazoles were prepared in a one-pot operation by

Scheme 250



the reaction 2,3′-bisindolyl **975** with dialkyl acetylenedicarboxylates.[674]

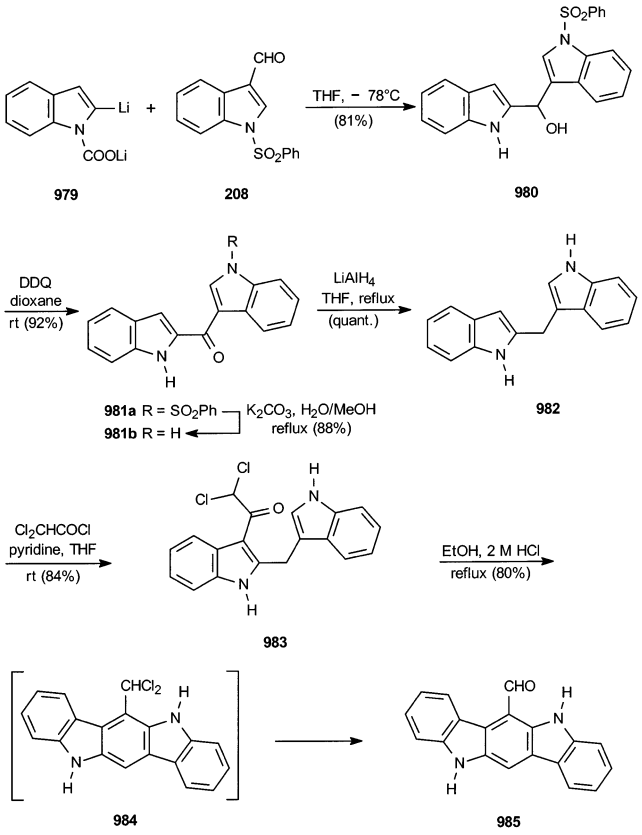
1.5. Synthesis of Indolo[3,2-b]carbazole

In 1961, Grotta and co-workers described the first synthesis of the parent indolo[3,2-*b*]carbazole **960** by vapor phase catalytic dehydrogenation of *N*,*N*′-diphenyl-*p*-phenylenediamine.[657] In 1963, Harley-Mason and Pavri reported another synthesis of indolo[3,2-*b*]carbazole **960** by Fischer indolization of cyclohexane-1,4-dione bisphenylhydrazone.[675] This method was also used by other groups for the synthesis of indolo[3,2-*b*]carbazole **960** in different yields.[676−678] In 1975, Lamm et al. claimed the synthesis of 5,11-dimethylindolo[3,2-*b*]carbazole by bidirectional photocyclization of *N*,*N*′-dimethyl-*N*,*N*′-diphenyl-*p*-phenylenediamine.[48] However, this product was later reassigned as *N*,*N*′-dimethylindolo[2,3-*c*]-carbazole by the groups of Grellmann[664] and Chakrabarty.[679] Kistenmacher and Müllen reported a two-step synthesis of indolo[3,2-*b*]carbazole **960** from 1,4-dibromo-2,5-dinitrobenzene **977**. The Suzuki coupling of phenylboronic acid **643d** with 1,4-dibromo-2,5-dinitrobenzene **977** afforded 1,4-diphenyl-2,5-dinitrobenzene **978**. Using Cadogan's conditions,[659] compound **978** was transformed to indolo[3,2-*b*]carbazole **960** in 35% yield (Scheme 250).[660]

In 1988, Ishii and co-workers described the formation of 6,12-disubstituted indolo[3,2-*b*]carbazoles by the acid-promoted tetramerization of indole **194a**, which is believed to proceed via the electrocyclization of an intermediate triene followed by oxidation.[680] Katritzky and co-workers reported in 1995 the synthesis of 6,12-dialkylindolo[3,2-*b*]carbazoles by a Lewis acid-promoted dimerization of 2-(1-benzotriazol-1-ylalkyl)indoles.[681] In the following year, Cheng et al. described the acid-promoted dimerization of a 2-(hydroxybutenyl)indole to give a 6,12-disubstituted indolo[3,2-*b*]carbazole.[682] Fang et al. prepared 5,6,11,12-tetramethyl-6,12-dihydroindolo-[3,2-*b*]carbazole by reaction of 2-lithio-1-methylindole with acetaldehyde and subsequent dimerization of the resulting alcohol,[683] a method previously applied by Ziegler and co-workers.[457]

Black and co-workers described the synthesis of methoxy-substituted indolo[3,2-*b*]carbazole derivatives by reaction of 4,6-dimethoxyindole with arylaldehydes in the presence of phosphoryl chloride, followed by self-condensation of the resulting intermediate.[661] In 1998, Biswas and co-workers obtained

Scheme 251



5,11-dimethyl-6-trifluoromethylindolo[3,2-*b*]carbazole (13% yield) by treatment of 3-hydroxymethyl-1-methylindole with trifluoroacetic anhydride.[684]

Tholander and Bergman described the synthesis of 6-formylindolo[3,2-*b*]carbazole **985**, an extremely potent ligand for the aryl hydrocarbon (Ah) receptor (or TCDD receptor). The 2-lithioindole **979**, prepared according to the Katritzky's protocol,[328] was treated with *N*-phenylsulfonyl-3-formylindole **208** to give the carbinol **980**. Oxidation of **980** with DDQ afforded the ketone **981a**. Deprotection to **981b** followed by reduction with lithium aluminum hydride provided quantitatively 2,3-diindolylmethane **982**. Dichloroacetylation of 2,3-diindolylmethane **982** using modified conditions[685] gave compound **983**. Finally, the acid-promoted tandem cyclization−hydrolysis of the dichloroacetyl compound **983** afforded 6-formylindolo-[3,2-*b*]carbazole **985**, presumably via the intermediate dichloromethyl compound **984** (Scheme 251).[686,687] The desired 6-formylindolo[3,2-*b*]carbazole **985** was accompanied by small amounts of the parent indolo-[3,2-*b*]carbazole **960**, which caused difficulties in the purification of **985**. However, using a sequence of Boc-protection and deprotection, the separation was achieved. The synthesis of further 6-substituted indolo[3,2-*b*]carbazoles was achieved by reaction of 2,3-diindolylmethane **982** with various electrophiles.[687]

In addition to the methods reported above, the same authors also used the double Fischer indolization of bisphenylhydrazones of cyclohexane-1,4-diones, the acid-promoted condensation of indole with aliphatic aldehydes, and the palladium-mediated oxidative cyclization of a *N*,*N*′-diphenyl-*p*-phenylenediamine for the synthesis of a range of 6,12-disub-

stituted indolo[3,2-*b*]carbazoles.[688] Also 6,12-diformylindolo[3,2-*b*]carbazole was found to represent an extremely efficient ligand for the aryl hydrocarbon (Ah) receptor.[688a] More recently, Bergman and his group described 5*H*,11*H*-indolo[3,2-*b*]carbazole-6,12-dione as an extremely potent Ah receptor ligand.[689]

2. Synthesis of the Natural Products and Biologically Active Congeners

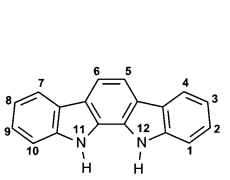
All the indolocarbazole alkaloids isolated so far from nature are indolo[2,3-*a*]carbazoles. They were obtained from soil organisms, slime molds, and marine sources.[296,609,611] Their history goes back for about two and a half decades. The indolo[2,3-*a*]-carbazole alkaloids and the biogenetically related bisindolylmaleimides constitute an important class of natural products with diverse and, in some cases, extraordinary biological activities.

In 1987 and 1989, Steglich described the isolation, synthesis, and biosynthetic relationship of indolocarbazoles.[609,610] In 1988, Bergman published a review on the various synthetic aspects of indolocarbazoles.[296] The detailed review published in 1993 by Gribble et al. covers the synthetic acitivity in this area from 1986 to 1993 and describes other aspects, in particular the exceptional biological activity of some indolo[2,3-*a*]carbazoles.[611] In the same year, Chakraborty reported a general review on carbazole alkaloids, including the occurrence of indolocarbazoles and some methods for their synthesis.[16] In 1997, Pindur published a review on the synthesis and antitumor activity of carbazoles and annulated indoles with the emphasis on indolocarbazoles.[302] Two years later, Pindur reported an updated review on the syntheses of indolocarbazoles covering the literature from 1993 to 1997 and including their inhibitory activities against the target enzymes protein kinase C (PKC) and topoisomerase I.[613] In addition to these reviews, Moody published in 1994 a personal account on the synthesis of staurosporinone,[17] and Prudhomme described in 1997 the anticancer activity of indolocarbazoles.[612]

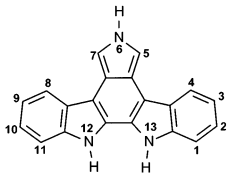
In view of the large number of excellent reviews on indolo[2,3-*a*]carbazole alkaloids that already appeared, the present section summarizes the field only briefly with a special emphasis on the most exciting results of the recent years. The occurrence, syntheses, and biological properties of the indolo[2,3-*a*]carbazoles **956** are described. Most of the compounds are in fact derivatives of the indolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazole ring system **986**, but for simplicity, they will be designated as indolo[2,3-*a*]carbazoles (Scheme 252).

In 1977, Omura and co-workers isolated the first indolo[2,3-*a*]carbazole alkaloid from *Streptomyces staurosporeus*.[690] Initially this alkaloid was called AM-2282, but it was later named staurosporine (**989**).[691,692] The structure of this new aminohexose-bound alkaloid with relative stereochemistry was not established completely until an X-ray crystal structure was obtained.[691] In 1994, the absolute configuration was established by the X-ray crystallographic analysis of 4′-*N*-methylstaurosporine methiodide.[693] Staurosporine (**989**) has very interesting biological

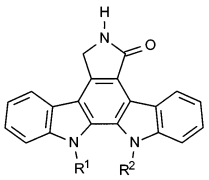
Scheme 252

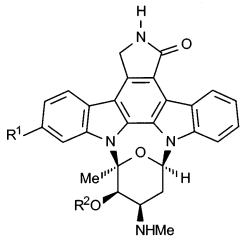


956
Indolo[2,3-*a*]carbazole



986
Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole





987 Staurosporinone (K-252c)
Staurosporine Aglycon
R^1, R^2 = H

988 Gö 6976
$R^1 = (CH_2)_2CN$; R^2 = Me

989 (+)-Staurosporine (AM-2282)
R^1= H; R^2 = Me

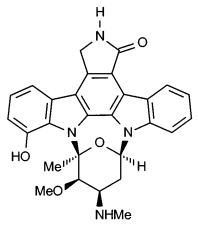
990 TAN-999
R^1 = OMe; R^2 = Me

991 Demethylstaurosporine
R^1, R^2 = H

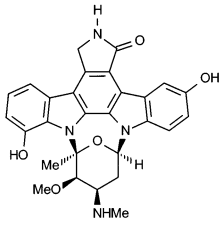
activities,[622] e.g. antimicrobial,[690,694] hypotensive,[694] cytotoxic,[695] inhibition of protein kinase C (PKC),[695,696] and platelet aggregation inhibition.[618] Since 1997 the number of isolated and structurally elucidated indolo-[2,3-*a*]carbazole alkaloids has grown considerably.[611,613] In 1986, the lactam heterocycle K-252c (**987**) was found in the *Nocardiopsis* strain K-290. The structure elucidation showed that K-252c (**987**) represents the aglycon of staurosporine (**989**). Therefore, **989** is also called staurosporinone.[624,697] In 1993, Schächtele et al. reported the synthetic nonglycosidic indolo[2,3-*a*]carbazole Gö 6976 (**988**),[698−700] which exhibited a selective inhibition of protein kinase C (PKC) and also acted as an antagonist of human immunodeficiency virus 1 (HIV-1).[701] The 10-methoxy derivative of staurosporine, TAN-999 (**990**), produced by the soil microbe *Nocardiopsis dassonvillei* C-71425, is a macrophage activator.[702−704] Researchers at Ciba-Geigy isolated in 1995 demethylstaurosporine (3′-demethoxy-3′-hydroxystaurosporine) (**991**), a novel staurosporine analogue from a blocked mutant of *Streptomyces longisporoflavus* R 19 (Scheme 252). This indolo[2,3-*a*]carbazole was less potent than staurosporine (**989**) but showed a more selective inhibition of protein kinase C (PKC) isotypes α, β-2, and γ.[705]

In 1992, Kinnel and Scheuer isolated 11-hydroxystaurosporine (**992**) and 3,11-dihydroxystaurosporine (**993**) from the Pohnpei tunicate *Eudistoma* sp (Scheme 253). These were the first examples of naturally occurring indolo[2,3-*a*]carbazoles from an animal source.[706] In 1989, (−)-TAN-1030a (**994**), the oxime analogue of staurosporine, was isolated from *Streptomyces* sp. C-71799 (Scheme 253).[702,703] The alkaloid **994** was shown to activate macrophage function on mice.[702] In the following year, (+)-RK-286c (**995**) was isolated from another strain of *Streptomyces* and found to be a weak inhibitor of protein kinase C (PKC).[707,708] Researchers at Abbott laboratories disclosed in 1994 the isolation of the micromo-

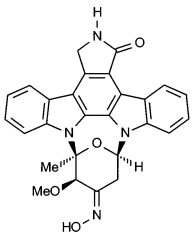
Scheme 253



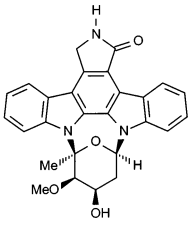
992 11-Hydroxystaurosporine



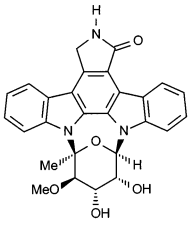
993 3,11-Dihydroxystaurosporine



994 (−)-TAN-1030a

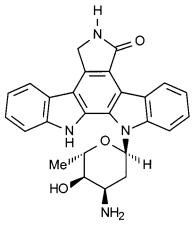


995 (+)-RK-286c

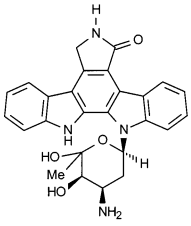


996 (+)-MLR-52

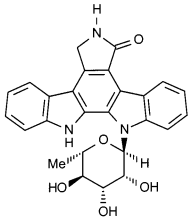
Scheme 254



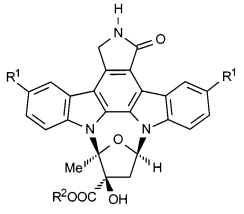
997 Holyrine A



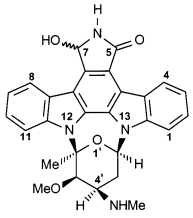
998 Holyrine B



999 (+)-K-252d



1000 (+)-K-252a (SF-2370)
R^1 = H; R^2 = Me
1001 (+)-K-252b
R^1, R^2 = H
1002 KT-6006
R^1 = OH; R^2 = Me

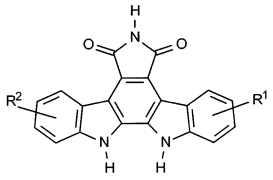


1003 UCN-01 and UCN-02

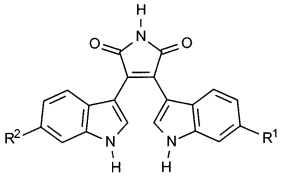
lar PKC inhibitor (+)-MLR-52 (**996**) (Scheme 253), which has potent in vitro immunosuppressive activity (IC_{50} = 1.9 ± 0.2 nM) similar to that of FK-506 (IC_{50} = 0.39 ± 0.12 nM), cyclosporine (IC_{50} = 2.5 ± 0.8 nM), and staurosporine (**989**) (IC_{50} = 1.3 ± 0.2 nM)[709] (Scheme 253).

In 1999, Andersen et al. isolated holyrine A (**997**) and holyrine B (**998**), two new members of the indolo-[2,3-*a*]carbazole alkaloids, from cultures of the marine *Actinomycete* st. N96C-47 (Scheme 254).[710] These alkaloids have only a single attachment of their sugar moiety to the aromatic aglycon, similar to (+)-K-252d (**999**) and rebeccamycin (**1014**) (see Scheme 256).[711] The isolation of (+)-K-252d (**999**), the α-L-rhamnose derivative of K-252c (**987**) (see Scheme 252), from *Nocardiopsis* sp was reported in 1986 by Kase and co-workers.[624] In 1985, Sezaki reported the isolation

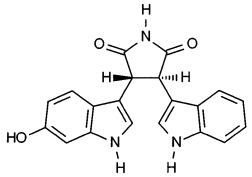
Scheme 255



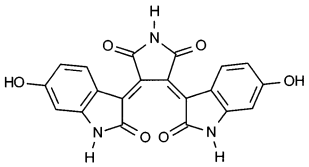
1004 Arcyriaflavin A
R^1, R^2 = H
1005 Arcyriaflavin B
R^1 = 2-OH; R^2 = H
1006 Arcyriaflavin C
R^1 = 2-OH; R^2 = 10-OH
1007 Arcyriaflavin D
R^1 = 2-OH; R^2 = 9-OH
1008 BE-13793c
R^1 = 1-OH; R^2 = 11-OH



1009 Arcyriarubin A
R^1, R^2 = H
1010 Arcyriarubin B
R^1 = H; R^2 = OH
1011 Arcyriarubin C
R^1, R^2 = OH

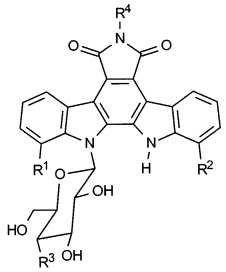


1012 Dihydroarcyriarubin B

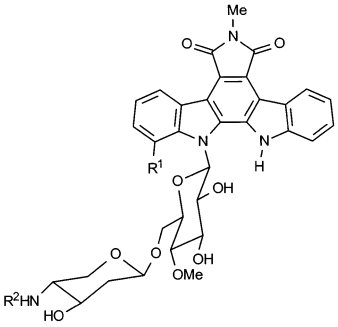


1013 Arcyriaverdin C

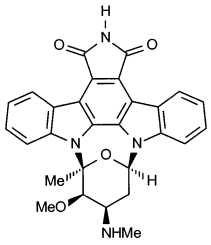
Scheme 256



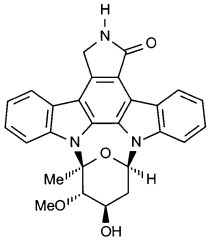
1014 Rebeccamycin
R^1, R^2 = Cl; R^3 = OMe; R^4 = H
1015 11-Dechlororebeccamycin
R^1 = Cl; R^2, R^4 = H; R^3 = OMe
1016 Bromorebeccamycin
R^1, R^2 = Br; R^3 = OMe; R^4 = H
1017 ED-110
R^1, R^2, R^3 = OH; R^4 = H
1018 NB-506
R^1, R^2, R^3 = OH; R^4 = NHCHO



1019 AT2433-A_1
R^1 = Cl; R^2 = Me
1020 AT2433-A_2
R^1 = Cl; R^2 = H
1021 AT2433-B_1
R^1 = H; R^2 = Me
1022 AT2433-B_2
R^1, R^2 = H



1023 Bmy-41950
(RK-1409 or 7-Oxostaurosporine)



1024 RK-1409B

and structural elucidation of the furanosylated congener, SF-2370 (**1000**), from *Actinomadura* sp. (Scheme 254).[712] A year later Kase et al. described

the isolation of (+)-K-252a, a compound that proved to be identical with SF-2370,[623,697] along with the structurally related (+)-K-252b (**1001**) from a different source *Nocardiopsis* sp.[624,697] These indolo[2,3-*a*]-carbazoles are potent inhibitors of protein kinase C (PKC).[623] Prudhomme et al. described in 1996 the synthetic K-252a derivative KT-6006 (**1002**), which has shown protein kinase C (PKC) inhibition by interacting with the ATP binding site of the enzyme.[713] However, such nonselective PKC inhibitors may be responsible for serious side effects. In 1987, Takahashi et al. isolated the two epimeric 7-hydroxystaurosporines UCN-01 and UCN-02 (**1003**) from *Streptomyces* sp. N-126.[714,715] The configuration of the hydroxy group of the individual stereoisomers is unknown, and in acid or alkaline media, the two isomers are in equilibrium (Scheme 254).[627,716]

A relatively large number of indolo[2,3-*a*]carbazoles and of the biogenetically related bisindolylmaleimides was found to occur in various slime molds.[609,610] The brightly colored *Arcyria nutans* and *Arcyria denudata* contain the arcyriaflavins A (**1004**), B (**1005**), and C (**1006**) (Scheme 255).[609,717] The arcyriaflavins B (**1005**) and C (**1006**) were also found in *Metatrichia vesparium*.[718] These indolo[2,3-*a*]carbazoles are classified according to the number of hydroxy groups present in the 2- and 10-positions. The only exception is arcyriaflavin D (**1007**) from *Dictydiaethalium plumbeum*, which has a 2,9-dihydroxylation pattern (Scheme 255).[610] The arcyriaflavins exhibit moderate antibiotic and antifungal activities.[610] The alkaloid BE-13793c (**1008**), a compound isomeric to the arcyriaflavins C (**1006**) and D (**1007**), was isolated from the microorganism *Steptoverticillium mobaraense* and reported to be an inhibitor of both topoisomerase I and II (Scheme 255).[719] The arcyriarubins A−C (**1009**−**1011**) represent the most simple members of the bisindolylmaleimides, a family of pigments produced by slime molds (*Myxomycetes*).[609,610,717,720] These bisindolylmaleimides were found along with dihydroarcyriarubin B (**1012**) and arcyriaverdin C (**1013**) in *Arcyria denudata* (Scheme 255).[609,717] Arcyriarubin C (**1011**) was also detected in *Arcyria ferruginea*.[719] The arcyriarubins A−C (**1009**−**1011**) are structurally related to the aglycon of staurosporine,[690−692] rebeccamycin,[711] and other biologically active metabolites from *Streptomycetes*. Bisindolylmaleimides are selective inhibitors of protein kinase C (PKC)[721] and show potential for a novel therapy of autoimmune diseases.[722]

Several members of the indolo[2,3-*a*]carbazole alkaloids have a single *N*-glycosidic bond. The most well-known of this group is rebeccamycin (**1014**), isolated in 1985 from *Saccharothrix aerocolonigenes* (formerly *Nocardia aerocolonigenes*).[711] The structure and absolute configuration of rebeccamycin was determined by X-ray crystallography. 11-Dechlororebeccamycin (**1015**), which is lacking the chlorine at C-11, was also obtained from the same source (Scheme 256).[723,724] Both compounds are potent antitumor agents.[621] Rebeccamycin, which is currently at the last stage of clinical evaluation as an anticancer agent, induces topoisomerase I mediated DNA cleavage.[725] In 1991, Lam et al. obtained the water soluble derivative bromorebeccamycin (**1016**) by culturing *S. aerocolonigenes* in the presence of bromide ions to increase the antitumor potency (Scheme 256).[726] Bromorebeccamycin (**1016**) is being evaluated in clinical trials.[726,727]

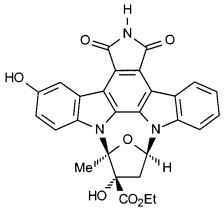
The semisynthetic derivative ED-110 (**1017**), prepared by enzymatic glycosylation of BE-13793c (**1008**) (see Scheme 255), has enhanced anti-topoisomerase I activity and increased water solubility.[728] ED-110 exhibited in vitro cytotoxicity against a variety of tumor cell lines, as well as in vivo antitumor activity in xenotransplanted nude mice.[729] Another semisynthetic derivative, NB-506 (**1018**), shows potent anti-topoisomerase I activity as well as in vitro and in vivo antitumor activity (Scheme 256).[730] A phase I clinical trial of NB-506 (**1018**) showed a reduction of tumor-specific markers in ovarian and breast cancer patients clinically resistant to taxol therapy.[730] Four indolo[2,3-*a*]carbazoles with an aminodisaccharide and an *N*-methylimide have been isolated from *Actinomadura melliaura*: AT2433-A_1 (**1019**), AT2433-A_2 (**1020**), AT2433-B_1 (**1021**), and AT2433-B_2 (**1022**) (Scheme 256).[731−733]

In 1991, researchers at Bristol-Myers Squibb isolated the antitumor antibiotic Bmy-41950 (**1023**) from *Streptomyces staurosporeus* strain R10069. This compound showed in vitro activity against human colon cancer cells (HCT-116l).[734] In the same year, Isono et al. isolated from *Streptomyces platensis* sub sp. *malvinus* the indolo[2,3-*a*]carbazole alkaloid RK-1409, which turned out to be identical with Bmy-41950.[735] The protein kinase C (PKC) inhibitor RK-1409 (7-oxostaurosporine) inhibited the morphological change of a human chronic erythroleukemia cell, K-562, induced by phorbol 12,13-dibutyrate (PD-Bu).[736] From the same source these authors isolated also RK-1409B (**1024**) (Scheme 256),[737] a new inhibitor of protein kinase C, which is isomeric to (+)-RK-286c (**995**) (see Scheme 253).

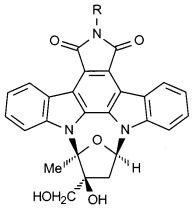
In 1999, Ubukata et al. isolated indocarbazostatin (**1025**) from a culture broth of a *Streptomyces* sp. This alkaloid is a potent inhibitor of NGF-induced neurite outgrowth from PC12 cells (Scheme 257).[738] Among the various synthetic K-252a derivatives there are, besides KT-6006 (**1002**) (see Scheme 254), the two compounds, KT-6124 (**1026**) and KT-6528 (**1027**), which differ only in the substitution at the imide nitrogen (Scheme 257). They showed less potency as PKC inhibitors, but they exhibited a broad spectrum of antiproliferative activity against human tumor cell lines in vitro and are inhibitors of topoisomerase I.[713,739] In 1990, Moore et al. isolated the simple indolo[2,3-*a*]carbazoles **1028**, **1029**, and **1030** from the blue-green alga *Nostoc sphaericum* (Scheme 257).[651] They are moderately active against *Herpes simplex* type 2 and they are weakly cytotoxic against human cancer cell lines. Although the alkaloids **1028** (major) and **1029** (minor) were not separable, their structures could be assigned on the bais of long-range coupling correlations and NOE experiments. For a total synthesis of 5-cyano-6-methoxy-11-methylindolo[2,3-*a*]carbazole **1028** (=**970b**), see Scheme 246.[653]

The blue-green algae *Tolypothrix tjiapanasensis* produces a wide range of indolo[2,3-*a*]carbazole al-

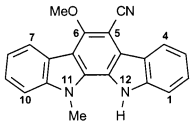
Scheme 257



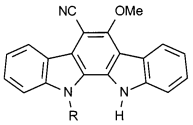
1025 Indocarbazostatin



1026 KT-6124
R = NH_2
1027 KT-6528
R = OH

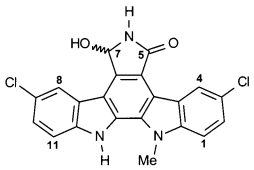


1028 5-Cyano-6-methoxy-11-methyl-indolo[2,3-*a*]carbazole

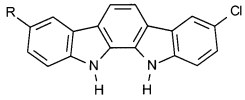


1029 6-Cyano-5-methoxy-11-methyl-indolo[2,3-*a*]carbazole
R = Me
1030 6-Cyano-5-methoxy-indolo[2,3-*a*]carbazole
R = H

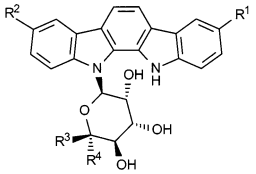
Scheme 258



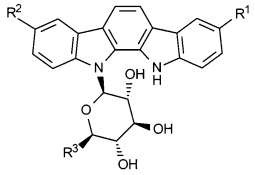
1031 Tjipanazole J



1032 Tjipanazole D
R = Cl
1033 Tjipanazole I
R = H



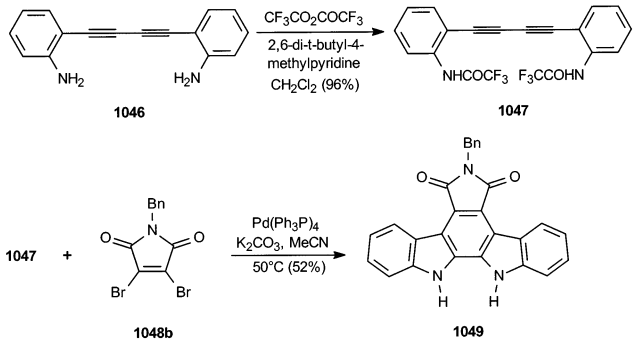
1034 Tjipanazole A1
R^1, R^2 = Cl; R^3 = Me; R^4 = H
1035 Tjipanazole A2
R^1, R^2 = Cl; R^3 = H; R^4 = Me
1036 Tjipanazole C1
R^1 = Cl; R^2, R^4 = H; R^3 = Me
1037 Tjipanazole C2
R^1, R^4 = H; R^2 = Cl; R^3 = Me
1038 Tjipanazole C3
R^1 = Cl; R^2, R^3 = H; R^4 = Me
1039 Tjipanazole C4
R^1, R^3 = H; R^2 = Cl; R^4 = Me
1040 Tjipanazole G1
R^1, R^2, R^4 = H; R^3 = Me
1041 Tjipanazole G2
R^1, R^2, R^3 = H; R^4 = Me



1042 Tjipanazole B
R^1, R^2 = Cl; R^3 = H
1043 Tjipanazole E
R^1, R^2 = Cl; R^3 = CH_2OH
1044 Tjipanazole F1
R^1 = Cl; R^2, R^3 = H
1045 Tjipanazole F2
R^1, R^3 = H; R^2 = Cl

kaloids with moderate fungicidal activity, the tjipanazoles **1031**−**1045** (Scheme 258).[740] Among these, only tjipanazole J (**1031**) has the characteristic pyrrolo[3,4-*c*]ring of UCN-01 and UCN-02 (**1003**) (see Scheme 254). The tjipanazoles D (**1032**) and I (**1033**) are simple chlorinated indolo[2,3-*a*]carbazoles. The tjipanazoles A1, A2 (**1034**, **1035**); C1−C4 (**1036**−**1039**); G1, G2 (**1040**, **1041**); B (**1042**); E (**1043**); and F1, F2 (**1044**, **1045**) have a chlorine and/or a glycosidic (β-D-glucosyl, β-6-deoxy-D-gulosyl, β-L-rhamnosyl, or β-D-xylosyl) substituent at the polyheteroaromatic framework.

Scheme 259



The synthetic methods used for the construction of the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole ring system involve oxidative cyclizations of bisindolylmaleimides, metal-catalyzed coupling reactions, Diels−Alder reactions, and Fischer indolizations. The classification of the total syntheses described in this chapter is based on the key step furnishing the heterocyclic framework.

2.1. Palladium(0)-Catalyzed Synthesis of N-Benzylindolo-[2,3-a]pyrrolo[3,4-c]carbazole

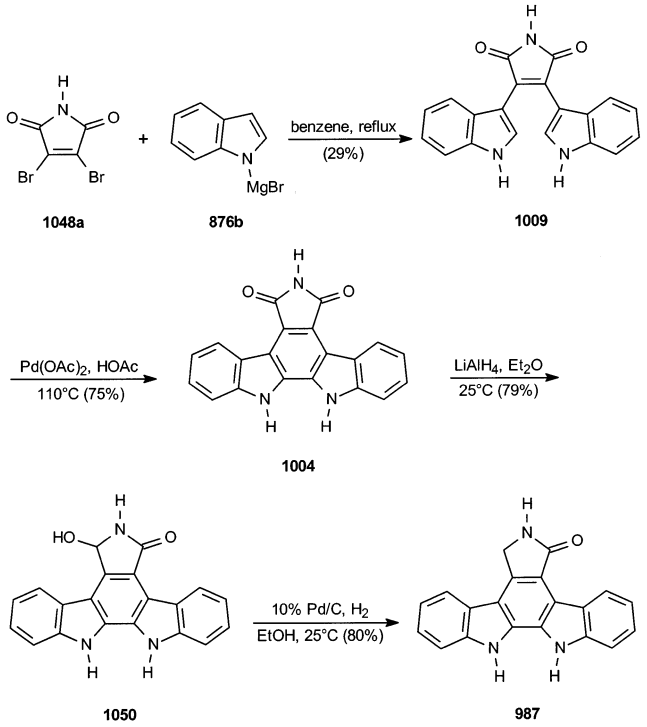
In 1995, Saulnier and co-workers reported the synthesis of *N*-benzylindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole **1049** starting from the diacetylene **1046**. Treatment with trifluoroacetic anhydride converted the readily available diacetylene **1046**[741,742] to the corresponding bistrifluoroacetanilide **1047** in 96% yield. The reaction of compound **1047** with *N*-benzyldibromomaleimide **1048b** and anhydrous K_2CO_3 in the presence of tetrakis(triphenylphosphine)-palladium(0) in dry acetonitrile afforded *N*-benzylindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole **1049** in 52% yield (Scheme 259).[743] This novel palladium(0)-catalyzed polyannulation generates four bonds and three rings in a one-pot process.

2.2. Palladium-Mediated Syntheses of Indolo[2,3-a]-carbazoles

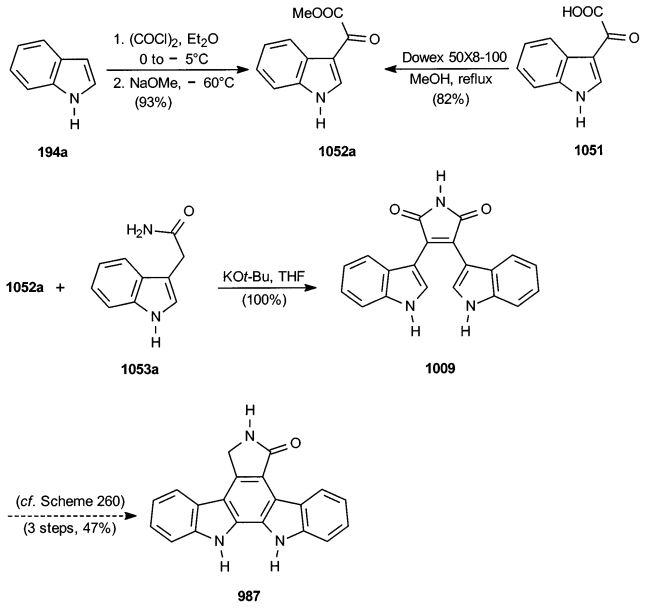
Synthesis of Staurosporinone (K-252c). In 1993, Hill et al. reported an efficient short synthesis of staurosporinone (K-252c) (**987**) and analogues using a palladium-mediated oxidative cyclization of the bisindolylmaleimide arcyriarubin A (**1009**) as the key step. The key intermediate arcyriarubin A (**1009**) was prepared in one step without protection of the imide nitrogen by reaction of dibromomaleimide **1048a** with 4 equiv of indolylmagnesium bromide **876b** in benzene under reflux. Oxidative cyclization of arcyriarubin A (**1009**) with 1 equiv of palladium(II) acetate in acetic acid provided in 75% yield arcyriaflavin A (**1004**). Hydride reduction of **1004** followed by hydrogenolytic deoxygenation of the resulting hydroxy lactam **1050** afforded staurosporinone (**987**) (Scheme 260).[316a] This synthesis leads to staurosporinone (**987**) in four steps and 14% overall yield based on dibromomaleimide **1048a**. The same sequence was applied to the synthesis of a 12-methyl analogue.[316a]

In 1995, Faul et al. reported an improved synthesis of arcyriarubin A (**1009**) by reaction of indolylmag-

Scheme 260



Scheme 261



nesium bromide **876b** with dichloromaleimide. Following Hill's route (Scheme 260),[316a] **1009** was transformed in three steps to staurosporinone (**987**), which was obtained in four steps and 34% overall yield from dichloromaleimide. This approach provides so far the shortest synthesis of staurosporinone (**987**) with the best overall yield.[744]

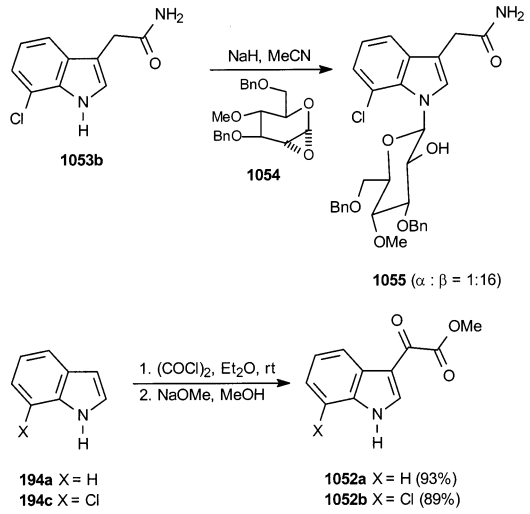
The same authors reported in 1998 a new route to arcyriarubin A (**1009**) starting from methyl indole-3-glyoxylate **1052a** and indole-3-acetamide **1053a**. Methyl indole-3-glyoxylate **1052a** was prepared either by treatment of indole **194a** with oxalyl chloride, followed by addition of sodium methoxide at low temperature, or by refluxing 3-indole glyoxylic acid **1051** in methanol with Dowex 50 × 8−100 ion-exchange resin. An intramolecular Perkin-type condensation of methyl indolyl-3-glyoxylate **1052a** and indole-3-acetamide **1053a** in the presence of a 1 M solution of potassium *tert*-butoxide in tetrahydrofuran provided quantitatively arcyriarubin A (**1009**). Although this synthesis requires two steps, arcyriarubin A **1009** was obtained in a high overall yield. Using Hill's three-step sequence (palladium-mediated oxidative cyclization, reduction, and deoxygenation)[316a] compound **1009** was transformed to staurosporinone (**987**) (Scheme 261).[745] This method was also applied to the synthesis of unsymmetrical bisindolylmaleimides.

Burtin and co-workers used the same strategy for the synthesis of the aglycon of KT-5823. The synthetic indolo[2,3-*a*]carbazole KT-5823 is the *N*,*O*-dimethyl derivative of K-252a and represents a selective protein kinase G inhibitor. Application of Hill's route,[316a] starting from dichloro-*N*-methylmaleimide and indolylmagnesium bromide **876b**, provided via 6-methylarcyriaflavin A the KT-5823 aglycon (=6-methylstaurosporinone) in four steps and 36% overall yield.[746]

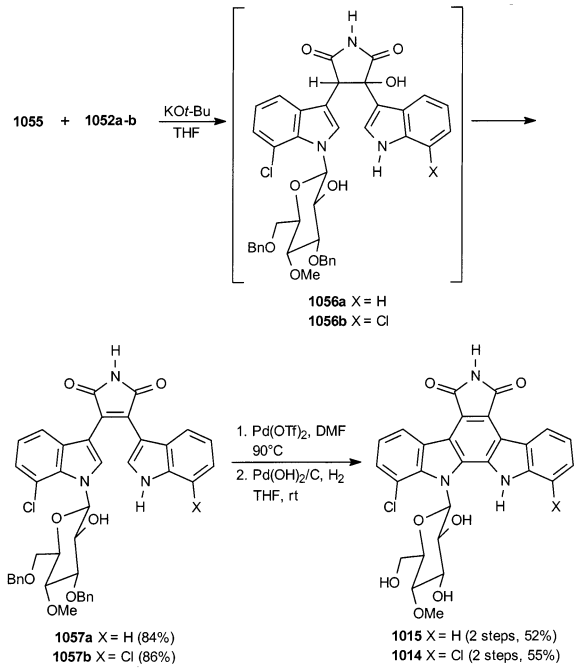
Total Synthesis of Rebeccamycin and 11-Dechlororebeccamycin. In 1999, Faul and co-workers applied their condensation method described above to the total syntheses of rebeccamycin (**1014**) and 11-dechlororebeccamycin (**1015**) via the symmetrical and unsymmetrical bisindolylmaleimides **1057a,b**. The bisindolylmaleimides **1057a,b** were prepared by condensation of the glycosylated 7-chloroindole-3-acetamide **1055** with the methyl indole-3-glyoxylates **1052a**,**b**. Using Danishefsky's method,[747] a selective formation of the *β*-*N*-glycoside of 7-chloroindole-3-acetamide **1053b** was accomplished. The α-1,2-anhydrosugar **1054** was prepared from commercially available tri-*O*-acetyl-D-glucal in four steps and 15:1 α/*β*-selectivity (80% overall yield). Deprotonation of 7-chloroindole-3-acetamide **1053b** (obtained from 7-chloroindole in three steps and 65% overall yield)[748−750] with sodium hydride in acetonitrile followed by treatment with the α-1,2-anhydrosugar **1054** afforded the *β*-*N*-glycoside **1055** in 40% yield. The *β*/α-selectivity of the reaction was 16:1 and the minor α-isomer was removed by chromatography to afford the *β*-isomer in >98% diasteromeric purity. The methyl indole-3-glyoxylates **1052a**,**b** were readily prepared from the indoles **194a** and **194c** by reaction with oxalyl chloride at room temperature followed by addition of sodium methoxide (Scheme 262).

The intramolecular Perkin-type condensation of the glycosylated 7-chloroindole-3-acetamide **1055** and methyl indole-3-glyoxylate **1052a** initiated by a 1 M solution of potassium *tert*-butoxide in tetrahydrofuran at room temperature afforded, via the intermediate hydroxyimide **1056a**, the bisindolylmaleimide **1057a**. The oxidative cyclization of the bisindolylmaleimide **1057a** using palladium(II) triflate in *N*,*N*-dimethylformamide at 90 °C and debenzylation with Pearlman's catalyst [$Pd(OH)_2$/C] provided 11-dechlororebeccamycin (**1015**) in 52% overall yield. An analogous route starting from compound **1055** and methyl 7-chloroindole-3-glyoxylate **1052b** afforded rebeccamycin (**1014**) in three steps and 47% overall yield (Scheme 263).[751]

Scheme 262



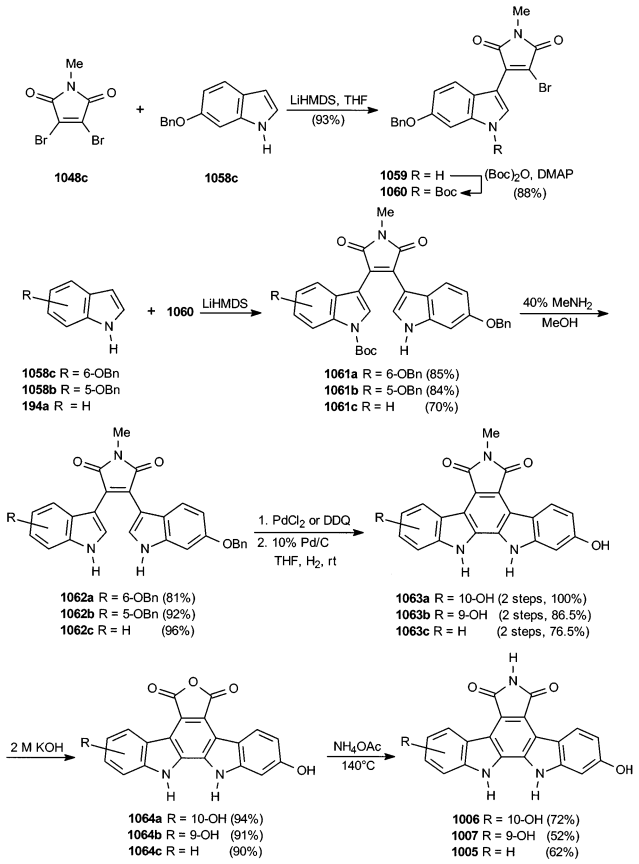
Scheme 263



Wang et al. described the synthesis of the rebeccamycin aglycon (1,11-dichloroindolo[2,3-*a*]pyrrolo-[3,4-*c*]carbazole-5,7(6*H*)-dione) using a palladium(II)-catalyzed oxidative cyclization of an *N*-protected 2,3-bis(6-chloroindol-3-yl)maleimide.[752] The Wacker-type catalytic system that they applied was used previously for the oxidative cyclization of anilino-1,4-benzoquinones to carbazole-1,4-quinones.[197,230,416]

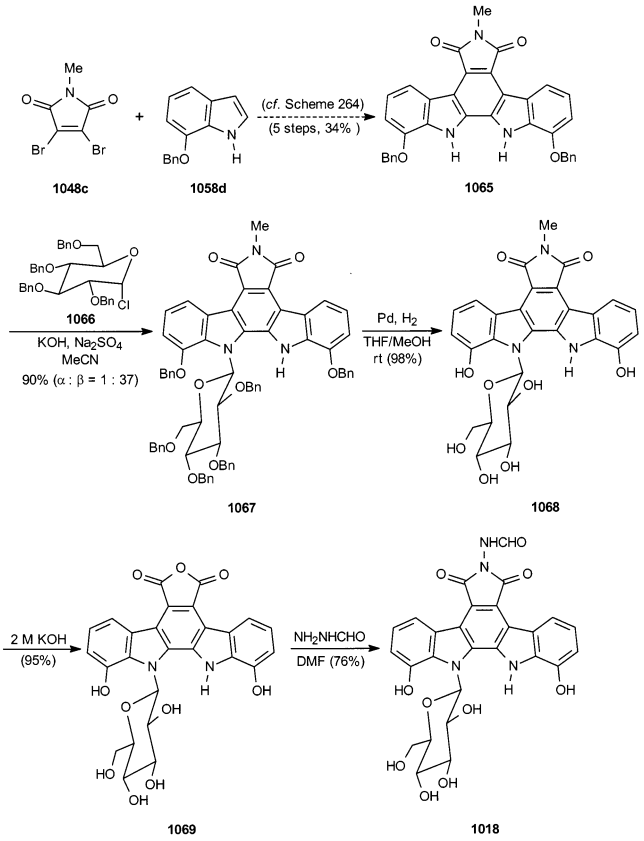
Total Synthesis of the Arcyriaflavins B−D and Synthesis of NB-506 and ED-110. In 1996, Ohkubo and co-workers reported the synthesis of the arcyriaflavins B−D (**1005**−**1007**) using as key steps the base-induced coupling of dibromo-*N*-methylmaleimide **1048c** with indoles and the palladium-mediated oxidative cyclization of the bisindolylmaleimides **1062**. The reaction of 6-benzyloxyindole **1058c**[753,754] and dibromo-*N*-methylmaleimide **1048c**[755] with lithium hexamethyldisilazide (LiHMDS) as the base afforded the monoindolyl derivative **1059** in 93% yield. Protection of **1059** by the Boc group led in 88% yield to compound **1060**. The base-induced coupling of the indoles **1058c**, **1058b**, and **194a** with **1060** provided the bisindolyl derivatives **1061a**−**c**. Removal of the Boc group with methylamine[756] afforded in good yields the deprotected compounds **1062a**−**c**. Cyclization of **1062a** and **1062c** using DDQ followed by debenzylation using catalytic amounts of palladium on charcoal provided the corresponding products **1063a** and **1063c**. The cyclization of **1062b** with DDQ gave only traces of the desired product. However, the oxidative cyclization of **1062b** using palladium(II) chloride in *N*,*N*-dimethylformamide followed by debenzylation led to the desired compound **1063b** in 86.5% yield over both steps. Treatment of **1063a**−**c** with aqueous potassium hydroxide afforded the anhydrides **1064a**−**c**. Finally, ammonolysis of the anhydrides **1064a**−**c** provided the arcyriaflavins C (**1006**), D (**1007**), and B (**1005**) (Scheme 264).[757]

Scheme 264

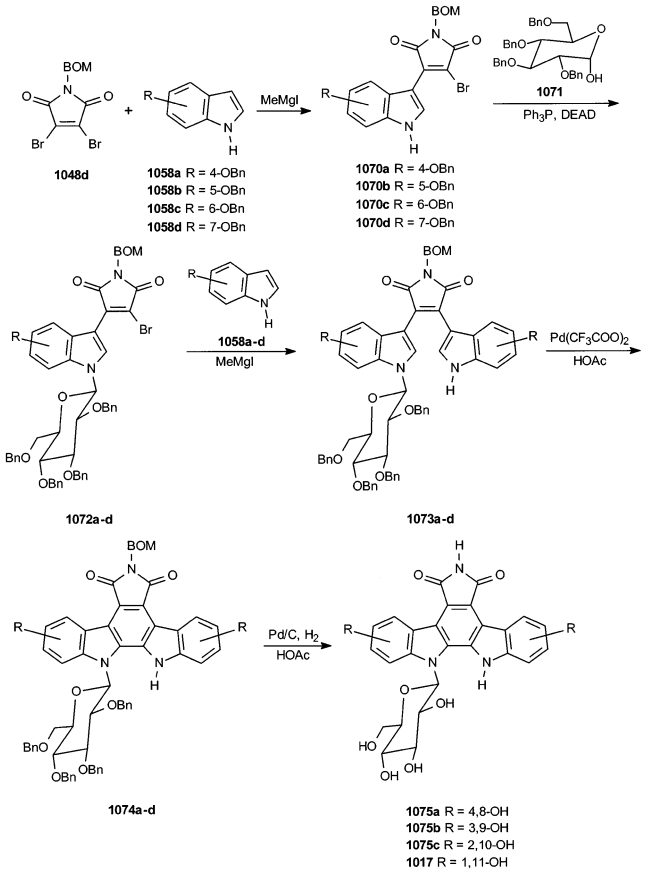


The same group applied this method to the synthesis of unsymmetrical indolocarbazole glycosides.[758] A further extension was achieved by the synthesis of the new anticancer agent NB-506 (**1018**) from dibromo-*N*-methylmaleimide **1048c** and 7-benzyloxyindole **1058d**. Using slightly modified conditions, dibromo-*N*-methylmaleimide **1048c** and 7-benzyloxyindole **1058d** were transformed in five steps and 34% overall yield to the aglycon **1065** (compare Scheme 264).[757] The glycosylation of the indolocarbazole **1065** with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride **1066**[759] was achieved with high stereoselectivity ($\alpha/\beta = 1:37$) by reaction of the indolyl dianion of **1065** with the α-halogen compound **1066**. Removal of the benzyl groups of the glycoside **1067** by hydrogenolysis

Scheme 265



Scheme 266



with catalytic amounts of palladium on charcoal afforded the hydroxy derivative **1068**. Hydrolysis of compound **1068** with aqueous potassium hydroxide led to the dicarboxylic anhydride **1069**, which on treatment with formic hydrazide provided NB-506 (**1018**) (Scheme 265).[760]

Using appropriate hydrazine derivatives, the dicarboxylic anhydride **1069** was recently transformed to the corresponding 6-*N*-amino analogues of NB-506, which are topoisomerase I inhibitors.[761] Starting from the same synthetic precursors, dibromo-*N*-methylmaleimide **1048c** and 7-benzyloxyindole **1058d**, the route described above was also applied to the synthesis of ED-110 (**1017**).[728,760]

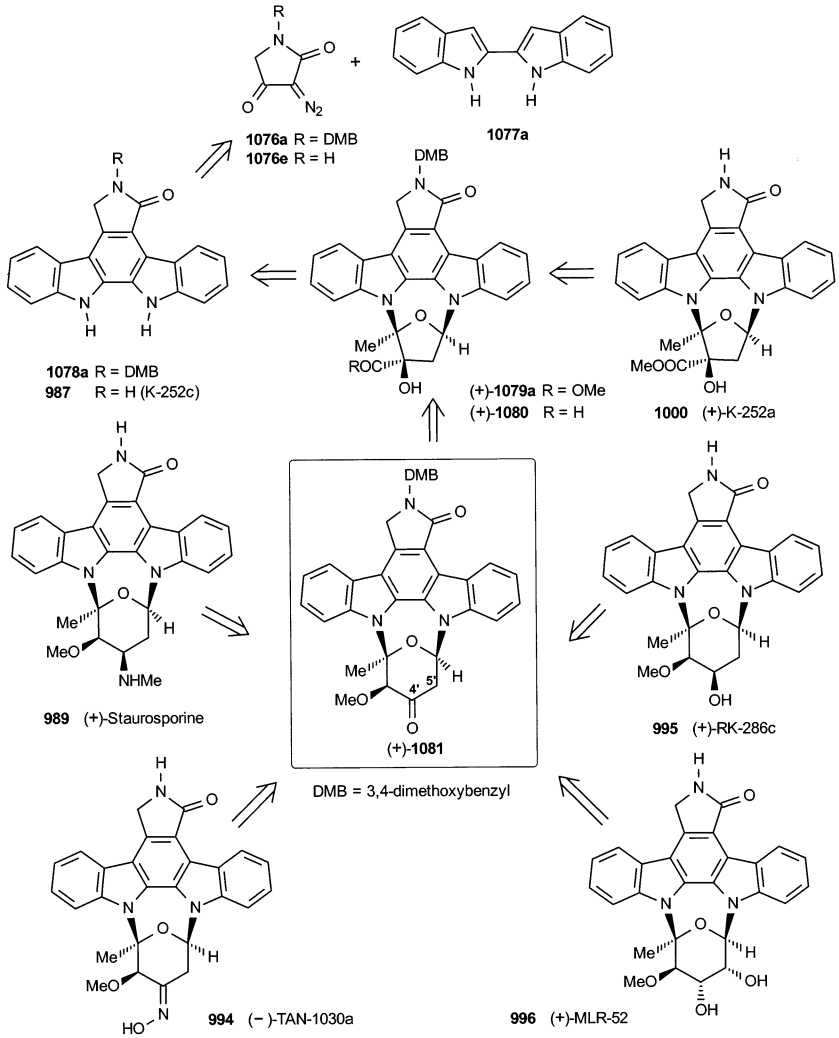
Synthesis of ED-110 and Regioisomeric Analogues. In 1999, Zembower and co-workers reported the synthesis of the three symmetrical regioisomeric ED-110 analogues **1075a**−**c** and ED-110 (**1017**), which differ in the position of the hydroxy groups. The reaction of *N*-(benzyloxymethyl)dibromomaleimide **1048d** (prepared by protection of dibromomaleimide with benzyloxymethyl chloride)[762,763] with the magnesium halide salts of the benzyloxyindoles **1058a**−**d**[764] provided the monoindolylmaleimides **1070a**−**d**. The monoindolylmaleimides **1070a**−**d** were glycosylated with 2,3,4,6-tetra-*O*-benzyl-α-D-glucose **1071** under Mitsunobu conditions[758,765] to afford the glycosyl derivatives **1072a**−**d**. Introduction of the second indole moiety by addition of the magnesium halide salts of the benzyloxyindoles **1058a**−**d** afforded the bisindolylmaleimides **1073a**−**d**. The oxidative cyclization of **1073a**−**d** with palladium(II) trifluoroacetate in acetic acid led to the indolocarbazoles **1074a**−**d**. Removal of the protecting group by hydrogenolysis with catalytic amounts of palladium on charcoal provided the ED-110 analogues **1075a**−**c** and ED-110 (**1017**) (Scheme 266).[766]

2.3. Rhodium-Catalyzed Synthesis of Indolo[2,3-a]-carbazoles

Wood and co-workers envisaged a synthetic strategy that would provide easy access to (+)-staurosporine (**989**), (−)-TAN-1030a (**994**), (+)-RK-286c (**995**), and (+)-MLR-52 (**996**) via a common intermediate. The α-methoxy ketone (+)-**1081** was considered ideal, since all common stereogenic centers of **989**, **994**, **995**, and **996** are already in place and additional stereocontrolled functionalizations at C-4′ and C-5′ are feasible (Scheme 267). Starting from the ketone (+)-**1081**, a reductive amination would produce staurosporine (**989**), formation of the oxime would lead to (−)-TAN-1030a (**994**), reduction at C-4′ from the convex face would provide (+)-RK-286c (**995**), and *β*-elimination of either a C-4′-amine (via Cope elimination) or a C-4′-hydroxyl (via Martin's sulfurane dehydration or Burgess dehydration) followed by dihydroxylation would provide (+)-MLR-52 (**996**).

The α-methoxy ketone (+)-**1081** might be accessible from the aldehyde (+)-**1080** via a Demjanov−Tiffeneau-like ring expansion. The aldehyde (+)-**1080** should be readily available by reduction of (+)-**1079a**, a precursor of (+)-K-252a (**1000**). For the synthesis of (+)-K-252a (**1000**) a single-step cycloglycosidation of the selectively protected aglycon **1078a** with an appropriate furanose was projected as the most

Scheme 267

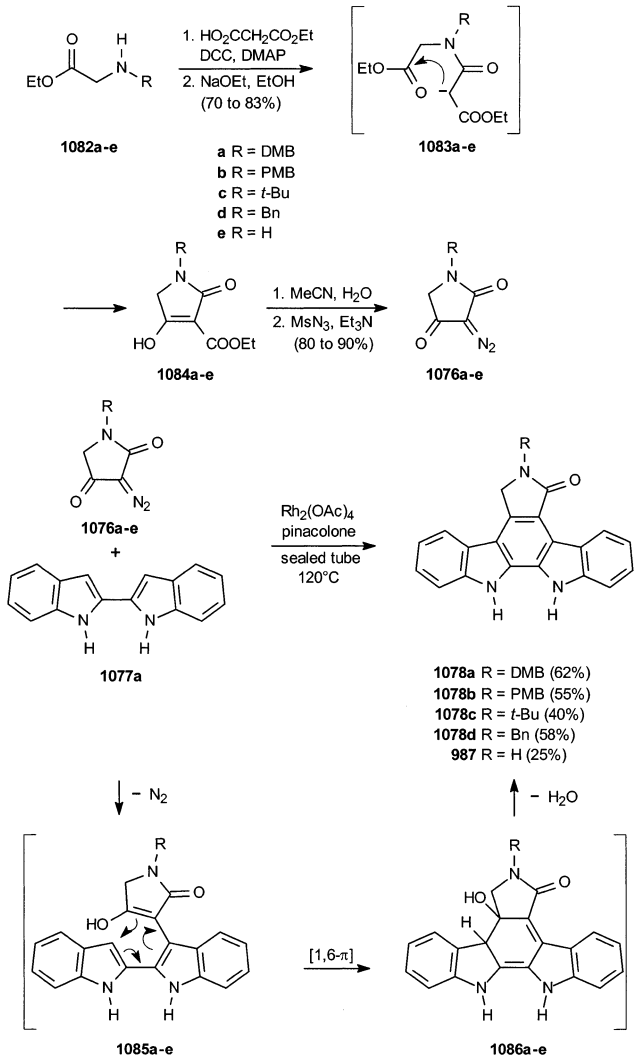


efficient approach. The protected aglycon **1078a** should be available by a rhodium-catalyzed coupling of 2,2′-bisindole **1077a** with the α-diazo-*β*-keto-*γ*-lactam **1076b** (Scheme 267).

The 2,2′-bisindole **1077a**, required for the synthesis of staurosporinone (K-252c) **987** and the protected aglycons **1078a**−**d**, was prepared by a double Madelung cyclization as reported by Bergman.[767] For the synthesis of the diazolactams **1076a**−**e**[768] the *N*-substituted glycine esters **1082a**−**e**[769,770] were transformed to the lactams **1084a**−**e** by DCC/DMAP-promoted coupling with ethyl hydrogen malonate, followed by Dieckmann cyclization. The lactams **1084a**−**e** were heated in wet acetonitrile and then treated with mesyl azide (MsN_3) and triethylamine. This decarboethoxylation and diazo-transfer reaction provided the diazolactams **1076a**−**e** in a one-pot process. Coupling of the diazolactams **1076a**−**e** with 2,2′-bisindole **1077a** in the presence of catalytic amounts of $Rh_2(OAc)_4$ and degassed pinacolone provided directly staurosporinone (K-252c) (**987**) (25% yield) and the protected aglycons **1078a**−**d** (40−62% yield). This annulation is believed to proceed via the intermediates **1085a**−**e** and **1086a**−**e**. The degassed pinacolone is both, a good solvent for the 2,2′-bisindole substrate and compatible with the carbenoid chemistry (Scheme 268).

For the asymmetric synthesis of the furanose (−)-**1090a**,**b**, a novel tandem [3,3]/[1,2]-rearrangement protocol was developed to combine (*R*)-(−)-1-nonen-3-ol [(*R*)-(−)-**1087**] with methyl 2-diazo-3-oxobutyrate **1088**.[771] The reaction of (*R*)-(−)-**1087** and **1088** in the presence of catalytic $Rh_2(OAc)_4$ followed by addition of boron trifluoride etherate afforded (*R*)-(+)-**1089** in 77% yield. Ozonolysis of (*R*)-(+)-**1089** and subsequent acid-mediated cyclization provided a mixture of (−)-**1090a**,**b** and (+)-**1091** in 80% yield. McCombie cycloglycosidation[772] of the 3,4-dimethoxybenzyl (DMB)-protected aglycon **1078a** with (−)-**1090a**,**b**/(+)-**1091** in 1,2-dichloroethane using camphorsulfonic acid as catalyst afforded in 80% yield a 2:1 regioisomeric mixture of the furanosylated indolocarbazoles (+)-**1079a** and (+)-**1092a**. This reaction led selectively to a stereochemistry with the C-3′ hydroxyl group oriented syn to the indolocarbazole moiety. Moreover, the major regioisomer corresponded to the *N*-protected K-252a (+)-**1079a**. Removal of the 3,4-dimethoxybenzyl group using trifluoroacetic acid and thioanisole as cation scavenger[773,774] provided (+)-K-252a (**1000**) in 83% yield (Scheme 269).[775,776] This synthesis afforded (+)-K-252a (**1000**) in seven steps and 31% overall yield based on the ethyl glycinate **1082a**. The same route was applied to the syntheses of racemic K-252a and nonnatural (−)-K-252a from the DMB-

Scheme 268

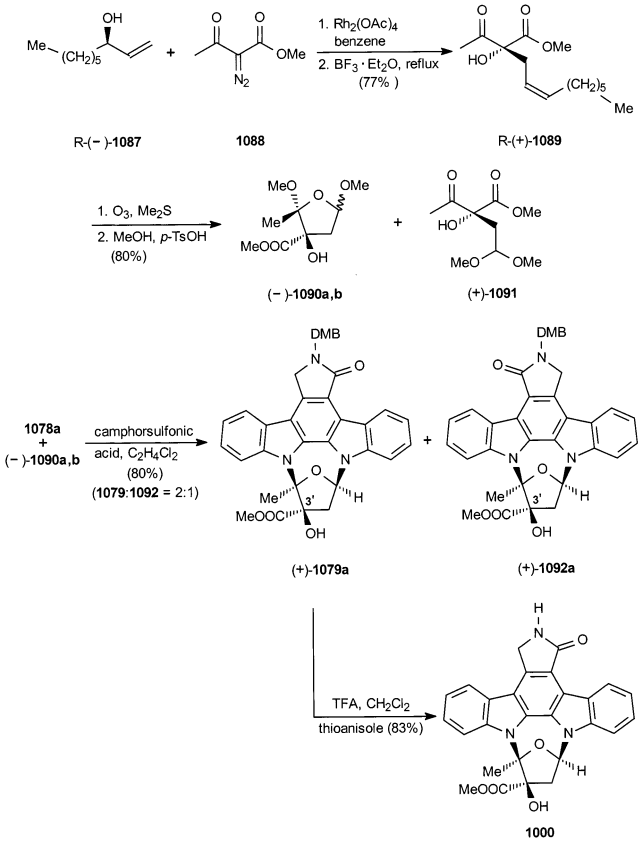


protected aglycon **1078a** and the carbohydrates (±)-**1090a**,**b**/(±)-**1091** and (+)-**1090a**,**b**/(−)-**1091** as precursors.[775,776]

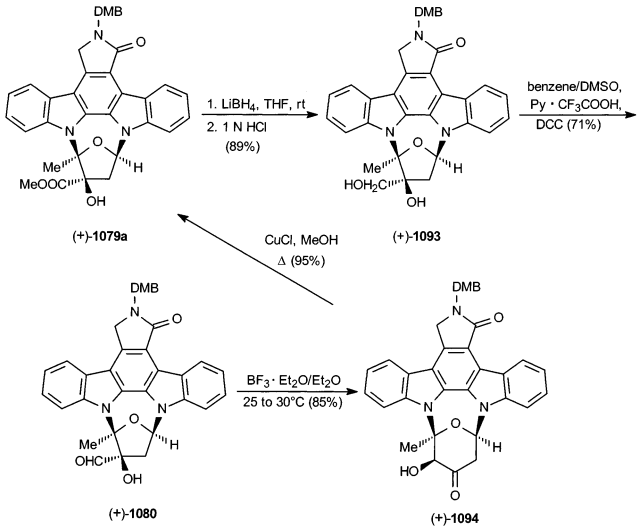
To get access to the entire family of glycosylated indolocarbazoles, (+)-staurosporine (**989**), (−)-TAN-1030a (**994**), (+)-RK-286c (**995**), and (+)-MLR-52 (**996**), from a common synthetic precursor, the *N*-protected K-252a (+)-**1079a** was subjected to a regio- and stereoselective ring expansion.[777−779] Compound (+)-**1079a** was subjected to a lithium borohydride reduction followed by Moffatt−Pfitzner oxidation to give the aldehyde (+)-**1080**. On treatment with boron trifluoride etherate, the aldehyde (+)-**1080** underwent a rearrangement with ring expansion to the α-hydroxy ketone (+)-**1094** (Scheme 270).[780]

Reduction of the α-hydroxy ketone (+)-**1094** using sodium borohydride afforded the diol (+)-**1095**. The selective alkylation at the C-3′ hydroxy group with sodium hydride and iodomethane provided the alcohol (+)-**1096** in 80% yield. This selectivity was ascribed to the steric environment of the equatorial (C-3′) and the axial (C-4′) hydroxy groups. Removal of the DMB protecting group by treatment of (+)-**1096** with trifluoroacetic acid in anisole afforded (+)-RK-286c (**995**) in 75% yield (Scheme 271).[780]

Scheme 269



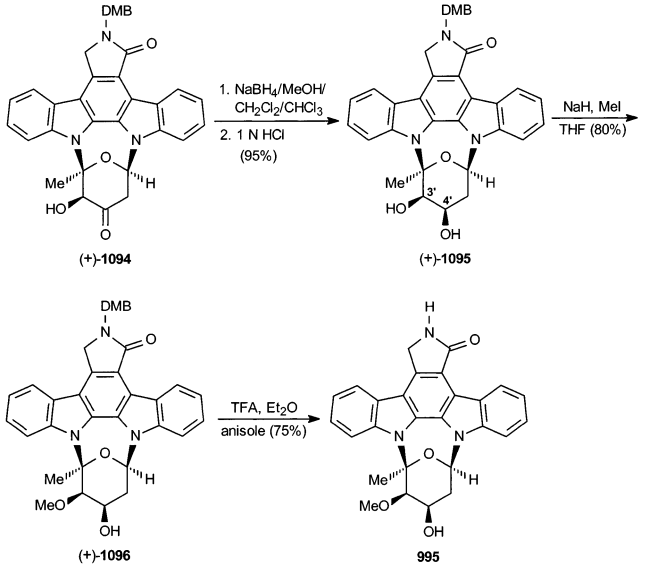
Scheme 270



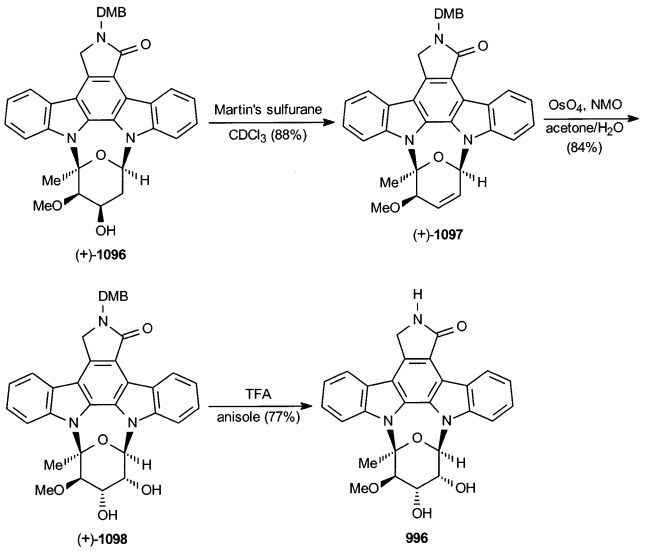
Dehydration of the alcohol (+)-**1096** with Martin's sulfurane led to the olefin (+)-**1097**, which was stereoselectively dihydroxylated using osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide (NMO) to give the dihydroxy derivative (+)-**1098**. Deprotection provided (+)-MLR-52 (**996**) in 77% yield (Scheme 272).[780]

Treatment of the α-hydroxy ketone (+)-**1094** with hydroxylamine hydrochloride gave the oxime (−)-**1099** in 95% yield. A bis-methylation of (−)-**1099** under phase-transfer conditions afforded the corresponding dimethyl derivative (−)-**1100**. Stereoselective hydrogenation of (−)-**1100** using H_2/PtO_2 led to

Scheme 271



Scheme 272



the amine (+)-**1101**. Monomethylation of the amine (+)-**1101** to compound (+)-**1102** followed by deprotection provided (+)-staurosporine (**989**) (Scheme 273).[780]

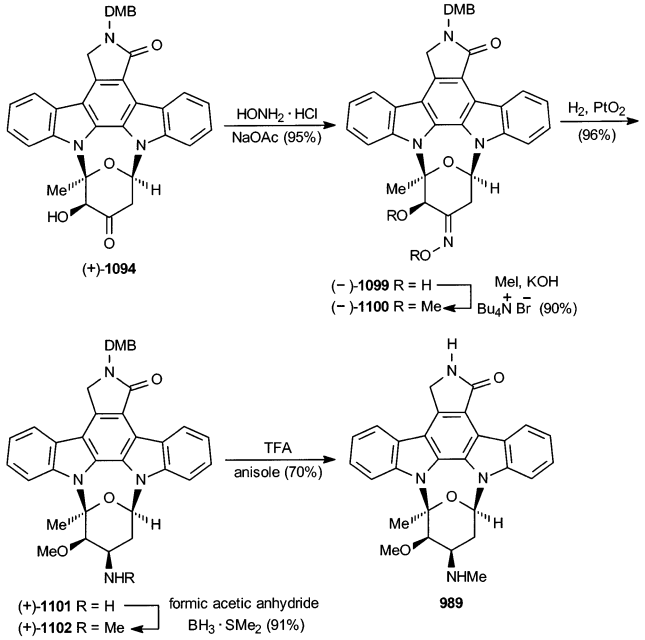
The reaction of the α-hydroxy ketone (+)-**1094** with *O*-benzylhydroxylamine hydrochloride afforded the benzyl-protected oxime (−)-**1103**. *O*-Methylation under phase-transfer conditions led to the *O*-methyl derivative (−)-**1104**. Removal of the DMB protecting group to the lactam (−)-**1105** followed by treatment with iodotrimethylsilane afforded (−)-TAN-1030a (**994**) (Scheme 274).[780]

More recently, Wood et al. applied the rhodium carbenoid approach to the synthesis of C7-methyl derivatives of K-252a,[781a] C2′-alkyl derivatives of (±)-K-252a,[781b] and (−)-(7*S*)- and (+)-(7*R*)-K-252a dimers.[781c]

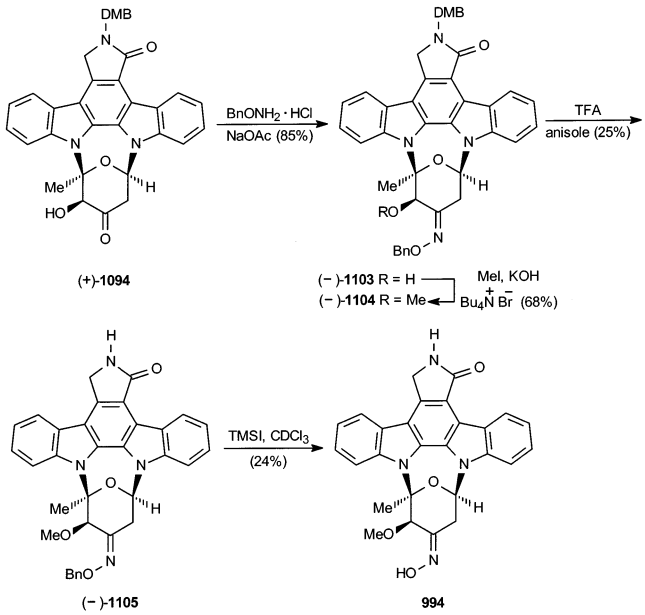
2.4. Photoinduced Cyclization of 1,2-Bis(Indol-3-yl)-cis-alkenes

Synthesis of the Staurosporine Aglycon (Staurosporinone or K-252c). Winterfeldt and Sarstedt

Scheme 273

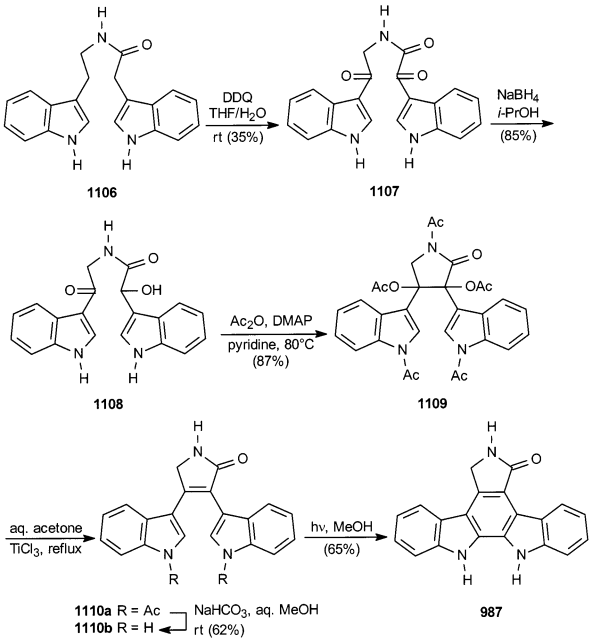


Scheme 274



described the first synthesis of the staurosporine aglycon **987** starting from tryptamine and 3-indolylacetyl chloride by sequential base- and photoinduced cyclizations. This synthesis features an electrocyclization as a biosynthetic model reaction. Acylation of tryptamine by 3-indolylacetyl chloride provided the amide **1106** (77% yield), which was oxidized with DDQ containing small amounts of water in tetrahydrofuran.[782] The diketone **1107** was selectively reduced to the hydroxy ketone **1108** and then cyclized to the pentaacetyl derivative **1109** with acetic anhydride in the presence of base. Reduction of **1109** with $TiCl_3$ in aqueous acetone[783,784] led to the bisindolyl lactam **1110a**. Deacetylation of **1110a** with sodium bicarbonate in aqueous methanol afforded compound **1110b**. The cyclization of **1110b** by irradiation in methanol provided the staurosporine aglycon **987** in

Scheme 275

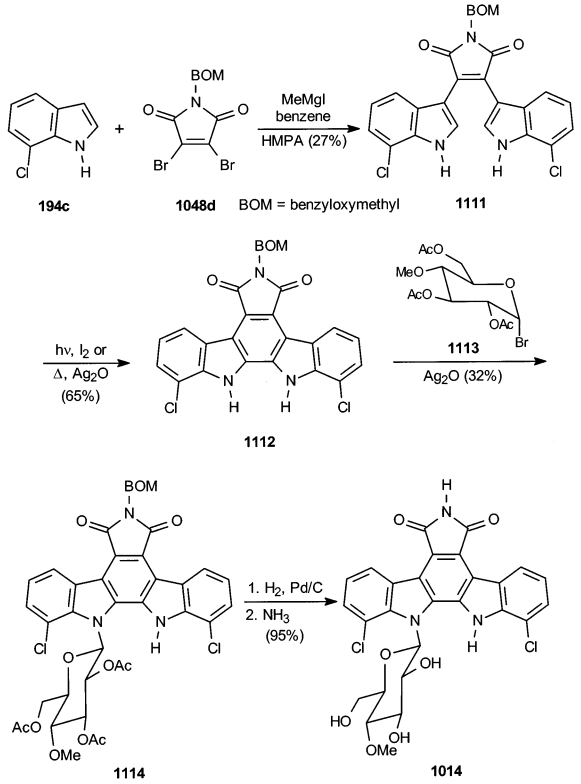


65% yield (Scheme 275).[785] Using *N*-substituted 3-indolylacetic acid as starting material, this method was applied to the regioselective synthesis of monosubstituted staurosporine precursors.[786] Recently, Trost et al. prepared monosubstituted isomerically pure staurosporine precursors by palladium-catalyzed asymmetric allylic alkylation.[787]

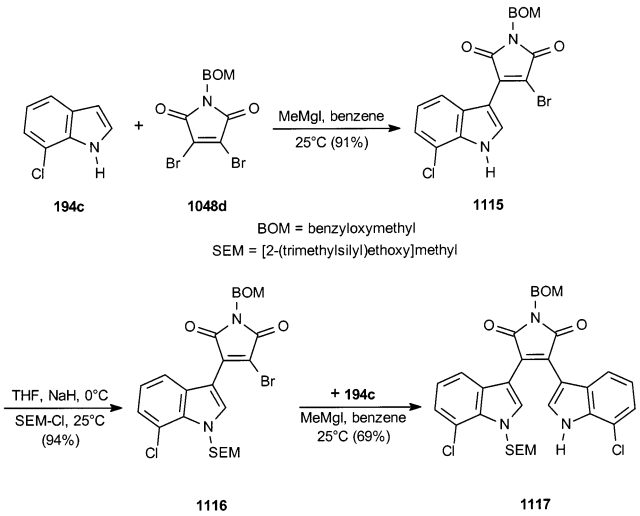
It is interesting to note that 3 years after the first synthesis of the staurosporine aglycon **987** by Winterfeldt and Sarstedt in 1983,[785] Nakanishi et al. isolated this compound from *Nocardiopsis* strain K-290 and named it staurosporinone or K-252c.[624,697]

Total Synthesis of Rebeccamycin. Kaneko et al. reported a total synthesis of rebeccamycin (**1014**) from 7-chloroindole **194c** and *N*-(benzyloxymethyl)-dibromomaleimide **1048d** by photolytic electrocyclization of the imide **1111** and subsequent glycosidation. Using the indole-Grignard route, 7-chloroindole **194c**[748] was coupled with *N*-(benzyloxymethyl)dibromomaleimide **1048d** to the bis(indolyl)maleimide **1111** in benzene containing hexamethylphosphoramide (HMPA). The subsequent photocyclization afforded the indolocarbazole **1112** in 65% yield. Alternatively, the indolocarbazole **1112** could be obtained by a two-step process (21% yield) from the readily available 7,7′-dichloroindigo.[788] Wolff−Kishner reduction of 7,7′-dichloroindigo followed by acetylation led to a monoacetylbisindole,[789] which on heating with *N*-benzyloxymethylmaleimide provided the indolocarbazole **1112**. Glycosidation of **1112** with 1-bromo-2,3,6-tri-*O*-acetyl-4-*O*-methylglucose **1113**[790] in refluxing benzene afforded the *N*-glycoside **1114**. A more convenient method is the one-pot cyclization and glycosidation by heating in benzene under reflux in the presence of silver oxide. It is presumed that the triene **1111** is thermally cyclized and silver oxide acts as an oxidizing agent. Removal of the benzyloxymethyl group by hydrogenation and of the acetyl groups by ammonolysis provided rebeccamycin (**1014**) in 95% yield (Scheme 276).[791]

Scheme 276



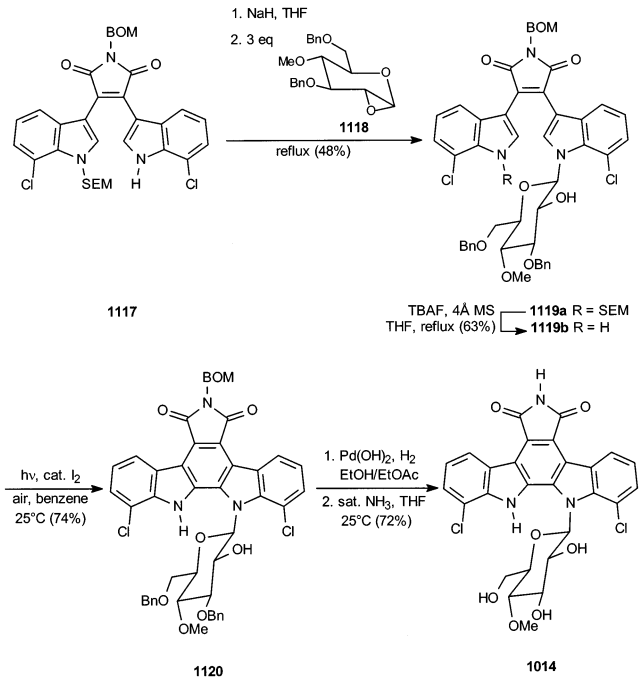
Scheme 277



Using the method of Kaneko et al.,[791] Danishefsky and co-workers described in 1993 the synthesis of the secoaglycon **1117** as a precursor of rebeccamycin (**1014**). Deprotonation of 7-chloroindole **194c**[748] with methylmagnesium iodide and addition to *N*-(benzyloxymethyl)dibromomaleimide **1048d** afforded the monoindolyl derivative **1115** in 91% yield.[791] Protection of the indole nitrogen by the SEM group[422] to **1116** and addition of the 7-chloroindole Grignard compound provided the secoaglycon **1117** (Scheme 277).

The glycosidation of the secoaglycon **1117** was achieved by reaction of the sodium salt of **1117** with the α-1,2-anhydrosugar **1118** to give the β-glucopyranoside **1119a** in 48% yield. After the removal of the SEM protecting group with tetrabutylammonium

Scheme 278



fluoride (TBAF), the photocyclization of compound **1119b** afforded the indolocarbazole glucopyranoside **1120**. Hydrogenation of **1120** over Pearlman's catalyst [$Pd(OH)_2$] followed by ammonolysis to complete the cleavage of the benzyloxymethyl protecting groups provided rebeccamycin (**1014**) in 72% yield (Scheme 278).[747]

Recently, Routier and his group applied the photoinduced oxidative cyclization to the synthesis of 1-aza- and 1,11-diazaindolo[2,3-*a*]carbazole derivatives.[792]

Total Synthesis of (+)-Staurosporine. In 1995, Danishefsky et al. described the synthesis of the staurosporine secoaglycon **1121**. Using sequential indole-Grignard additions to *N*-(benzyloxymethyl)-dibromomaleimide, the unsymmetrical secoaglycon **1121** was obtained in three steps and 57% overall yield (cf. the synthesis of the secoaglycon **1117** in Scheme 277).[747] The glycosylation was achieved by reaction of the sodium salt of **1121** with the 1,2-anhydrosugar **1122**.[793−795] The C2′-hydroxyl function was removed from the indole glycoside **1123** by the Barton deoxygenation to give compound **1124**.[796] Deprotection by removal of the C6′-PMB and the indole-SEM group followed by photocyclization of **1125** provided the hexacyclic imide **1126a**.[797] The alcohol was transformed into the iodo derivative **1126b**, and subsequent elimination of hydrogen iodide with 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) afforded the *exo*-glycal **1127** (Scheme 279).

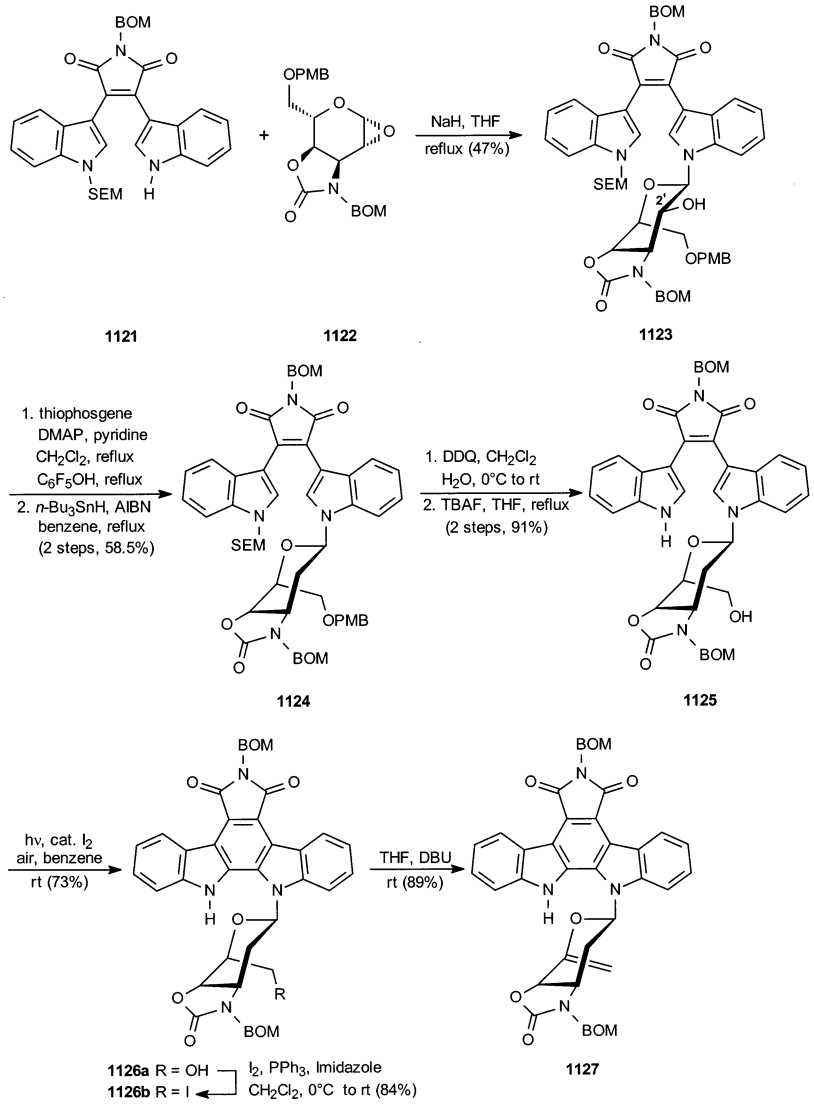
The intramolecular glycosylation of **1127** with potassium *tert*-butoxide in the presence of iodine provided the glycoside **1128**. Deiodination of **1128** with tri-*n*-butyltin hydride, removal of the BOM groups, selective Boc protection of the oxazolidinone nitrogen, and BOM reprotection of the maleimide nitrogen afforded compound **1129**. The Boc group at the oxazolidinone ring plays a crucial role in the smooth disconnection of the oxazolidinone.[798,799] Treatment of **1129** with cesium carbonate in methanol provided by cleavage of the oxazolidinone the hydroxy amine **1130**. *O*-Methylation and single *N*-methylation, cleavage of the BOM group by hydrogenation over Pearlman's catalyst, and removal of the Boc group led to 7-oxostaurosporine (**1131**) in 70% overall yield. Reduction of the imide with sodium borohydride to the hydroxy lactam[800] and further reduction with phenylselenol in the presence of a catalytic amount of *p*-toluenesulfonic acid provided a 1:1 mixture of (+)-staurosporine (**989**) and isostaurosporine (**1132**) (Scheme 280).[795]

Syntheses of Staurosporinone (K-252c). In 1994, Xie and Lown reported a facile synthesis of staurosporinone (**987**) starting from the bisindolyl derivative **1134**. The key step of this synthesis is a photochemically induced oxidative cyclization of **1134**. A new coupling protocol was developed for an improved synthesis of *N*-benzyldibromomaleimide **1048b**. Reaction of dibromomaleic acid with benzylamine in the presence of 1,3-dicyclohexylcarbodiimide and a trace of 4-(dimethylamino)pyridine afforded **1048b** in 92% yield. Using the Grignard route, compound **1048b** was transformed to the *N*-(benzyl)bisindolylmaleimide **1133**. Under basic conditions,[720] compound **1133** was converted to the bisindolyl maleic anhydride **1134**. The photolytically induced electrocyclization of **1134** in the presence of iodine as the oxidizing agent provided the indolocarbazole anhydride **1135** in 90% yield. Transformation of the anhydride **1135** to the corresponding imide by heating with ammonium acetate afforded arcyriaflavin A (**1004**). Finally, reduction of **1004** with zinc amalgam led to staurosporinone (**987**) in 58% yield (Scheme 281).[801] By this route staurosporinone (**987**) was obtained in six steps and 25% overall yield from dibromomaleic acid.

In 1998, Beccalli and co-workers described a new synthesis of staurosporinone (**987**) starting from the readily accessible ethyl 3-cyano-2-hydroxy-3-(1*H*-indol-3-yl)acrylate **1136**. The reaction of compound **1136** with ethyl chloroformate led to **1137**, which was selectively deethoxycarbonylated to compound **1138** with dimethylamine. Treatment of **1138** with trifluoromethanesulfonic anhydride in the presence of *N*,*N*-diisopropylethylamine afforded the triflate **1139**. The palladium-catalyzed coupling of the triflate **1139** with 1-phenylsulfonyl-3-tributylstannylindole **1140**[802] led to the 1,2-bis(indol-3-yl)-*cis*-alkene **1141a** in 89% yield. Deprotection of both nitrogen atoms with sodium ethoxide in ethanol to **1141b** and oxidative photocyclization afforded the 5,6-disubstituted indolo-[2,3-*a*]carbazole **1142** in 82% yield. Formation of the lactam ring by reductive cyclization of **1142** with sodium borohydride and cobalt(II) chloride[803,804] provided staurosporinone (**987**) in 92% yield (Scheme 282).[643]

Stereocontrolled Total Synthesis of (+)-K-252a. In 1999, Fukuyama and co-workers reported the total synthesis (+)-K-252a (**1000**) starting from indole-3-acetic acid **213**. Formation of the allyl ester followed by regioselective bromination led to the 2-bromoindole **1143**. The *N*-glycosidation[805] of com-

Scheme 279



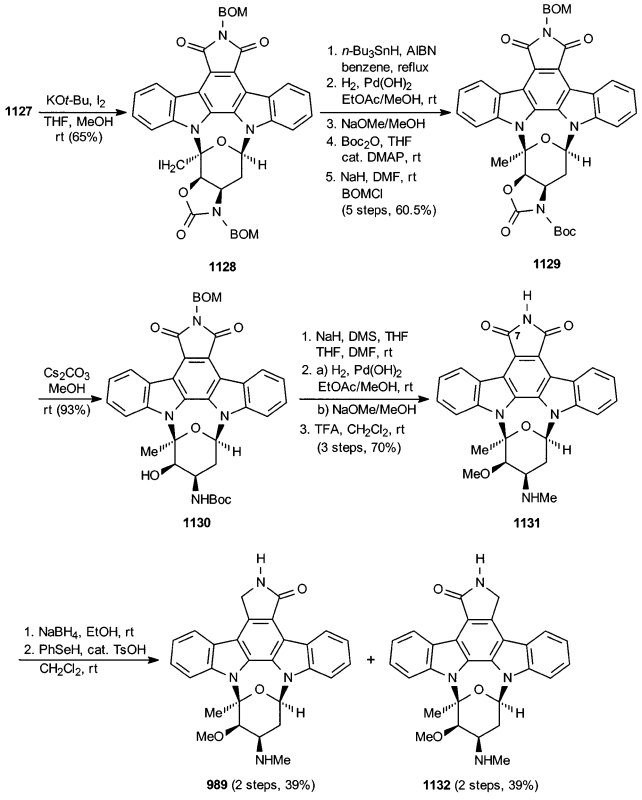
pound **1143** was carried out by deprotonation with sodium hydride and subsequent addition of the readily available 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose **1144**[806] and afforded the *β*-*N*-glycoside **1145** as the sole product. Compound **1145** was transformed to the diacetyl bisindole **1146** in four steps and 52% overall yield by cleavage of the allyl ester, reaction of the resulting acid with tryptamine to the amide, regioselective oxidation at the benzylic position to the ketone, and diacetylation of the indole and amide nitrogens. The base-catalyzed cyclization of the diacetyl bisindole **1146** with catalytic amounts of 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) and 4 Å molecular sieves (MS) afforded the lactam **1147**. A nonoxidative photocyclization of the lactam **1147** by sunlight in the presence of *N*,*N*-diisopropylethylamine to promote the dehydrobromination provided almost quantitatively the desired indolocarbazole **1148a**. Hydrolysis of all acyl groups followed by treatment with iodine, triphenylphosphine, and imidazole[807] led to a selective conversion of the primary alcohol to the corresponding iodide **1148b** (Scheme 283).

The conversion of the iodide **1148b** to the olefin **1149** was achieved by a conventional four-step sequence (Scheme 284). Treatment of **1149** with iodine, potassium iodide, and DBU provided the cycloglycoside **1150a** in 93% yield. Radical deiodination of **1150a**,[808] cleavage of the acetate **1150b**, and Moffatt−Pfitzner oxidation of the resulting alcohol **1150c** afforded the ketone **1151**. The ketone **1151** was transformed to the acetylcyanohydrin **1152** with hydrogen cyanide and pyridine, followed by acetylation. An attempted acid-promoted methanolysis of **1152** afforded mainly the ketone **1151** along with only a trace of (+)-K-252a (**1000**). Therefore, compound **1152** was transformed to the amide **1153** followed by alkaline hydrolysis to the acid and treatment with diazomethane to provide (+)-K-252a (**1000**) (Scheme 284).[809] This synthesis affords (+)-K-252a (**1000**) in 23 steps and 10% overall yield based on indole-3-acetic acid **213**.

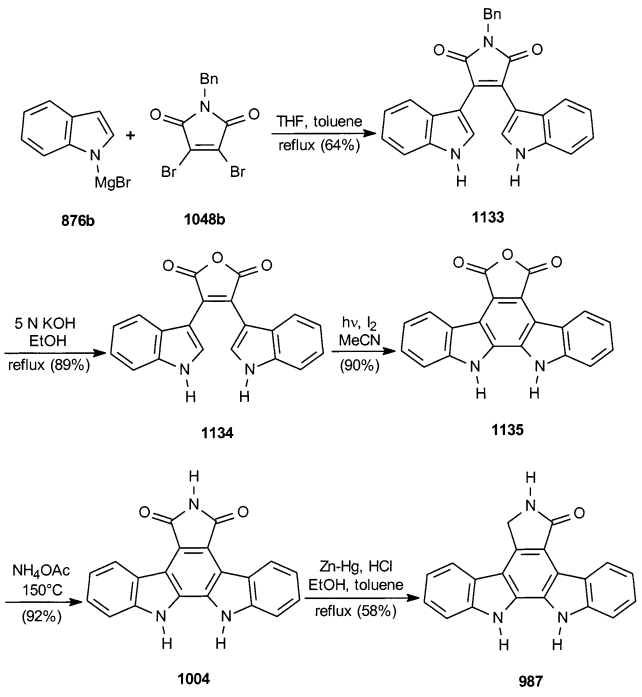
2.5. DDQ-Mediated Oxidative Cyclization

Synthesis of *N*-Benzylstaurosporinone. In 1984, Weinreb and co-workers described the synthesis of *N*-benzylstaurosporinone (**1078d**) using a variation of Steglich's methodology.[717] The reaction of *N*-benzyldibromomaleimide **1048b** with indolylmagnesium bromide **876b** led to the bisindolylmale-

Scheme 280



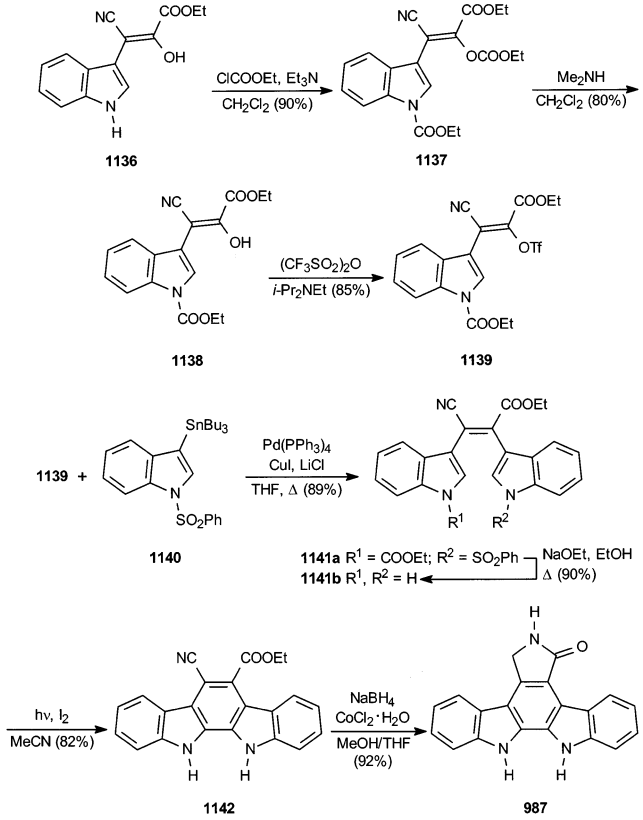
Scheme 281



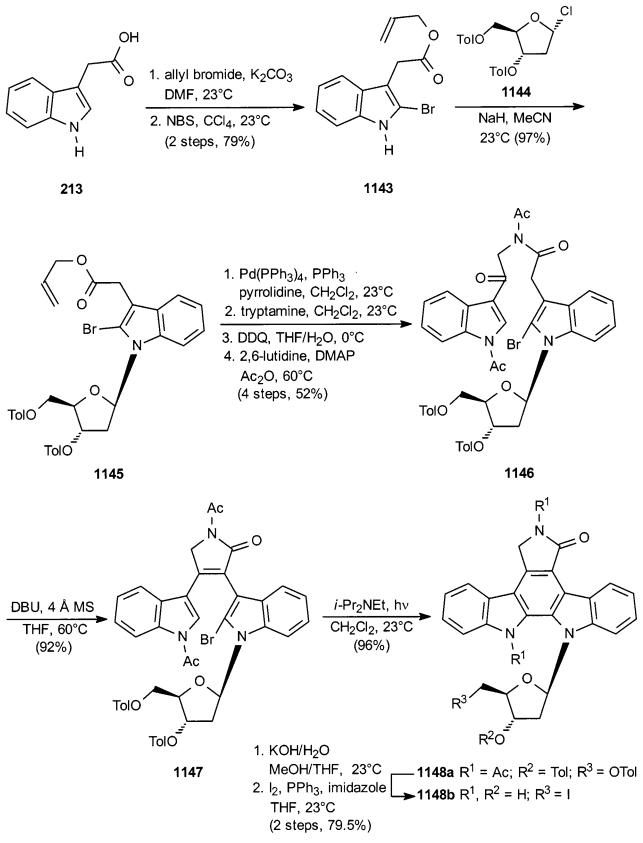
imide **1133**. Oxidative cyclization of **1133** with a mixture of *p*-toluenesulfonic acid and DDQ in benzene under reflux provided the hexacyclic imide **1049** in 87% yield. The conditions for the Clemmensen reduction used by Hughes and Raphael[810,811] afforded *N*-benzylstaurosporinone (**1078d**) (Scheme 285).[812,813] *N*-Benzylstaurosporinone (**1078d**) is a potential intermediate for a synthetic approach to staurosporine.

Bergman and co-workers achieved a synthesis of the hexacyclic imide **1049** using a different method.

Scheme 282

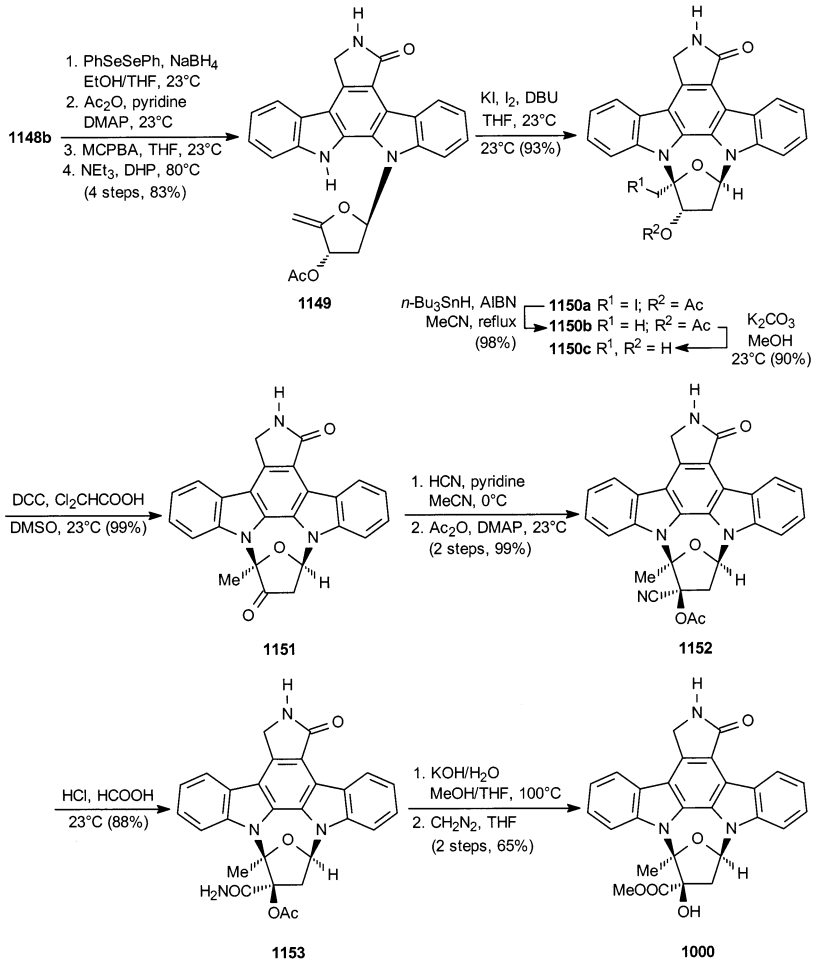


Scheme 283

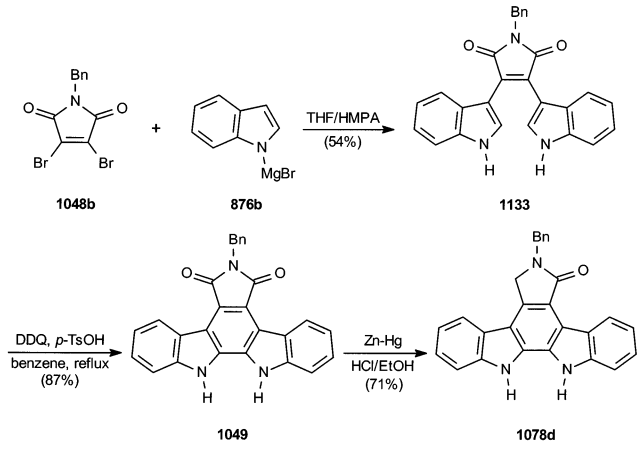


The key step of their approach is an oxidative coupling of the indole-3-acetic acid trianion **1155**[814] or the methyl indol-3-ylacetate dianion **1158**.[815] Sequential addition of 2 equiv of butyllithium and 1

Scheme 284



Scheme 285



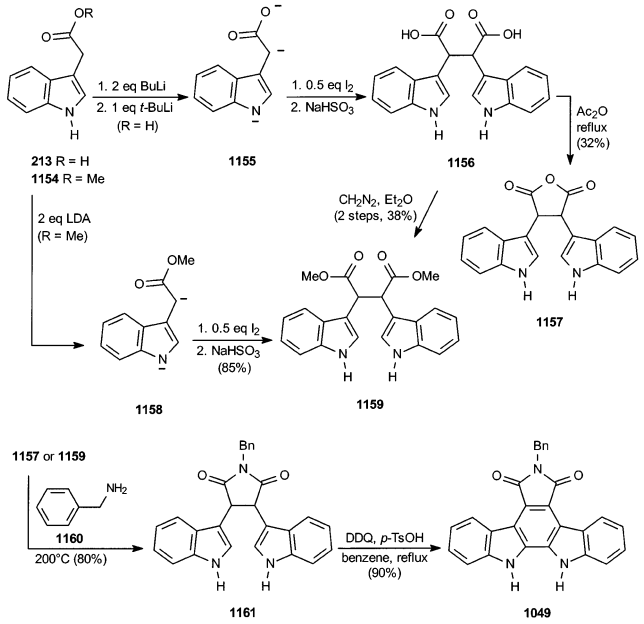
equiv of *tert*-butyllithium to indole-3-acetic acid **213** generated the trianion **1155**. Oxidative coupling of **1155** with iodine followed by acidic workup afforded 2,3-diindol-3-ylsuccinic acid **1156**. Treatment of the diacid **1156** with either diazomethane or acetic anhydride provided a diastereomeric mixture of the diester **1159** (38% yield) or the diastereomerically pure anhydride **1157**, respectively. However, the diester **1159** could be prepared in a much better overall yield (85%) by the iodine-promoted oxidative coupling of the dianion **1158**, obtained by addition of 2 equiv of lithium diisopropylamide (LDA) to methyl indol-3-ylacetate **1154**. Heating of the diester **1159** or the anhydride **1157** with benzylamine **1160** afforded the bisindolylsuccinimide **1161** in 80% yield. Oxidation of **1161** with 2 equiv of DDQ[812,813] in the presence of catalytic amounts of *p*-toluenesulfonic acid in benzene under reflux provided the hexacyclic imide **1049** in 90% yield (Scheme 286).[816]

In the following years, Schächtele and co-workers applied this approach to the synthesis of a wide range of novel lactam and imide indolocarbazoles.[699,700] The required bisindolylmaleimides were prepared from the appropriately substituted indoles and 1-methylindole-3-acetic acids.[628,817]

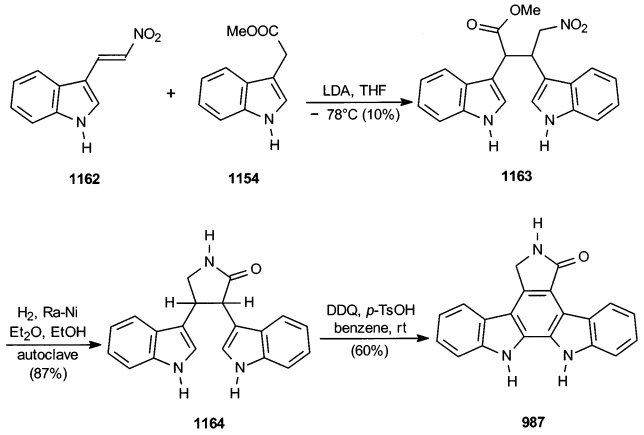
Synthesis of Staurosporinone (K-252c). In 1999, Mahboobi et al. described a novel synthesis of staurosporinone (**987**). The intermolecular Michael addition of 1-(indol-3-yl)-2-nitroethene **1162** to methyl indol-3-ylacetate **1154** provided with high diastereoselectivity methyl 2,3-bis(indol-3-yl)-4-nitrobutanoate **1163**. Catalytic hydrogenation and lactamization afforded 2,3-bis(indol-3-yl)-γ-butyrolactam **1164** in 87% yield. Oxidative cyclization of the *cis*-lactam **1164** with DDQ in the presence of catalytic amounts of *p*-toluenesulfonic acid led to staurosporinone (**987**) (Scheme 287).[818]

Recently, Faul and Sullivan introduced phenyliodine(III) bis(trifluoroacetate) (PIFA) as oxidant for the conversion of 2,3-bis(indol-3-yl)maleimides to indolo[2,3-*a*]carbazoles.[819]

Scheme 286



Scheme 287

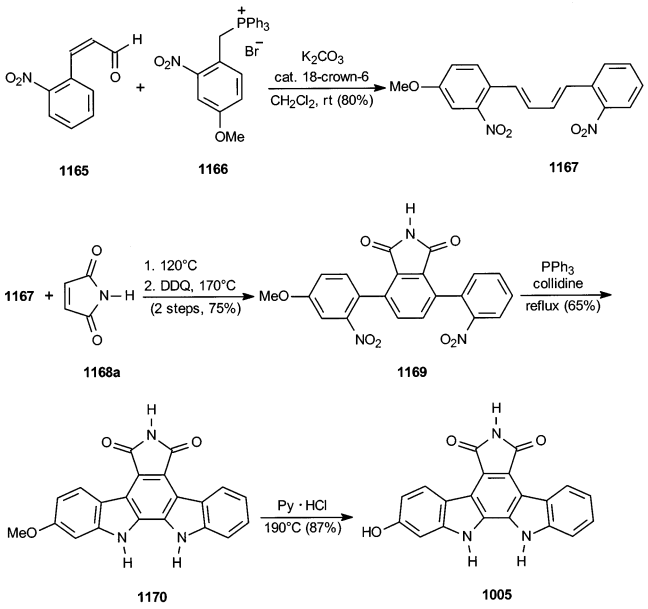


2.6. Diels–Alder Reactions of 1,4-Bis(o-nitrophenyl)-butadienes and Maleimides

Total Synthesis of Arcyriaflavin B and Staurosporinone (K-252c). In 1983, Raphael and coworkers reported an elegant synthesis of arcyriaflavin B (**1005**). Condensation of 2-nitrocinnamaldehyde **1165** and the Wittig reagent obtained from phosphonium bromide **1166** afforded the 1,4-diarylbutadiene **1167**. The Diels−Alder cycloaddition of **1167** by heating with neat maleimide **1168a** and subsequent dehydrogenation with DDQ gave the terphenyl imide **1169**. The double nitrene insertion of **1169** using Cadogan's method[274,659] led to *O*-methylarcyriaflavin B (**1170**). Ether cleavage by heating in molten pyridine hydrochloride[820] provided arcyriaflavin B (**1005**) (Scheme 288).[810,811]

Due to difficulties with *N*-maleimide protecting groups and reduction of the imide to the lactam, Raphael et al. modified their method in 1990 for the synthesis of staurosporinone (**987**). The key steps are a Diels−Alder cycloaddition of dimethyl acetylenedicarboxylate with 1,4-bis(*o*-nitrophenyl)butadiene **1171**, conversion to the anhydride and then to the imide with ammonia, reduction to the lactam, and

Scheme 288



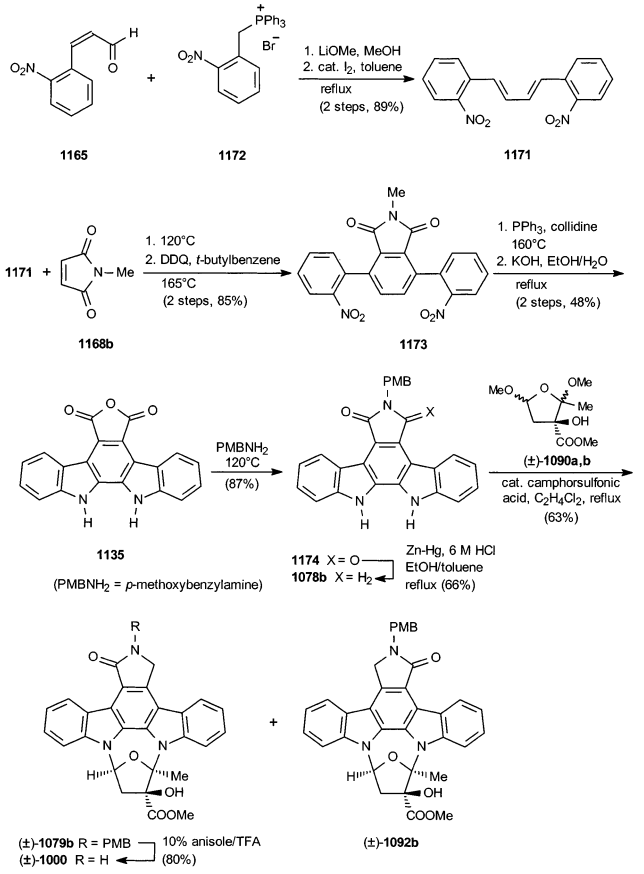
the final transformation to staurosporinone (**987**) by application of the double nitrene insertion.[811]

Total Synthesis of (±)-K-252a. In 1995, Lowinger and co-workers applied the method of Raphael[811] to the total synthesis of (±)-K-252a (**1000**) using the anhydride **1135** as a key intermediate. The condensation of 2-nitrocinnamaldehyde **1165** with the Wittig reagent obtained from the phosphonium bromide **1172** afforded 1,4-bis(*o*-nitrophenyl)butadiene **1171**. Diels−Alder cycloaddition of the butadiene **1171** with neat *N*-methylmaleimide **1168b** followed by subsequent dehydrogenation with DDQ led to the terphenyl **1173**. Double nitrene insertion of **1173** by refluxing with triphenylphosphine in collidine provided after basic hydrolysis the anhydride **1135**. Aminolysis with *p*-methoxybenzylamine ($PMBNH_2$) followed by reduction of the resulting imide **1174** to the lactam afforded the PMB-protected aglycon **1078b**. The camphorsulfonic acid-catalyzed double glycosidation[812] of the aglycon **1078b** with the furanose (±)-**1090a**,**b**[821] in refluxing dichloromethane[772] gave a 2:1 mixture of the regioisomeric bis-glycosides (±)-**1079b** and (±)-**1092b** in 63% yield. Removal of the PMB group from compound (±)-**1079b** using trifluoroacetic acid in the presence of anisole provided (±)-K-252a (**1000**) in 80% yield (Scheme 289).[821]

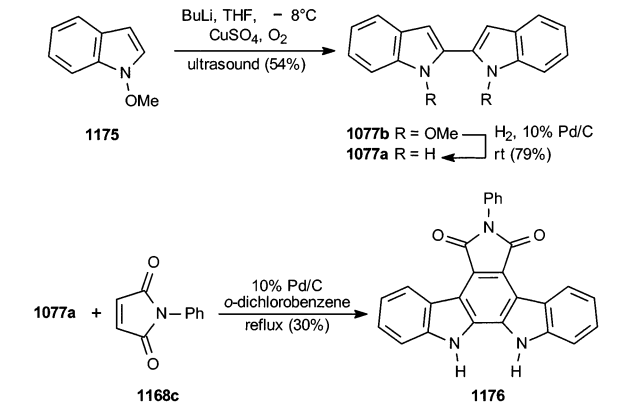
2.7. Diels–Alder Reactions of 2,2′-Bisindoles

Synthesis of 6-Phenylarcyriaflavin A. In 1992, Somei and Kodama described the synthesis of 6-phenylarcyriaflavin A (**1176**) using a Diels−Alder reaction of 2,2′-bisindole **1077a**[789a,822] and *N*-phenylmaleimide **1168c** as the key-step. Deprotonation of 1-methoxyindole **1175** with butyllithium to 2-lithio-1-methoxyindole[823,824] followed by a novel oxidative coupling with anhydrous copper(II) sulfate and ultrasound under oxygen atmosphere afforded 2,2′-bis-(1-methoxyindole) **1077b** in 54% yield. Catalytic hydrogenation of **1077b** provided 2,2′-bisindole **1077a**. The Diels−Alder cycloaddition of 2,2′-bisindole **1077a** with *N*-phenylmaleimide **1168c** in the presence of

Scheme 289



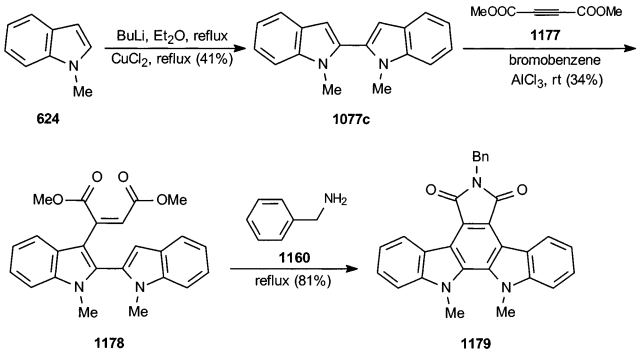
Scheme 290



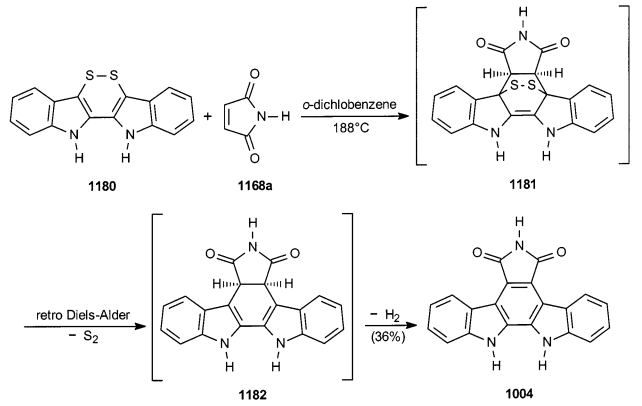
catalytic amounts of 10% palladium on activated carbon in *o*-dichlorobenzene at reflux afforded 6-phenylarcyriaflavin A (**1176**) in 30% yield (Scheme 290).[650]

Wallace and co-workers reported in 1995 an improved synthesis of 6-phenylarcyriaflavin A (**1176**) using the same synthetic precursors but replacing *o*-dichlorobenzene as solvent with diethyl oxalate.[634] They also applied this method to the synthesis of the AT2433-B aglycon by a Diels−Alder reaction of 2,2′-bisindole **1077a** with *N*-methylmaleimide.[634] In 1997, Hudkins and Diebold described the application of 2,2′-bisindole **1077a**[825] to the synthesis of a lactam regioisomer of staurosporinone by an acid-catalyzed tandem Michael condensation reaction.[826] In this synthesis compound **1077a** was treated with either maleimide or ethyl *cis*-*β*-cyanoacrylate in the presence of trifluoroacetic acid or ethylaluminum dichloride, respectively.

Scheme 291



Scheme 292



Synthesis of 6-Benzyl-12,13-dimethylarcyriaflavin A. Pindur and co-workers reported the synthesis of 6-benzyl-12,13-dimethylarcyriaflavin A (**1179**). The reaction of 2,2′-bis(1-methylindole) **1077c**[827] with dimethyl acetylenedicarboxylate **1177** in the presence of aluminum trichloride in bromobenzene afforded the 2,2′-bisindol-3-yl-substituted dimethyl maleate **1178**.[828,829] Cyclization with benzylamine **1160** led directly to 6-benzyl-12,13-dimethylarcyriaflavin A (**1179**) in 81% yield (Scheme 291).[830]

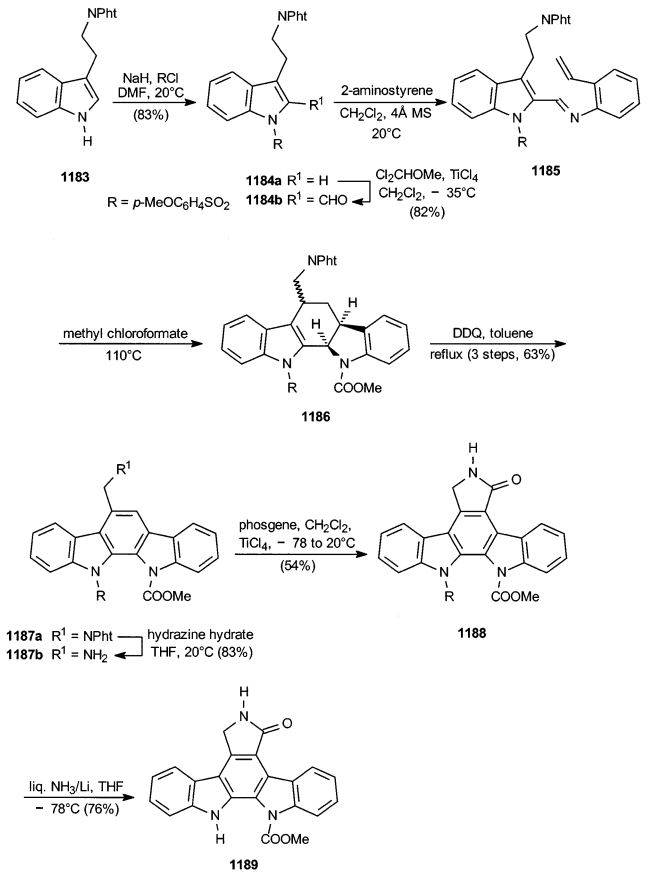
The same group described further applications of 2,2′-bis-(1-methylindole) **1077c** in Diels−Alder reactions with various dienophiles for the synthesis of substructures of the staurosporine family.[831,641,642]

2.8. Total Synthesis of Arcyriaflavin A by Diels–Alder Reaction of 2,2′-Bisindolyl-3,3′-dithiete

Lobo et al. described the synthesis of arcyriaflavin A (**1004**) starting from 2,2′-bisindolyl-3,3′-dithiete **1180**. Heating of 2,2′-bisindolyl-3,3′-dithiete **1180** with maleimide **1168a** in *o*-dichlorobenzene at 188 °C afforded in 36% yield directly arcyriaflavin A (**1004**) (Scheme 292).[832] This reaction is believed to proceed via a Diels−Alder reaction to the cycloadduct **1181**, followed by a retro-Diels−Alder reaction with extrusion of singlet-S_2 to 4c,7a-dihydroarcyriaflavin A (**1182**) and dehydrogenation by dissolved oxygen or extruded sulfur to arcyriaflavin A (**1004**).

The same group developed a synthesis of arcyriaflavin A (**1004**) by a 2-fold sulfur extrusion reaction.[833,834]

Scheme 293



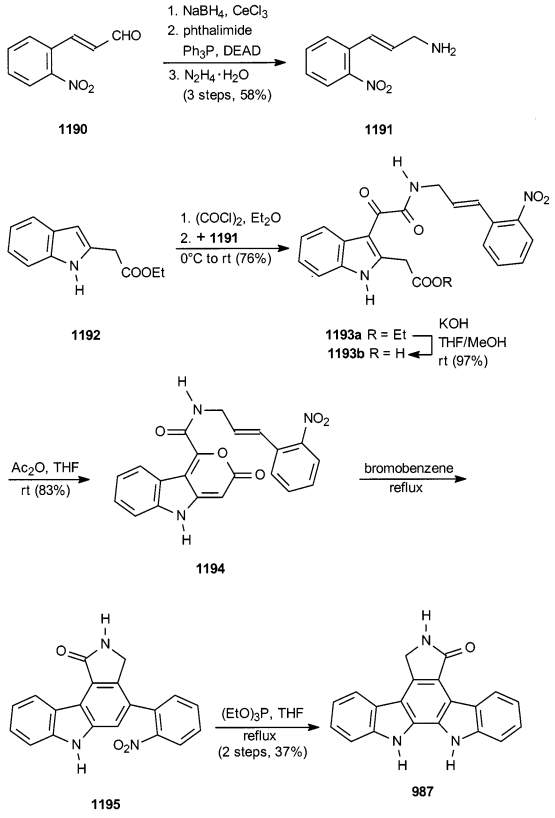
2.9. Synthesis of 13-Methoxycarbonylstaurosporinone

Magnus and co-workers described the synthesis of 13-methoxycarbonylstaurosporinone (**1189**). Tryptamine was converted to the phthalimido derivative **1183** using a standard procedure.[835] Protection of the indole as the 1-(*p*-methoxyphenylsulfonyl) derivative **1184a** followed by formylation with α,α-dichloromethyl methyl ether and titanium tetrachloride afforded the 2-formyl derivative **1184b**. Condensation of **1184b** with 2-aminostyrene to the imine **1185** and subsequent treatment with methyl chloroformate provided a 4:1 diastereoisomeric mixture of the pentacyclic carbamate **1186** via an intramolecular Diels−Alder cycloaddition of the intermediate indole-2,3-quinodimethane. Dehydrogenation of **1186** with DDQ to the indolo[2,3-*a*]carbazole **1187a**, selective cleavage of the phthalimido protecting group using hydrazine hydrate to the amine **1187b**, and addition of phosgene in dichloromethane followed by titanium tetrachloride-promoted intramolecular acylation afforded the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole **1188**. A selective removal of the *p*-methoxyphenylsulfonyl group under Birch reduction conditions led to 13-methoxycarbonylstaurosporinone (**1189**) (Scheme 293).[640,836]

2.10. Total Synthesis of Staurosporinone (K-252c) by Intramolecular Diels–Alder Reaction

In 1990, Moody and Rahimtoola reported a short synthesis of staurosporinone (**987**) without the use of protecting groups at the indole or the lactam nitrogen. Their method is based on an intramolecular

Scheme 294



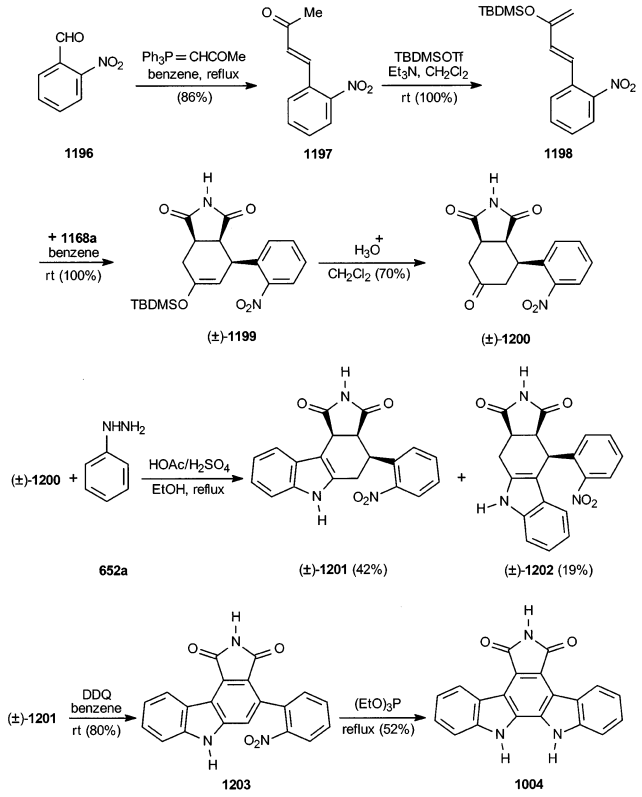
Diels−Alder reaction of the pyrano[4,3-*b*]indol-3-one **1194**[837a,838] and a subsequent cyclization by nitrene insertion.[274,659] The pyrano[4,3-*b*]indol-3-one **1194** was obtained in four steps from ethyl indol-2-yl acetate **1192**. Reaction of ethyl indol-2-yl acetate **1192** with oxalyl chloride followed by quenching with *ortho*-nitrocinnamylamine **1191** (prepared in three steps from commercial 2-nitrocinnamaldehyde **1190**) afforded the 2,3-disubstituted indole **1193a**.[839,471] Hydrolysis of the ester **1193a** followed by cyclodehydration of the keto acid **1193b** with acetic anhydride led to the pyrano[4,3-*b*]indol-3-one **1194**. The intramolecular Diels−Alder reaction of the pyrano[4,3-*b*]indol-3-one **1194** with concomitant loss of carbon dioxide by heating in bromobenzene under reflux and a subsequent aromatization by oxidation in air gave the carbazole **1195**. Cyclization of the carbazole **1195** with Cadogan's method by heating in triethyl phosphite provided staurosporinone (K-252c) (**987**) (Scheme 294).[837b,471] This synthesis leads to staurosporinone (**987**) in six steps and 23% overall yield based on ethyl indol-2-ylacetate **1192**.[471]

More recently, Snyder and Nomak used an intramolecular inverse electron-demand Diels−Alder reaction of a pyridazino[4,5-*b*]indole for the synthesis of 12-ethoxycarbonyl-6-methylstaurosporinone.[840]

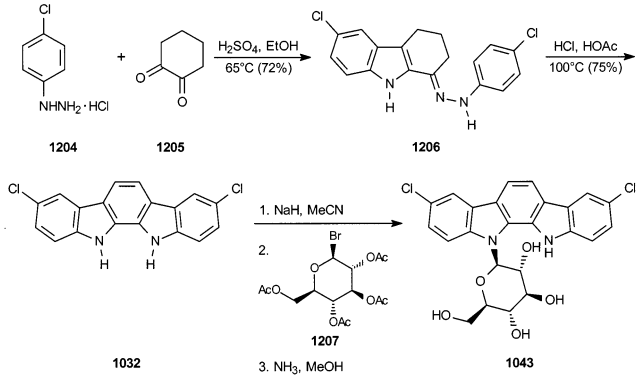
2.11. Total Synthesis of Arcyriaflavin A by Fischer Indolization

In 2000, Tomé and co-workers described a synthesis of arcyriaflavin A (**1004**) from commercially available 2-nitrobenzaldehyde **1196**. The construction of the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole framework was achieved by successive Diels−Alder cycloaddi-

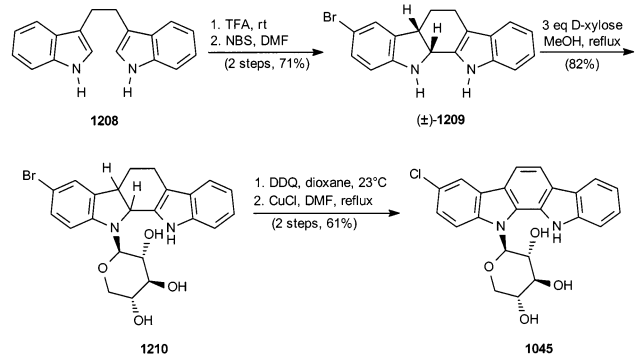
Scheme 295



Scheme 296



Scheme 297



tion, Fischer indolization, and nitrene insertion. A Wittig reaction of 2-nitrobenzaldehyde **1196** to the ketone **1197**, followed by reaction with *tert*-butyldimethylsilyl triflate in the presence of triethylamine, led to the diene **1198** in high yield. The Diels−Alder reaction of the diene **1198** with maleimide **1168a** afforded the endo-cycloadduct (±)-**1199**.[841] Acidic hydrolysis of compound (±)-**1199** gave the perhydroisoindole-1,3,5-trione (±)-**1200**, which on Fischer indolization with phenylhydrazine **652a** provided the regioisomers (±)-**1201** and (±)-**1202** in a 2:1 ratio. Dehydrogenation of (±)-**1201** with DDQ to the carbazole **1203** and nitrene insertion using Cadogan's procedure by heating in triethyl phosphite afforded arcyriaflavin A (**1004**) (Scheme 295).[842] This method was also applied to the synthesis of 3-methoxy-6-phenylarcyriaflavin A.[842]

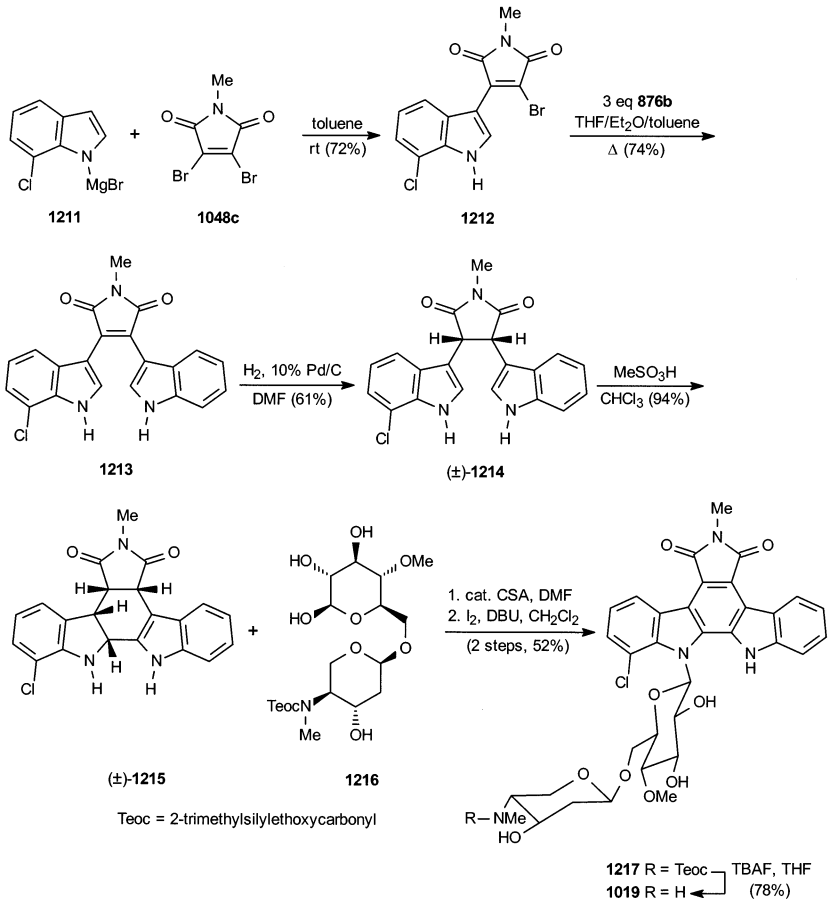
2.12. Total Synthesis of Tjipanazoles and AT2433-A$_1$

In 1991, Bonjouklian et al. reported along with the isolation also the synthesis of tjipanazole D (**1032**) and E (**1043**). Condensation of 2 equiv of *p*-chlorophenylhydrazine hydrochloride **1204** with 1,2-cyclohexanedione **1205** in the presence of air and stepwise Fischer indolization provided tjipanazole D (**1032**) in 54% yield. Coupling of **1032** with 1-bromo-α-D-glucopyranosyl-2,3,4,6-tetraacetate **1207** followed by removal of the protecting groups afforded tjipanazole E (**1043**) (Scheme 296).[740]

In 1996, Van Vranken et al. described the synthesis of tjipanazole F2 (**1045**) by introduction of the halide and the glycosidic substituent at the heterocyclic skeleton without the use of protecting groups and with complete control of regioselectivity. The indolo[2,3-*a*]carbazole framework of tjipanazole F2 (**1045**) was obtained by a trifluoroacetic acid-promoted Mannich cyclization[640,843] of the readily available 1,2-bis(indol-3-yl)ethane **1208**.[844] A subsequent bromination with NBS gave the racemic bromoindoline **1209**. Compound **1209** was regioselectively glycosylated at the indoline nitrogen[845] with 3 equiv of D-xylopyranose in methanol under reflux to afford a 1:1 diastereoisomeric mixture of **1210**. A convergent aromatization of the diastereoisomers **1210** with DDQ followed by halogen exchange using copper(I) chloride provided tjipanazole F2 (**1045**) in 61% yield over two steps (Scheme 297).[846] In the following year, this method was also applied to the total synthesis of tjipanazole F1 (**1044**).[847]

In 2000, the same group applied the acid-promoted Mannich cyclization to a regiocontrolled total synthesis of AT2433-A$_1$ (**1019**). The chlorinated bisindolylsuccinimide (±)-**1214** was prepared via the indole Grignard pathway.[744] Reaction of the 7-chloroindole Grignard compound **1211** with 1 equiv of (*N*-methyl)dibromomaleimide **1048c** to the monoaddition product **1212** followed by addition of indolylmagnesium bromide **876b** afforded the unsymmetrical bisindolylmaleimide **1213** in 74% yield. A catalytic hydrogenation of **1213** to the bisindolylsuccinimide (±)-**1214** followed by Mannich cyclization with methanesulfonic acid in chloroform provided the hexacyclic compound (±)-**1215** with high regio- and stereoselectivity. Glycosylation of the racemic chlorinated indoline (±)-**1215** with the aminodisaccharide **1216**[848,849] in the presence of camphorsulfonic acid (CSA) in DMF and subsequent aromatization with DBU and iodine in dichloromethane afforded the trimethylsilylethyl carbamate **1217**. Removal of the 2-trimethylsilylethoxycarbonyl (Teoc) group with TBAF pro-

Scheme 298



vided AT2433-A_1 (**1019**) (Scheme 298).[849] Using a symmetrical bisindole as Mannich substrate, this method was applied to the total synthesis of AT2433-B_1 (**1021**).[849]

2.13. Total Syntheses by Double Fischer Indolization

In 1989, Bergman and Pelcman reported a direct synthesis of arcyriaflavin A (**1004**) by a double Fischer indolization. A Diels−Alder cycloaddition of 2,3-bis(trimethylsilyloxy)butadiene **1218**[850] with maleimide **1168a** to compound **1219a** and subsequent condensation with phenylhydrazine **652a** in the presence of acetic acid afforded the bis(phenylhydrazone) **1220a**. The double Fischer indolization of **1220a** using polyphosphoric acid trimethylsilyl ester (PPSE)[851,852] led to 4c,7a-dihydroarcyriaflavin A (**1182**), which without isolation could be dehydrogenated to arcyriaflavin A (**1004**) in 68% yield (Scheme 299).[853]

The double Fischer indolization of the bis(2-chlorophenylhydrazone) **1221** (Scheme 299), obtained from 2-chlorophenylhydrazine and compound **1219a**, provided the rebeccamycin aglycon (1,11-dichloroindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione).[853] Further applications of this method using various bis(phenylhydrazone) derivatives led to the synthesis of a wide range of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-diones.[853]

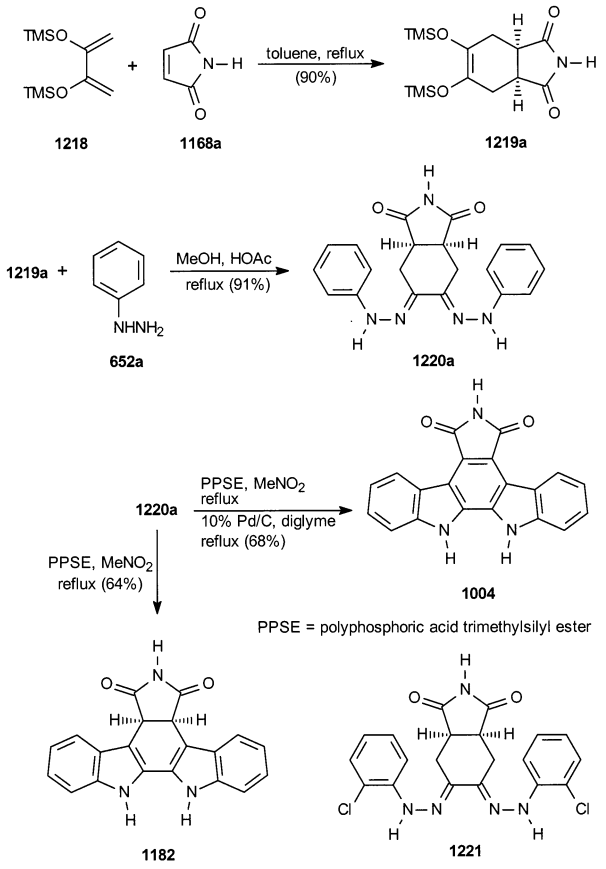
In 1992, Gribble and Berthel used a similar approach to 6-methylarcyriaflavin A (**1224**), which represents the aglycon of AT2433-B_1 and AT2433-B_2. The cycloaddition of 2,3-bis(trimethylsilyloxy)-butadiene **1218** (commercially available or prepared from **1222**)[854] with *N*-methylmaleimide **1168b** afforded the Diels−Alder adduct **1219b**. Oxidation of **1219b** with *m*-chloroperbenzoic acid (MCPBA)[855] to the intermediate 1,2-dione **1223** followed by addition of 2 equiv of phenylhydrazine **652a** gave the bisphenylhydrazone (osazone) **1220b**. Using Bergman's conditions,[853] the osazone **1220b** was smoothly transformed to 6-methylarcyriaflavin A (AT2433-B aglycon) (**1224**) (Scheme 300).[856]

Gribble and Berthel also described a synthesis of arcyriaflavin A (**1004**) and 6-methylarcyriaflavin A (AT2433-B aglycon) (**1224**) from the commercially available cyclohexene imides **1225a** and **1225b**. Although this appoach is much shorter, the overall yield is lower. The cyclohexene derivatives **1225** were converted to the labile dialdehydes followed by treatment with 2 equiv of phenylhydrazine **652a** to give the bis(phenylhydrazones) **1226**. Double Fischer indolization of the bis(phenylhydrazones) **1226** with polyphosphoric acid trimethylsilyl ester (PPSE) in nitromethane under reflux[853] provided aromatized indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles, arcyriaflavin A (**1004**) and 6-methylarcyriaflavin A (AT2433-B aglycon) (**1224**) (Scheme 301).[611,856]

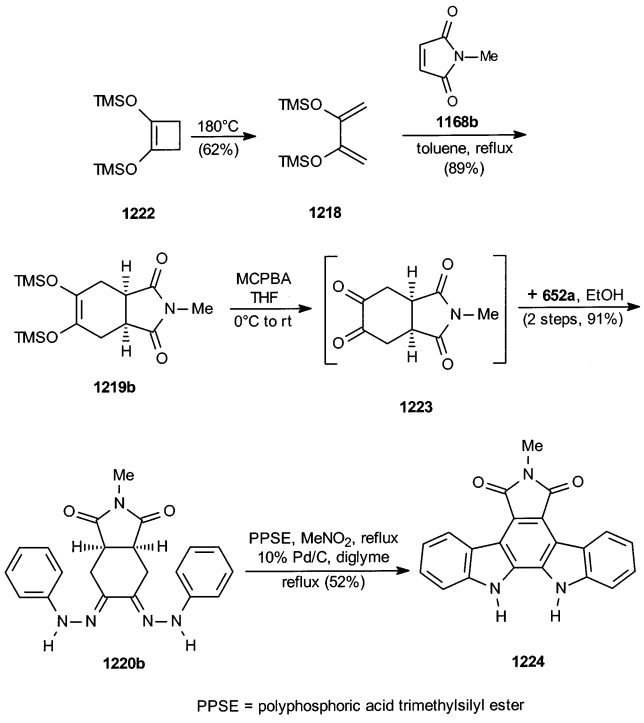
IX. Dimeric Carbazole Alkaloids

The dimeric carbazole alkaloids contain previously known monomeric carbazoles as structural subunits. All dimeric carbazole alkaloids were isolated only

Scheme 299

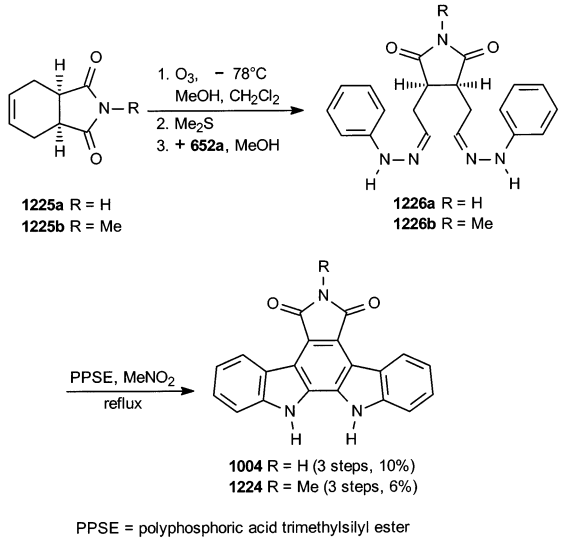


Scheme 300

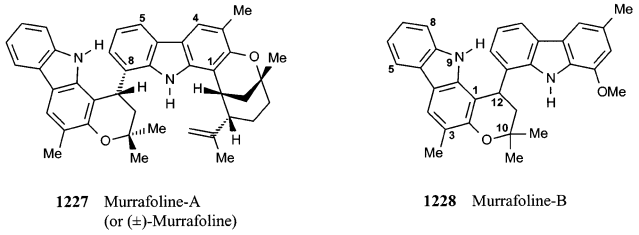


from plants of the genus *Murraya* until 1996, when clausenamine-A **1251** (see Scheme 308) was isolated from the stem bark of *C. excavata*. The plant *M. euchrestifolia* Hayata is one of the richest source of carbazole alkaloids. The dimeric carbazoles co-occur often with monomeric carbazoles in its root bark,

Scheme 301

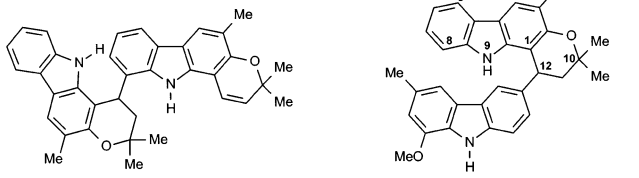


Scheme 302



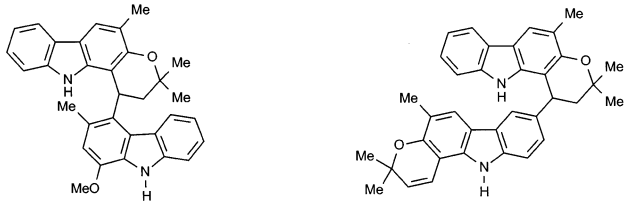
1227 Murrafoline-A (or (±)-Murrafoline)

1228 Murrafoline-B



1229 Murrafoline-C

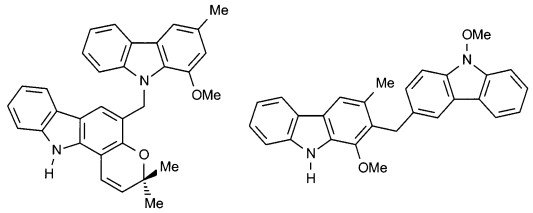
1230 Murrafoline-D



1231 Murrafoline-G

1232 Murrafoline-H

Scheme 303

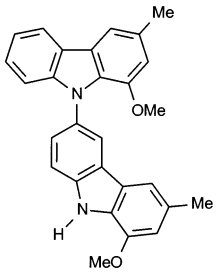


1233 Murrafoline-E

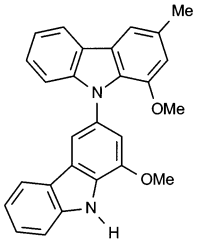
1234 Murrafoline-F

stem bark, and leaves. Many reviews appeared on monomeric carbazole alkaloids.[5,6,8,9,14,16] However, in these papers only some dimeric carbazole alkaloids

Scheme 304

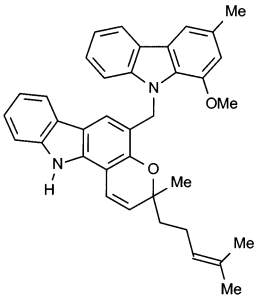


1235 Murrastifoline-A

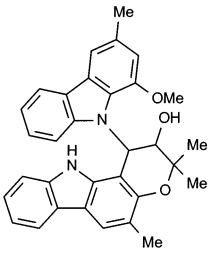


1236 Murrastifoline-B

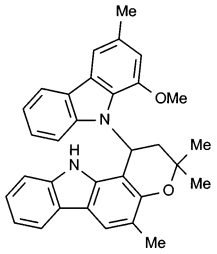
Scheme 305



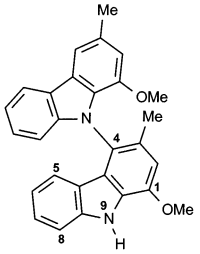
1237 Murrastifoline-C



1238 Murrastifoline-D

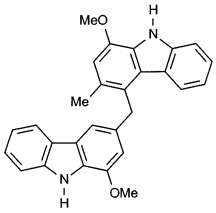


1239 Murrastifoline-E

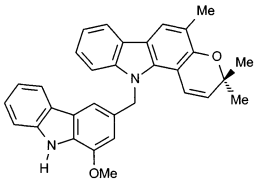


1240 Murrastifoline-F

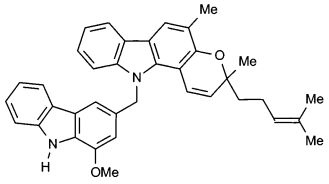
Scheme 306



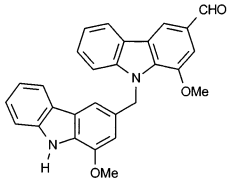
1241 Chrestifoline-A



1242 Chrestifoline-B



1243 Chrestifoline-C

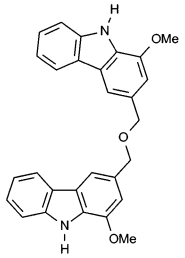


1244 Chrestifoline-D

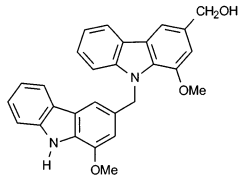
were listed.[9,14,16] Furukawa compiled the dimeric carbazole alkaloids that were known till the end of 1992.[857] There are no reviews concerning the synthesis of this class of natural products. The aspect of atropisomerism for the axially chiral dimeric carbazoles was considered only recently. Therefore, in many cases it is not clear whether the isolated natural products are racemic or enantiomerically pure. Moreover, only little attention has been paid to the relationship of their stereochemistry and the biological activity. In this section we summarize the isolation and the syntheses of the dimeric carbazole alkaloids known to date.

In 1983, Furukawa and co-workers isolated the first dimeric carbazole alkaloid, murrafoline-A [or (±)-murrafoline] (**1227**), from the plant *M. euchrestifolia* Hayata.[858] Murrafoline-A (**1227**) consists of a dihydrogirinimbine unit (cf. girinimbine **458**, Scheme

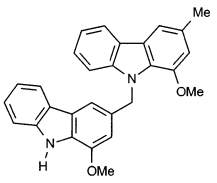
Scheme 307



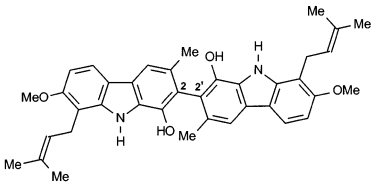
1245 Oxydimurrayafoline



1246 Bismurrayafolinol

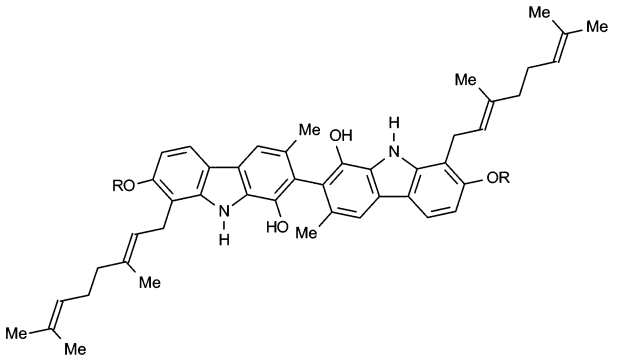


1247 Bismurrayafoline-A

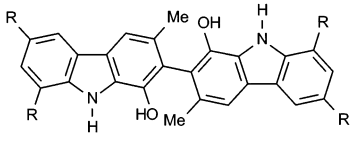


1248 Bismurrayafoline-B

Scheme 308

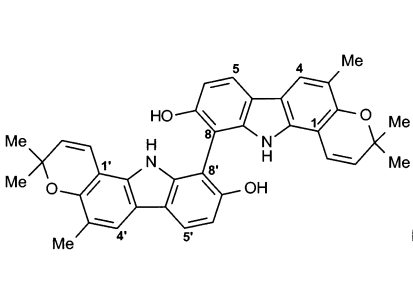


1249 Bismurrayafoline-C
R = H
1250 Bismurrayafoline-D
R = Me

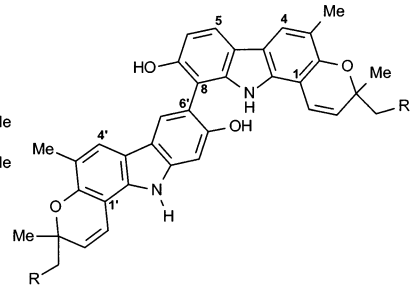


1251 Clausenamine-A
R = OMe
1252 Bis(*O*-demethylmurrayafoline-A)
R = H

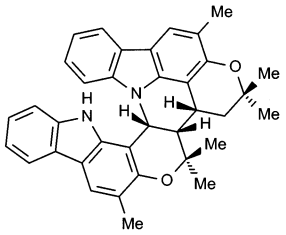
Scheme 309



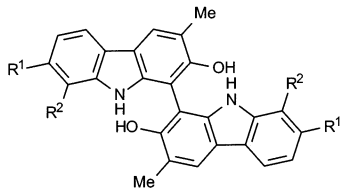
1253 Bis-7-hydroxygirinimbine-A



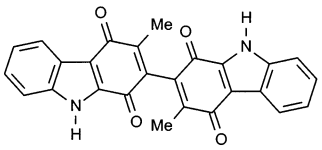
1254a Bis-7-hydroxygirinimbine-B
R = H
1254b Bismahanine
R = Prenyl



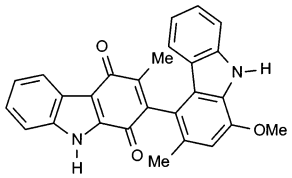
1255 Murranimbine



1256a 1,1'-Bis(2-hydroxy-3-methylcarbazole)
R^1, R^2 = H
1256b Bismurrayafoline-E
R^1 = OMe; R^2 = geranyl

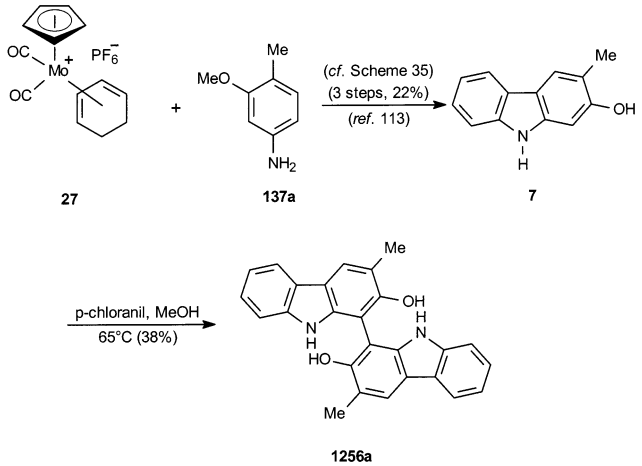


1257 Bismurrayaquinone-A



1258 Bikoeniquinone-A

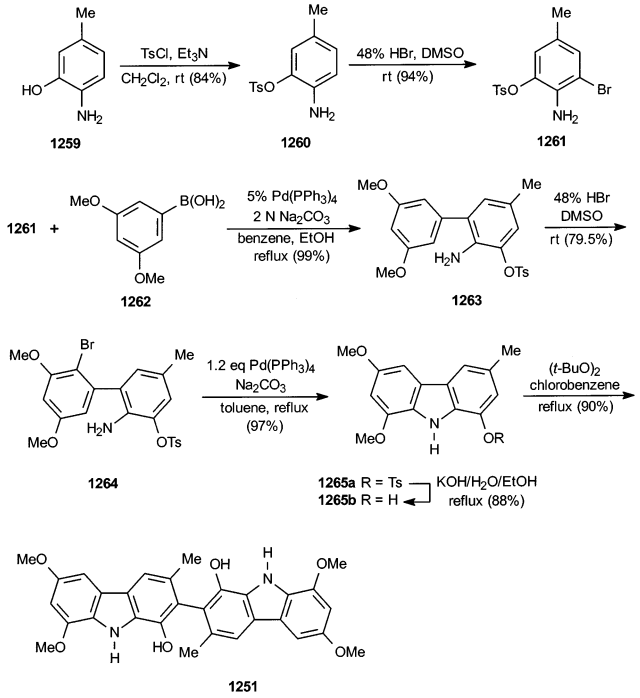
Scheme 310



27 **137a** **7** **1256a**

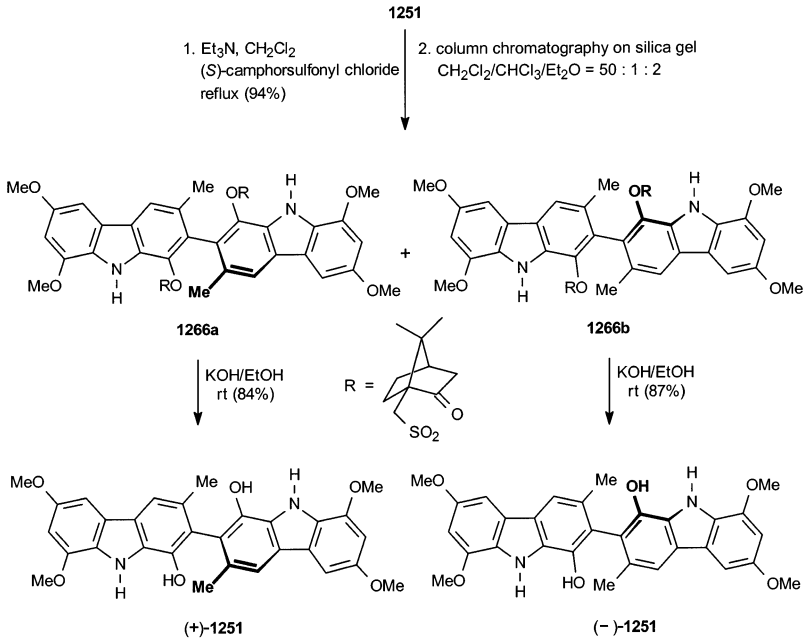
132) that is attached at C-12 to the C-8 of cyclomahanimbine (see Scheme 315). Both monomeric carbazole alkaloids co-occur with murrafoline-A (**1227**). The complete structure and the relative stereochemistry of murrafoline-A (**1227**) was established by X-ray analysis.[858] From the same natural source Furukawa and his group isolated in 1985 and in 1993 further dimeric carbazole alkaloids: murrafoline-B

Scheme 311

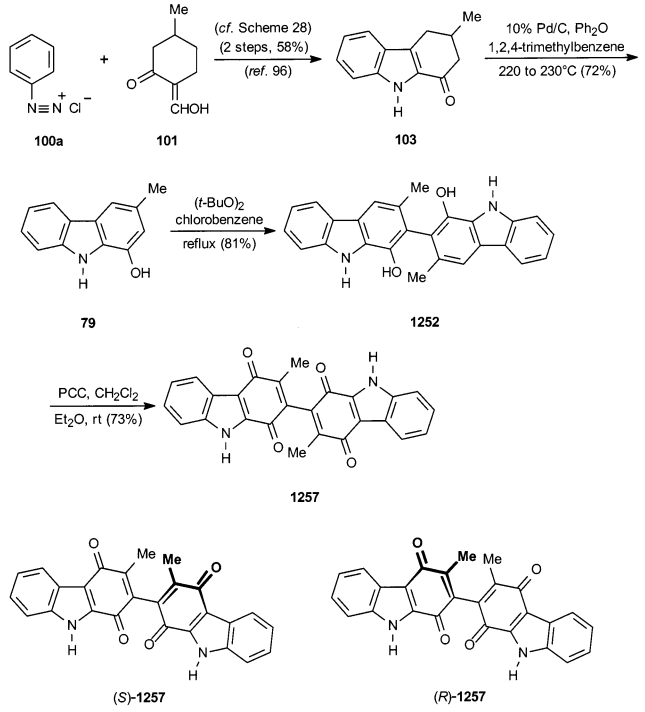


1259 **1260** **1261** **1262** **1263** **1264** **1265a** R = Ts **1265b** R = H **1251**

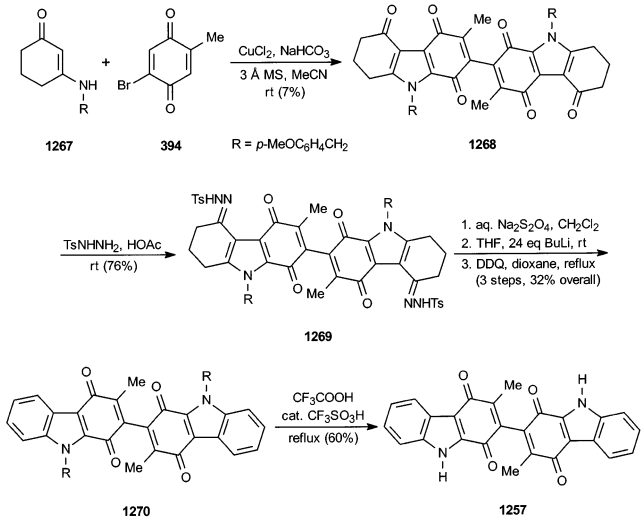
Scheme 312



Scheme 313



Scheme 314



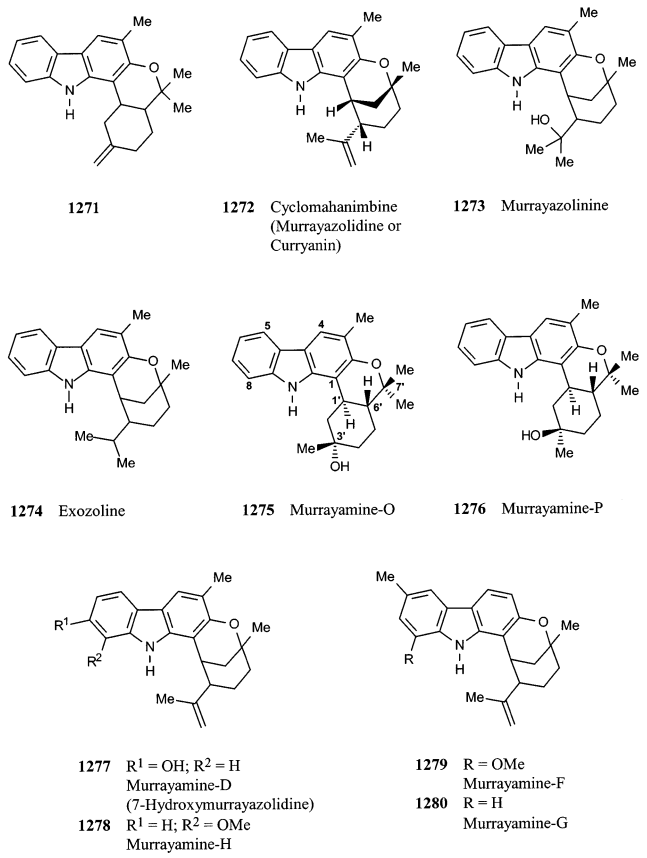
(**1228**), -C (**1229**), -D (**1230**), -G (**1231**), and -H (**1232**). Their common structural feature is a dihydrogirinimbine attached at C-12 to a second carbazole moiety (Scheme 302).[859,860]

In 1988, Ito et al. reported the isolation of the structurally interesting dimeric carbazole alkaloids murrafoline-E (**1233**) and -F (**1234**) from the same plant source. Murrafoline-E was the third example of an *N*-benzyl-linked dimeric carbazole alkaloid from a *Murraya* plant. Murrafoline-F (**1234**) was the first dimeric *N*-methoxycarbazole alkaloid isolated from a natural source (Scheme 303).[184]

In 1990, Furukawa and his group described the isolation of murrastifoline-A (**1235**), -B (**1236**), -C (**1237**), -D (**1238**), and -E (**1239**) from the plant *M. euchrestifolia* Hayata. Their common substructure is a 1-methoxy-3-methylcarbazole [murrayafoline A (**2**)], which is attached at the *N*-atom to a second carbazole moiety (Schemes 304 and 305).[259,861] In 1993, Furukawa and co-workers reported the isolation of murrastifoline-F (**1240**) from *M. koenigii* (Scheme 305).[862] This alkaloid consists of two molecules of 1-methoxy-3-methylcarbazole with the nitrogen of the first attached to C-4 of the second. It is isomeric to murrastifoline-A (**1235**) (see Scheme 304), which has a linkage between the nitrogen and C-6 of the second carbazole.

In 1990 and 1992, Furukawa et al. described the isolation of chrestifoline-A (**1241**), -B (**1242**), -C (**1243**), and -D (**1244**) from the plant *M. euchrestifolia* Hayata. The chrestifolines contain as a common structural unit, a 1-methoxy-3-methylcarbazole [murrayafoline A (**2**)], which is connected to the second carbazole via the methyl group at C-3 (Scheme 306).[861,863] Chrestifoline-D (**1244**) could also be ob-

Scheme 315



tained by DDQ oxidation of bismurrayafoline-A (**1247**) (see Scheme 307).[863]

In 1987, Ito et al. reported the isolation of oxydimurrayafoline (**1245**) and bismurrayafolinol (**1246**) from the stem bark of *M. euchrestifolia* Hayata.[110] Oxydimurrayafoline (**1245**) is the first example of a dimeric carbazole with an ether linkage. In 1983, Furukawa and co-workers described the isolation of bismurrayafoline-A (**1247**) and bismurrayafoline-B (**1248**) from the same natural source. Bismurrayafoline-B (**1248**) is a symmetrical dimer of two molecules of murrayafoline-B linked at the 2,2′-position (Scheme 307).[864]

In 1991, Furukawa et al. reported the isolation of bismurrayafoline-C (**1249**) and bismurrayafoline-D (**1250**) from the plant *M. euchrestifolia* Hayata. Bismurrayafoline-D is the dimethyl ether of bismurrayafoline-C.[112] In 1996, Wu and co-workers isolated clausenamine-A (**1251**) from the extracts of the stem bark of *C. excavata*, which are used as a folk medicine in China for the treatment of poisonous snakebites.[865] This is so far the only dimeric carbazole alkaloid not isolated from a *Murraya* species. The natural products **1249**−**1251** represent further examples of 2,2′-linked dimeric carbazole alkaloids. Clausenamine-A (**1251**) and its synthetic analogues exhibited potent cytotoxic activities in vitro against a variety of human cancer cell lines[866−868] and also showed moderate antimalarial activities.[869] Bringmann et al. reported the antiplasmodial activity of the nonnatural bis(*O*-demethylmurrayafoline-A) (**1252**) against *Plasmodium falciparum* in vitro (Scheme 308).[870]

In 1991, Wu et al. isolated bis-7-hydroxygirinimbine-A (**1253**) and bis-7-hydroxygirinimbine-B (**1254a**) from *M. euchrestifolia* (Scheme 309).[871] In bis-7-hydroxygirinimbine-A, two 7-hydroxygirinimbine units are connected at C-8 and C-8′, whereas in bis-7-hydroxygirinimbine-B, the two 7-hydroxygirinimbine units are connected at C-8 and C-6′. Structurally related is bismahanine (**1254b**), which was isolated in 1993 by Furukawa and his group from the stem bark of *M. koenigii*.[862] Ito and Furukawa reported in 1991 the isolation of murranimbine **1255** from *M. euchrestifolia*.[872a] Murranimbine (**1255**) derives from two molecules of girinimbine, which are unusually fused, different from other dimeric carbazole alkaloids. In 1993, Furukawa et al. isolated 1,1′-bis(2-hydroxy-3-methylcarbazole) (**1256a**) and the first dimeric carbazolequinone alkaloids, bismurrayaquinone-A (**1257**) and bikoeniquinone-A (**1258**), from the plant *M. koenigii* Spreng.[872b] Two years later, Bringmann and co-workers described the enantiomer resolution and the chiroptical properties of bismurrayaquinone-A (**1257**).[873] In 1999, a further novel 1,1′-linked dimeric carbazole alkaloid, bismurrayafoline-E (**1256b**), was isolated from the leaves of *M. koenigii* (Scheme 309).[874]

1. Molybdenum-Mediated Total Synthesis of 1,1′-Bis(2-hydroxy-3-methylcarbazole)

In 1996, we described the first total synthesis of 1,1′-bis(2-hydroxy-3-methylcarbazole) (**1256a**) via our molybdenum-mediated construction of the carbazole framework. The required monomer, 2-hydroxy-3-methylcarbazole **7**, was obtained in three steps and 22% overall yield starting from dicarbonyl(η^4-cyclohexa-1,3-diene)(η^5-cyclopentadienyl)molybdenum hexafluorophosphate **27** and 3-methoxy-4-methylaniline **137a** as synthetic precursors (see Scheme 35). Oxidative coupling of the monomer **7** using *p*-chloranil provided 1,1′-bis(2-hydroxy-3-methylcarbazole) (**1256a**) in 38% yield (Scheme 310).[113]

2. Palladium-Mediated Total Synthesis of Clausenamine-A

In 2000, Lin and Zhang reported the first total synthesis and the resolution of racemic clausenamine-A (**1251**) starting from 2-amino-5-methylphenol (**1259**) by a Suzuki cross-coupling and an oxidative dimerization as key steps (Scheme 311). For an *o*-amino bromination, the phenol **1259** was transformed to the tosylate **1260**. Electrophilic aromatic bromination[875] of **1260** using in situ generated bromodimethylsulfonium bromide gave the corresponding 2-bromo derivative **1261** in 94% yield. The required biphenyl **1263** was prepared quantitatively by Suzuki cross-coupling of 3,5-dimethoxyphenyl boronic acid **1262**[876] with **1261** using 5% $Pd(PPh_3)_4$ and aqueous sodium carbonate in benzene.[877] Bromination of **1263** using 48% HBr in dimethyl sulfoxide afforded the bromo derivative **1264**. A palladium-(0)-mediated cyclization[878] of compound **1264** led to the 9*H*-carbazole **1265a** in 97% yield. Cleavage of the tosylate followed by oxidative dimerization of the resulting 1-hydroxycarbazole **1265b** using di-*tert*-

butyl peroxide (t-BuO)$_2$ in chlorobenzene provided racemic clausenamine-A (**1251**) in 90% yield (Scheme 311).[868,869]

The resolution of racemic clausenamine-A (**1251**) was accomplished by silica gel column chromatography of the corresponding (+)-camphorsulfonates **1266a**,**b**[879−881] using dichloromethane/chloroform/diethyl ether (50:1:2) as the eluent. Basic hydrolysis of **1266a** and **1266b** provided optically pure clausenamine-A [(*R*)-(+)-**1251** and (*S*)-(−)**1251**] (Scheme 312).[869] The assignment of the absolute configuration was based on an X-ray analysis and the CD spectra. The same method was applied to the synthesis and resolution of the demethoxylated analogues of clausenamine-A including bis(*O*-demethylmurrayafoline-A) (**1252**).[90,869]

3. Total Synthesis of (±)-Bismurrayaquinone-A by Fischer Indolization

In 1995, Bringmann et al. described the first total synthesis of (±)-bismurrayaquinone-A (**1257**) starting from 1-hydroxy-3-methylcarbazole **79**. The monomeric carbazole **79** was prepared by Fischer indolization from phenyldiazonium chloride **100a** and 2-hydroxymethylene-5-methylcyclohexanone **101** as described previously by Chakraborty (see Scheme 28).[96] The yield for the dehydrogenation of the carbazolone **103** to 1-hydroxy-3-methylcarbazole **79** was improved from 45%[96] to 72%. A biomimetic oxidative dimerization of the monomer **79** with di-*tert*-butyl peroxide (t-BuO)$_2$ afforded the 2,2′-linked bis(*O*-demethylmurrayafoline-A) (**1252**) in 81% yield.[882] The oxidation of **1252** with pyridinium chlorochromate (PCC) in dichloromethane provided (±)-bismurrayaquinone-A (**1257**) in 73% yield (Scheme 313).[873] Chromatographic separation of the enantiomers of (±)-bismurrayaquinone-A (**1257**) using a Chiracel OF (Daicel Chem. Ind.) column enabled the determination of the absolute configuration for the bismurrayaquinone A enantiomers (*S*)-**1257** and (*R*)-**1257**. The calculated circular dichroism (CD) spectra based on these assignments were in agreement with those experimentally found.[873]

4. Total Synthesis of (±)-Bismurrayaquinone-A by Bromoquinone-Enaminone Annulation

In 1998, Murphy and Bertrand developed a second total synthesis of (±)-bismurrayaquinone-A (**1257**) via the bromoquinone−enaminone annulation. The reaction of the *p*-methoxybenzyl-protected enamino ketone **1267** and 5-bromo-2-methyl-1,4-benzoquinone **394** with copper(II) chloride in the presence of sodium bicarbonate and 3 Å molecular sieves (MS) afforded in low yield the dimer **1268**. Compound **1268** was transformed to the bis(tosylhydrazone) **1269**, followed by Shapiro reaction[205] and aromatization with DDQ in dioxane to afford the bis-*N*-protected bismurrayaquinone **1270**. Deprotection in trifluoroacetic acid with catalytic amounts of trifluoromethanesulfonic acid provided (±)-bismurrayaquinone-A (**1257**) in 60% yield (Scheme 314).[206]

In addition to the total syntheses described above, the following transformations were reported. Furukawa and co-workers obtained a mixture of murrafoline-D (**1230**), -G (**1231**), and -H (**1232**) (see Scheme 302) by refluxing a solution of murrayafoline-A (**2**) and girinimbine (**458**) in aqueous methanol for 27 h in the presence of ion-exchange resin (Nafion 117).[859,860] Chakrabarti and Chakraborty described the reaction of girinimbine (**458**) with BF_3 etherate in dichloromethane at room temperature, which afforded murrafoline-H (**1232**) in 21% yield.[883] In 1997, Shannon and his group observed the formation of a N−C3-linked dimer during the transformation of a 3-bromocarbazole to a 3-cyanocarbazole by reaction with copper(I) cyanide in *N*,*N*-dimethylformamide under reflux.[884] However, this procedure was not applied to the synthesis of naturally occurring dimeric carbazoles. Additional total syntheses of dimeric carbazole alkaloids are described in section XI.6.

X. Miscellaneous Carbazole Alkaloids

Many structurally diverse carbazoles were found in nature that are not covered by the previous sections because of their special framework. In this section, we describe these carbazole alkaloids. On the basis of their ring systems, they were divided into the following groups:

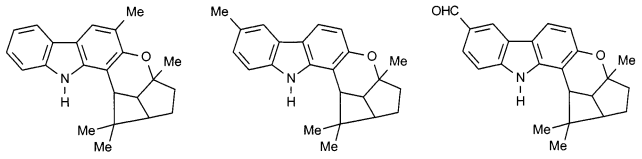
1. Cyclic Monoterpenoid Pyrano[3,2-*a*]carbazole Alkaloids
2. Carbazolelactone Alkaloids
3. Imidazo[4,5-*a*]pyrrolo[3,4-*c*]carbazole Alkaloids
4. Sesquiterpenoid Carbazole Alkaloids

The isolation of additional miscellaneous carbazole alkaloids is described in section XI.5.6.

1. Cyclic Monoterpenoid Pyrano[3,2-*a*]carbazole Alkaloids

In 1969, Dutta and co-workers isolated a pentacyclic pyrano[3,2-*a*]carbazole alkaloid (curryanin) from *M. koenigii* Spreng (Rutaceae) and assigned its structure as **1271** (Scheme 315).[268] The name curryanin derives from the vernacular name for this plant: currypatta or curry-leaf tree. One year later, Chakraborty and co-workers reported the isolation of the same alkaloid from the stem bark of the same plant and named it murrayazolidine.[885] In 1969, Kapil and co-workers isolated from the leaves of *M. koenigii* Spreng the pentacyclic pyrano[3,2-*a*]carbazole alkaloid cyclomahanimbine (**1272**).[886] Cyclomahanimbine (**1272**) derives from a 2-hydroxy-3-methylcarbazole that is fused to a monoterpene moiety at C-1 and via an ether linkage at C-2.[886,887] In 1974, Bandaranayake et al. achieved the synthesis of cyclomahanimbine (**1272**) by heating (±)-mahanimbine (**470**) (see Schemes 133 and 140) in benzene under reflux in the presence of an ion-exchange resin (Dowex-50W-X8, H^+).[887] They also examined the structure of murrayazolidine and curryanin and reassigned both as **1272**.[887] This reassignment was based on comparison of their NMR spectra with the NMR spectrum of synthetic cyclomahanimbine (**1272**). The stereochemistry of cyclomahanimbine (murrayazolidine or curryanin) (**1272**) was assigned by Furukawa et al. along with the structural elucidation

Scheme 316



1281 Bicyclomahanimbine **1282** Bicyclomahanimbicine **1283** Murrayamine-M

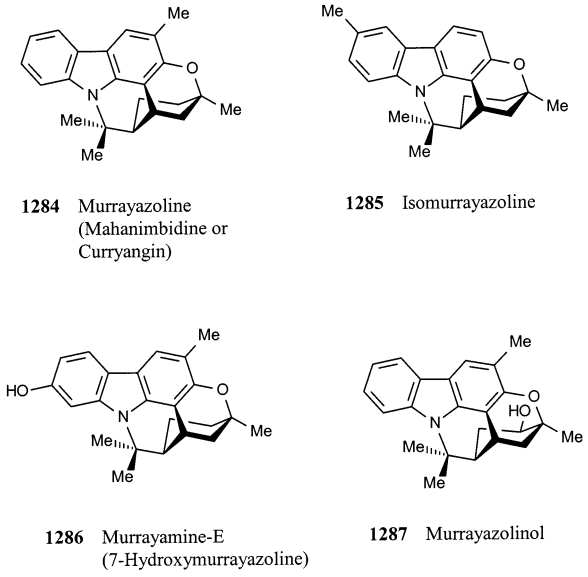
of the dimeric carbazole alkaloid murrafoline-A (see Scheme 302).[858,860] In 1973, Chakraborty and co-workers isolated from the stem bark of *M. koenigii* Spreng murrayazolinine (**1273**) (Scheme 315), which has the same pentacyclic framework with a hydroxyisopropyl group.[888] In 1978, Ganguly and Sarkar obtained from the leaves of *Murraya exotica* Linn the pentacyclic pyrano[3,2-*a*]carbazole alkaloid exozoline (**1274**) with an isopropyl group at the terpene unit. The structure of exozoline (**1274**) was confirmed by comparison with dihydrocyclomahanimbine obtained by hydrogenation of cyclomahanimbine (**1272**).[889]

During their phytochemical studies of *M. euchrestifolia*, Wu and co-workers described in 1995 the isolation of two cannabinol-skeletal carbazole alkaloids, murrayamine-O (**1275**) and murrayamine-P (**1276**), which are diastereoisomers at C-3′.[890] They also reported the isolation of murrayamine-D (**1277**) from the leaves of *M. euchrestifolia* collected during the winter (February). Murrayamine-D (**1277**) has the same bicyclic terpenoid skeleton as murrayazolidine (**1272**) with a hydroxy group at C-7 of the carbazole nucleus. Therefore, murrayamine-D (**1277**) is a 7-hydroxymurrayazolidine.[891] One year later in spring (May) the same group isolated from the leaves of the same plant murrayamine-H (**1278**), -F (**1279**), and -G (**1280**). The plant shows strong seasonal variations of carbazole alkaloids. The pharmacological activity of the extracts from this traditional Chinese medicinal plant is dependent on the collection time, which may be explained by the variation of biologically active carbazole alkaloids (Scheme 315).[892]

In 1969 and 1970, Kapil and co-workers described in two independent papers the isolation of the two isomeric carbazoles bicyclomahanimbine (**1281**)[887,893] and bicyclomahanimbicine (**1282**)[254,887] from the leaves of *M. koenigii*. For both alkaloids, the original structures were revised in 1974 by Bandaranayake et al.[887] In 1996, Wu and co-workers reported the isolation of murrayamine-M (**1283**) from the leaves of *M. euchrestifolia* Hayata collected in November in Taiwan. By spectroscopic analysis, the structure of this alkaloid was determined as the formyl analogue of bicyclomahanimbicine (Scheme 316).[894]

In 1972, Chakraborty and co-workers isolated murrayazoline (**1284**) from the alcoholic extract of the stem bark of *M. koenigii* Spreng (Scheme 317).[895] Three years before, this alkaloid was obtained from the leaves and the stem bark of the same plant by the groups of Kapil and Dutta and named mahanimbidine[893] and curryangin, respectively.[896] Murrayazoline (mahanimbidine or curryangin) (**1284**) represents a 2-hydroxy-3-methylcarbazole that is fused to the monoterpene fragment at three positions. In

Scheme 317



1284 Murrayazoline (Mahanimbidine or Curryangin)

1285 Isomurrayazoline

1286 Murrayamine-E (7-Hydroxymurrayazoline)

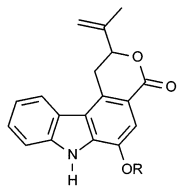
1287 Murrayazolinol

1985, Furukawa and co-workers reported the isolation of (+)-murrayazoline (**1284**) from a different source, *M. euchrestifolia* Hayata.[73] Extracts of the leaves and bark of this tree have been used as a folk medicine for analgesia and local anesthesia and for the treatment of eczema, rheumatism, and dropsy.[73] In 1982, Chakraborty and co-workers reported the isolation of isomurrayazoline (**1285**), a regioisomer of murrayazoline, from *M. koenigii* Spreng. Spectroscopic analysis of isomurrayazoline (**1285**) showed the presence of a 6-methylcarbazole skeleton annulated to the same monoterpene moiety as in murrayazoline.[897] In 1995, Wu et al. reported the isolation of murrayamine-E (**1286**) from the acetone extracts of the leaves of *M. euchrestifolia*.[891] This carbazole alkaloid is isomeric to murrayamine-D (**1277**) (see Scheme 315). The structural analysis of murrayamine-E (**1286**) led to the same framework as found for murrayazoline (**1284**) with an hydroxy group at C-7. Therefore, the structure of murrayamine-E (**1286**) was assigned as 7-hydroxymurrayazoline and additionally confirmed by a single-crystal X-ray analysis.[891] In 1989, Chakraborty and co-workers isolated murrayazolinol (**1287**) as a minor carbazole alkaloid from the stem bark of *M. koenigii* Spreng.[898] In 1994, this alkaloid was also obtained by Ahmad as a minor carbazole alkaloid from the benzene extracts of the root bark of *M. exotica* (Scheme 317).[899]

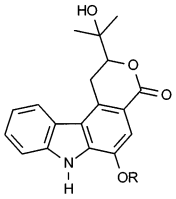
2. Carbazolelactone Alkaloids

In 1998, Ito and co-workers isolated clausamine-A (**1288**), -B (**1289**), and -C (**1290**) from the branches of *C. anisata* (Rutaceae) collected in Thailand. The clausamines have a 1-oxygenated carbazole framework with an annulated six-membered lactone in the 3,4-position. They represented the first carbazole alkaloids with a lactone moiety isolated from a natural source.[900] Later in the same year, Wu and his group isolated four further carbazolelactone alkaloids, clausevatine-D (**1291**), -E (**1292**), -F (**1293**), and -G (**1294**), from the root bark of *C. excavata* (Rutaceae).[901] This plant is a wild shrub that is used

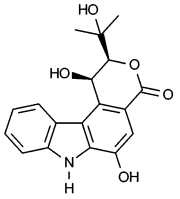
Scheme 318



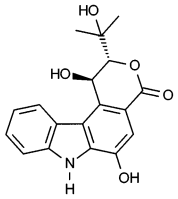
1288 R = H Clausamine-A
1289 R = Me Clausamine-B



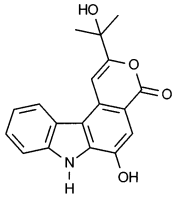
1290 R = Me Clausamine-C
1291 R = H Clausevatine-D



1292 Clausevatine-E

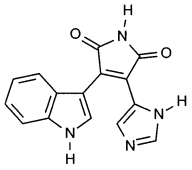


1293 Clausevatine-F

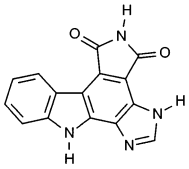


1294 Clausevatine-G

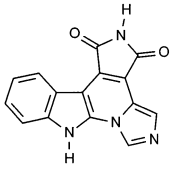
Scheme 319



1295 Didemnimide A



1296 Granulatimide



1297 Isogranulatimide

as a folk medicine for the treatment of snakebites and abdominal pain (Scheme 318).

3. Imidazo[4,5-*a*]pyrrolo[3,4-*c*]carbazole Alkaloids

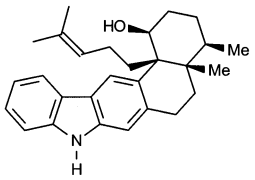
In 1998, Berlinck et al. isolated from the methanol extracts of the Brazilian ascidian *Didemnum granulatum*, along with the known didemnimide A (**1295**), the two novel alkaloids granulatimide (**1296**) and isogranulatimide (**1297**).[902] From the biogenetic point of view it appears reasonable that the co-occurring didemnimide A (**1295**) represents the precursor for the two pentacyclic alkaloids granulatimide (**1296**) and isogranulatimide (**1297**) (Scheme 319).

Granulatimide (**1296**) and isogranulatimide (**1297**) represent the first examples of a new class of G2 specific cell cycle checkpoint inhibitors, and they were identified through a rational screening program.[902] The use of a DNA-damaging agent in combination with a G2 specific cell cycle checkpoint inhibitor would provide a strategy to selectively target cancer cells.[903−906] The G2 checkpoint permits DNA repair before chromosomes are segregated in mitosis, thus preventing the propagation of genetic abnormalities.[902]

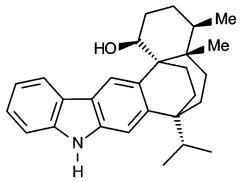
4. Sesquiterpenoid Carbazole Alkaloids

In 1989, Gloer and co-workers isolated tubingensin A (**1298**) from the hexane extract of the sclerotia of the fungus *Aspergillus tubingensis* (Scheme 320). Tubingensin A (**1298**) has an unprecedented 9*H*-octahydronaphtho[3,4-*b*]carbazole pentacyclic framework. Moreover, tubingensin A is active against the widespread crop pest *Heliothis zea* and shows in vitro antiviral activity against herpes simplex virus type 1.[907] In the same year, Gloer et al. isolated the cytotoxic carbazole alkaloid tubingensin B (**1299**) from the same natural source. Tubingensin B (**1299**) exhibited a similar biological acitivity as found for tubingensin A (**1298**), but was more cytotoxic to HeLa cells (IC_{50}: 4 μg/mL for **1299** vs 23 μg/mL for **1298**).[908] One year later, the same group described the isolation of aflavazole (**1300**), a new antiinsectan carbazole metabolite from the sclerotia of *Aspergillus flavus*.[909] This alkaloid shows a strong antifeedant activity against the fungivorous beetle *Carpophilus hemipterus*.[909,910]

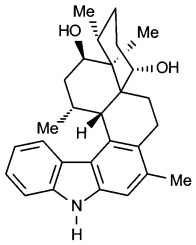
Scheme 320



1298 Tubingensin A

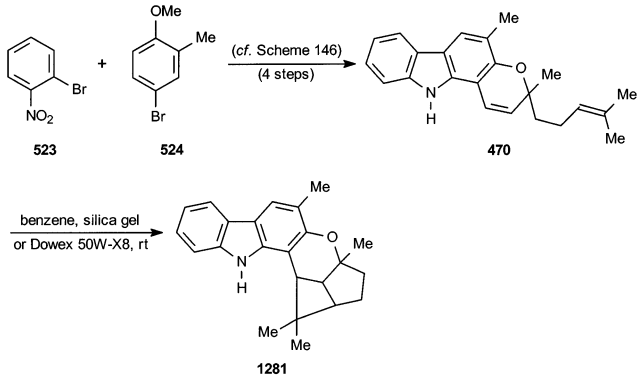


1299 Tubingensin B



1300 Aflavazole

Scheme 321



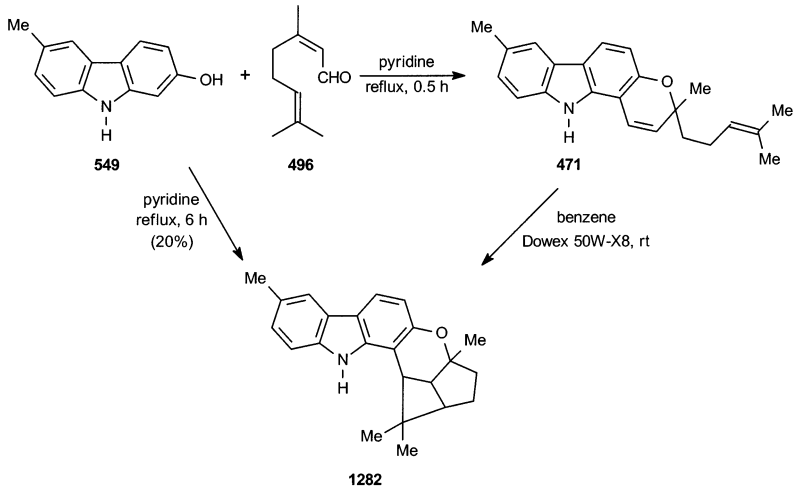
523 **524** **470** **1281**

5. Total Syntheses

5.1. Synthesis of Bicyclomahanimbine

In 1969, Popli and co-workers reported the synthesis of bicyclomahanimbine (**1281**) from (±)-mahanimbine (**470**). Ullmann coupling of 2-nitrobromobenzene **523** and 4-bromo-2-methylanisole **524**, followed by Cadogan's reductive cyclization of the resulting *o*-nitrobiaryl via a nitrene intermediate,[274,275] ether cleavage to 2-hydroxy-3-methylcarbazole, and condensation with citral led to (±)-mahanimbine (**470**) in four steps (see Scheme 146).[276]

Scheme 322



A biomimetic cyclization of (±)-mahanimbine (**470**) could be achieved under mild acidic conditions. Treatment of a solution of (±)-mahanimbine (**470**) in benzene with silica gel (48 h) or Dowex 50W-X8 ion-exchange resin (H^+) provided bicyclomahanimbine (**1281)** (Scheme 321).[276,893]

5.2. Synthesis of Bicyclomahanimbicine

The same method was subsequently applied to the synthesis of bicylomahanimbicine (**1282**) starting from 2-hydroxy-6-methylcarbazole **549**. The condensation of 2-hydroxy-6-methylcarbazole **549** with citral (**496**) by heating in pyridine under reflux for 30 min provided mahanimbicine (isomahanimbine) (**471**) in low yield. Shaking a solution of mahanimbicine (**471**) in benzene overnight in the presence of Dowex 50W-X8 ion-exchange resin (H^+) resulted in cyclization to bicyclomahanimbicine (**1282**). Moreover, the extension of the reaction time for the condensation of 2-hydroxy-6-methylcarbazole (**549**) with citral (**496**) in pyridine under reflux to 6 h led directly to bicyclomahanimbicine (**1282**) in 20% yield (Scheme 322).[254]

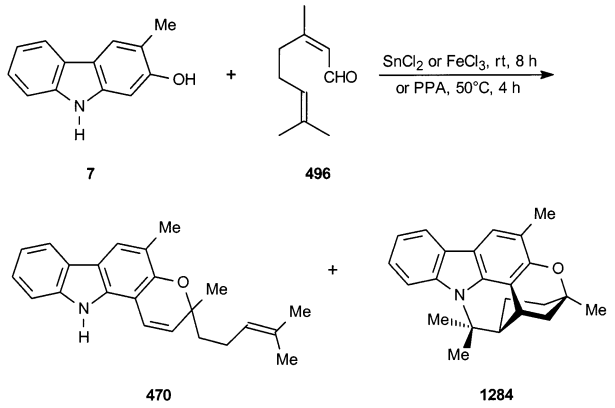
5.3. Synthesis of Murrayazoline

In 1969, Dutta and co-workers described the synthesis of murrayazoline (mahanimbidine or curryangin) (**1284**) along with (±)-mahanimbine (**470**). The condensation of 2-hydroxy-3-methylcarbazole **7** with citral (**496**) using either anhydrous tin(II) chloride or iron(III) chloride at room temperature for 8 h, or polyphosphoric acid (PPA) at 50 °C for 4 h, led to a mixture of (±)-mahanimbine (**470**) and murrayazoline (**1284**) (Scheme 323).[268]

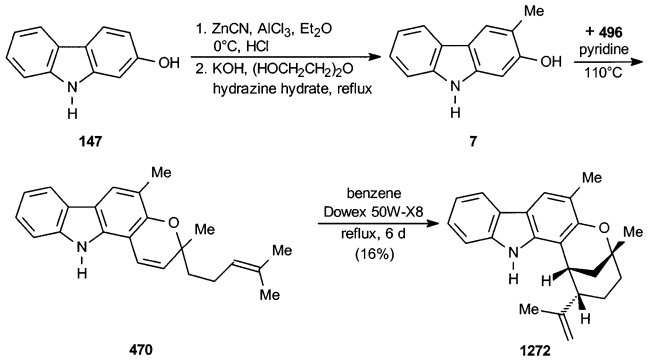
5.4. Synthesis of Cyclomahanimbine

In 1974, Bandaranayake et al. reported the synthesis of cyclomahanimbine (murrayazolidine or curryanin) (**1272**) starting from 2-hydroxycarbazole **147**. Formylation of 2-hydroxycarbazole **147** and subsequent Wolff−Kishner reduction provided 2-hydroxy-3-methylcarbazole **7**. Condensation of **7** with citral (**496**) by heating in pyridine at 110 °C led to (±)-mahanimbine (**470**). Heating a solution of (±)-mahanimbine (**470**) in benzene under reflux for 6 d over

Scheme 323



Scheme 324

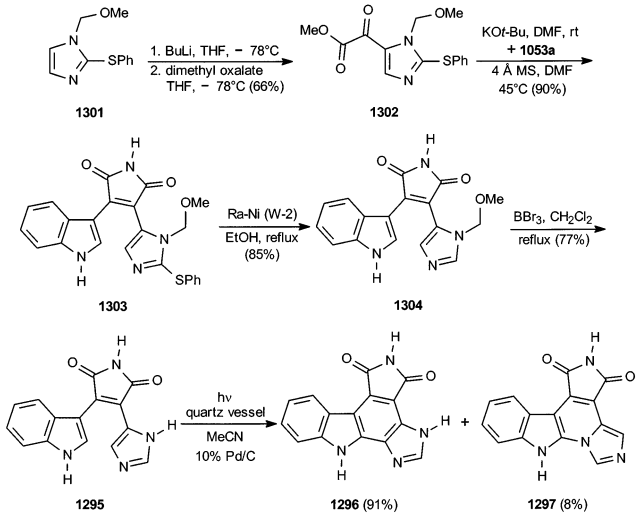


Dowex 50W-X8 ion-exchange resin (H^+) afforded cyclomahanimbine (**1272**) in 16% yield (Scheme 324).[887]

5.5. Synthesis of Granulatimide and 17-Methylgranulatimide

In 1998, Berlinck et al. described the total synthesis of granulatimide (**1296**) along with its isolation. The key step of this biomimetic approach is the photolytically induced bond formation between the indole C-2 and the imidazole C-4 carbon of didemnimide A (**1295**). Treatment of the substituted imidazole **1301**[911] with butyllithium followed by reaction of the intermediate 5-lithioimidazole with dimethyl oxalate afforded the α-keto ester **1302** in 66% yield.

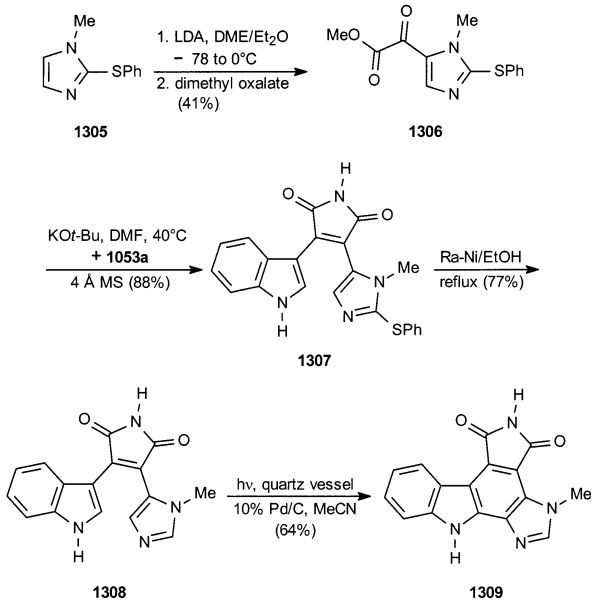
Scheme 325



The condensation of compound **1302** with indole-3-acetamide **1053a** in the presence of potassium *tert*-butoxide and 4 Å molecular sieves (MS) in *N*,*N*-dimethylformamide led to the maleimide **1303**.[745,912] After desulfurization of **1303** with Raney nickel (Ra−Ni) to compound **1304**, the methoxymethyl group was cleaved with boron tribromide to give didemnimide A (**1295**).[913,914] The photolysis[456,914,915] of a solution of didemnimide A (**1295**) in acetonitrile containing a small amount of palladium on charcoal provided granulatimide (**1296**) in 91% yield and isogranulatimide (**1297**) in 8% yield (Scheme 325).[902] This synthesis afforded granulatimide (**1296**) in five steps and 35% overall yield.

In 2000, Piers et al. described the synthesis of 17-methylgranulatimide (**1309**) by photocyclization of didemnimide C (**1308**).[916] Sequential treatment of 1-methyl-2-phenylthioimidazole (**1305**) with LDA and dimethyl oxalate afforded the α-keto ester **1306** as the major product. The condensation of **1306** with indole-3-acetamide **1053a** in the presence of potassium *tert*-butoxide and 4 Å molecular sieves (MS) in *N*,*N*-dimethylformamide gave the maleimide **1307**. Desulfurization of compound **1307** with Raney nickel (Ra−Ni) in ethanol afforded didemnimide C (**1308**).[913,914] The photocyclization of didemnimide C (**1308**) in the presence of palladium on charcoal provided 17-methylgranulatimide (**1309**) in 64% yield (Scheme 326).[916] By this route, 17-methylgranulatimide (**1309**) was obtained in four steps and 18% overall yield.

Scheme 326



XI. Addendum

Some more recent synthetic work and additional isolations of carbazole alkaloids from natural sources are briefly covered in this section.

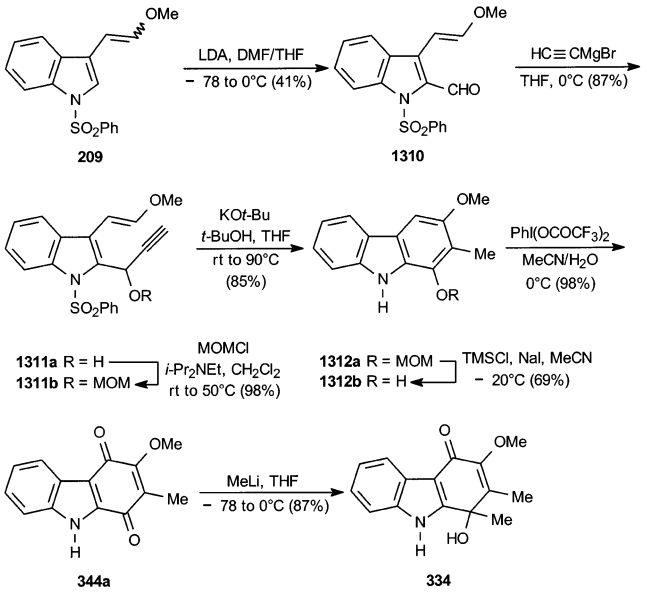
1. Total Synthesis of Carbazomycin G

Hibino and co-workers reported the third total synthesis of carbazomycin G (**334**) starting from the 3-vinylindole **209**. Treatment of a mixture of the *E*- and *Z*-isomer **209**[460] with LDA followed by addition of *N*,*N*-dimethylformamide afforded the 3-[(*E*)-2-methoxyethenyl)]indole-2-carbaldehyde **1310** in 41% yield, along with the unreactive *Z*-isomer **209** (14% yield). The lower reactivity of the lithiated *Z*-isomer toward DMF was explained by the formation of a more stable 6-membered ring chelate. Addition of ethynylmagnesium bromide to **1310** afforded the propargyl alcohol **1311a**, which was protected as the MOM ether **1311b**. The electrocyclic reaction of compound **1311b** using potassium *tert*-butoxide in *tert*-butyl alcohol and tetrahydrofuran at 90 °C led via an intermediate allene to the 1,3-dioxygenated carbazole **1312a**. Cleavage of MOM ether with trimethylchlorosilane[917] and sodium iodide gave the phenol **1312b**. Oxidation of **1312b** with [bis(trifluoroacetoxy)iodo]benzene[918,919] in aqueous acetonitrile provided the carbazole-1,4-quinone **344a**. Using the procedure for regioselective addition of methyllithium developed by us previously,[190,197] compound **344a** was transformed to carbazomycin G (**334**) (Scheme 327).[920] This seven-step sequence afforded carbazomycin G (**334**) in 17.5% overall yield based on the 3-vinylindole **209**.

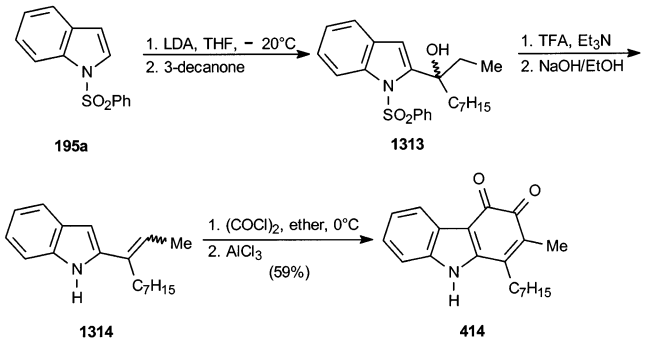
2. Total Synthesis of Carbazoquinocin C

Aygün and Pindur described a total synthesis of carbazoquinocin C (**414**) from *N*-(phenylsulfonyl)-indole **195a** using the polar cyclization of the 2-vinylindole **1314** with oxalyl chloride as the key step. Regioselective lithiation of *N*-(phenylsulfonyl)indole **195a** with LDA at C-2 followed by reaction with 3-decanone afforded the carbinol **1313**. Elimination of water with trifluoroacetic acid/triethylamine in chloroform followed by removal of the protecting group with sodium hydroxide in ethanol afforded the 2-vinylindole **1314** along with an undesired double bond regioisomer (ratio 2:1, no yield given).[921] The reaction of compound **1314** with oxalyl chloride led to the corresponding indole-3-glyoxyl chloride, which on treatment with aluminum(III) chloride provided carbazoquinocin C (**414**) in 59% yield (Scheme 328).[922]

Scheme 327



Scheme 328

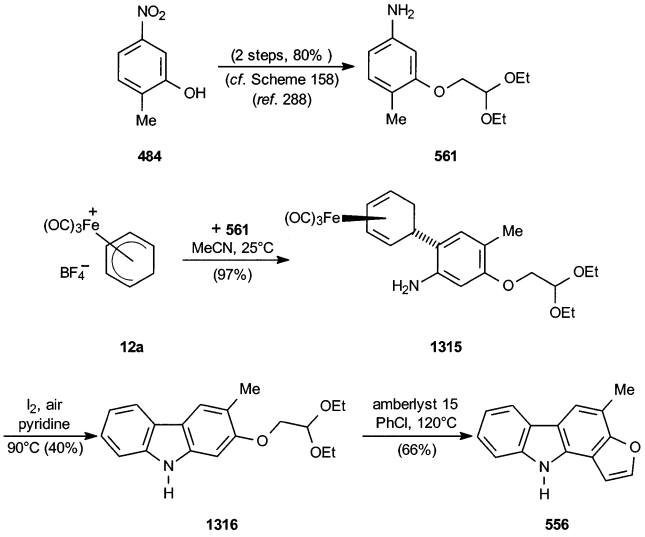


This three-step synthesis was applied to a range of carbazole-3,4-quinones.[922]

3. Total Synthesis of Furostifoline

We recently described full experimental details of our first total synthesis of furostifoline (**556**) along with an alternative approach.[923] The iron-mediated arylamine cyclization was applied again as key step for the formation of the carbazole ring. In our first synthesis, the benzofuran moiety was completed at the stage of the arylamine **559** before the construction of the carbazole framework (see Scheme 158).[288] Following the novel route, the carbazole heterocycle is formed prior to the annulation of the furan ring. Thus, our second approach features a reversal of the sequence of the two cyclization reactions with fewer steps and no need for an amino group protection. The electrophilic substitution of the arylamine **561**[288] by reaction with the iron complex salt **12a** in acetonitrile at room temperature provided the iron complex **1315** in high yield. A subsequent iron-mediated arylamine cyclization of complex **1315** with iodine in pyridine led to the carbazole **1316** in 40% yield. Annulation of the furan ring by reaction of the carbazole **1316** with catalytic amounts of amberlyst 15 in chlorobenzene at 120 °C afforded directly furostifoline (**556**) in 66% yield (Scheme 329). This synthesis provided furostifoline (**556**) in only five steps and 21% overall

Scheme 329



yield based on the nitrophenol **484**.[923] The first synthesis required seven steps and gave 19% overall yield based on the same starting material.[288]

More recently, Yasuhara and co-workers used the oxidative photocyclization of 3-(indol-2-yl)-2-(isopropenyl)furan (24% yield) as key step for the total synthesis of furostifoline (**556**). Their synthesis provides the natural product in four steps and 7% overall yield based on 2-acetyl-3-bromofuran.[924]

4. Synthesis of Benzo[*a*]carbazoles

Estévez and co-workers reported the synthesis of the benzo[*a*]carbazoles **1323a,b** starting from nitro keto esters **778a,b**. The catalytic hydrogenation of compound **778a**[432,433a] afforded directly the indole **1320a** in 71% yield by condensation of the carbonyl and the amino group of the intermediate amino keto ester **1319a**. Reduction of **1320a** with sodium borohydride in methanol led to the unstable alcohol **1321a**, which was transformed directly to the benzo[*a*]carbazole **1323a** by treatment with *p*-toluenesulfonic acid.[925] Similarly, the benzo[*a*]carbazole **1323b** was obtained from the nitro keto ester **778b**. Compound **778b** was prepared by Friedel−Crafts acylation of methyl 3,4-dimethoxyphenylacetate **1317** with 2-nitrophenylacetyl chloride **1318** (Scheme 330).[925]

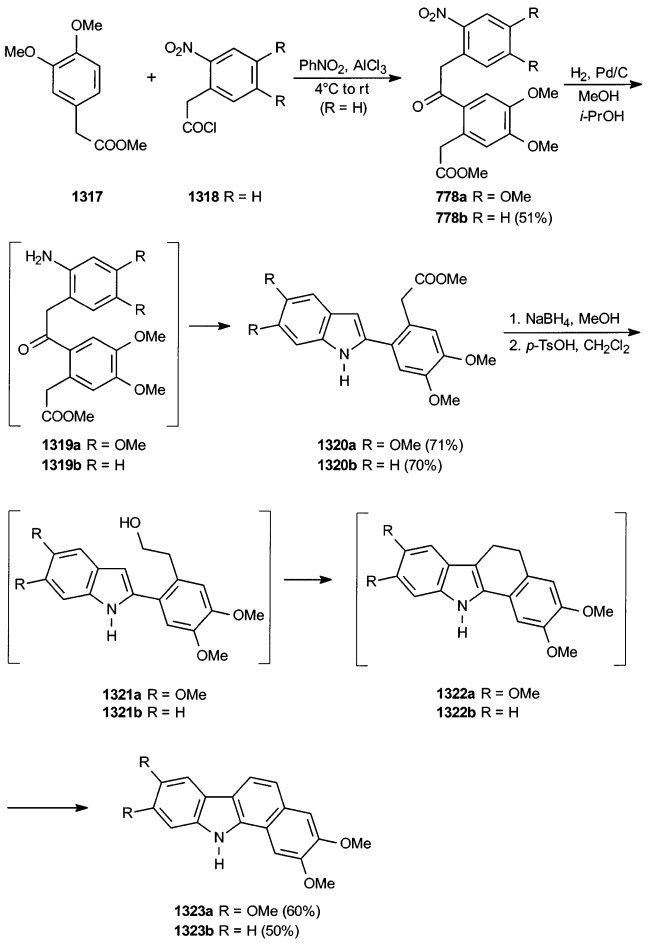
5. Isolation of Novel Carbazole Alkaloids

Some additional carbazole alkaloids are described in this section following the classification used in the previous sections.

5.1. 1-Oxygenated Tricyclic Carbazole Alkaloids

In 1994, Bhattacharyya and co-workers described the isolation and structural elucidation of 1-hydroxy-3-methylcarbazole (**79**) from the alcoholic extract of the stem bark of *M. koenigii*.[926] Even before the isolation, several independent syntheses of this carbazole alkaloid were reported, since it served as a precursor for the synthesis of 1-oxygenated carbazole alkaloids[90,96,97] and murrayaquinone A.[92,97] More recently, Chowdhury et al. isolated 6,7-dimethoxy-1-hydroxy-3-methylcarbazole (**406b**) from the leaves of *M. koenigii*.[927] The alkaloid **406b** was found to be

Scheme 330



1317 **1318** R = H **778a** R = OMe **778b** R = H (51%)

1319a R = OMe **1319b** R = H **1320a** R = OMe (71%) **1320b** R = H (70%)

1321a R = OMe **1321b** R = H **1322a** R = OMe **1322b** R = H

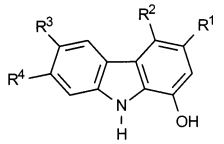
1323a R = OMe (60%) **1323b** R = H (50%)

active against Gram-positive and -negative bacteria and fungi. A synthetic route to compound **406b** was described earlier by the same group in the course of their synthesis of koeniginequinone B (**333**) (see Scheme 114).[188] In 1992, Wu and Huang isolated two new 4-prenylcarbazole alkaloids, clausine D (**1324**) and F (**1326a**) from the stem bark of *C. excavata*.[928] They were the first carbazole alkaloids that showed an inhibition of platelet aggregation. Four years later, clausine E (**1325**) and I (**1327a**) were isolated from the same natural source.[929] These carbazoles exhibited a significant inhibition of rabbit platelet aggregation and caused vasocontraction.[929] Clausine E (**1325**) and I (**1327a**) have the same molecular formula. However, clausine I (**1327a**) is isomeric to lansine (**131**) (see Scheme 31). Also in 1996, Wu and co-workers isolated clausine G (**1326b**) and clausine J (**1327b**) from *C. excavata*.[930a] In 1997, Ito and co-workers isolated clausine E (**1325**) from the same source and named it clauszoline-I (Scheme 331).[931]

5.2. 2-Oxygenated Tricyclic Carbazole Alkaloids

In 1993, Wu and his group described the isolation of clausine L (**1328**) from the leaves of *C. excavata*.[100a] One year later, Bhattacharyya and co-workers isolated the compound **1328** as methyl 2-methoxycarbazole-3-carboxylate along with 1-hydroxy-3-methylcarbazole (**79**) from the stem bark of *M. koenigii* (Scheme 332a).[926] In 1996, Wu and co-workers reported the isolation and structural elucidation of

Scheme 331



79 1-Hydroxy-3-methylcarbazole
R^1 = Me; R^2, R^3, R^4 = H
406b 6,7-Dimethoxy-1-hydroxy-3-methylcarbazole
R^1 = Me; R^2 = H; R^3, R^4 = OMe
1324 Clausine D
R^1 = CHO; R^2 = prenyl; R^3, R^4 = H
1325 Clausine E (Clauszoline-I)
R^1 = COOMe; R^2, R^3, R^4 = H
1326a Clausine F
R^1 = COOMe; R^2 = prenyl; R^3, R^4 = H
1326b Clausine G
R^1 = COOMe; R^2, R^4 = H; R^3 = OMe
1327a Clausine I
R^1 = CHO; R^2, R^4 = H; R^3 = OMe
1327b Clausine J
R^1 = CHO; R^2 = H; R^3 = OMe; R^4 = OH

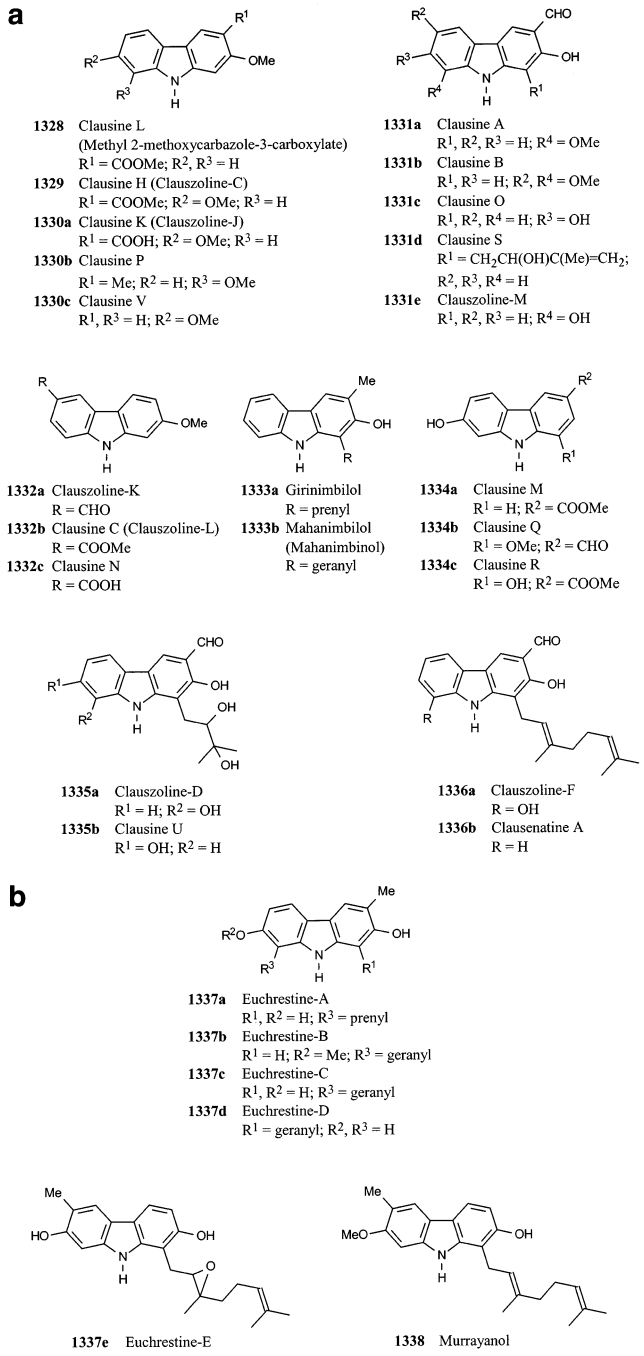
clausine H (**1329**), K (**1330a**), and B (**1331b**) from the stem bark of *C. excavata*.[929] Clausine K (**1330a**) and B (**1331b**) have the same molecular formula. In the same year, they also isolated clausine A (**1331a**) and C (**1332b**) from *C. excavata*.[930a] Ito and co-workers isolated independently clausine H (**1329**) from the same natural source and named it clauszoline-C.[932] More recently, Wu et al. isolated clausine P (**1330b**), V (**1330c**), O (**1331c**), S (**1331d**), N (**1332c**), M (**1334a**), Q (**1334b**), R (**1334c**), and U (**1335b**) and clausenatine A (**1336b**) from the root bark of *C. excavata*.[930b] In 1997, Ito and co-workers described the isolation of clauszoline-J (**1330a**), -M (**1331e**), -K (**1332a**), and -L (**1332b**) (Scheme 332a).[931] Clauszoline-J (**1330a**) and clauszoline-L (**1332b**) were previously isolated from the same natural source by Wu et al. and designated as clausine K and C, respectively.[929] In 1994, Reisch and co-workers isolated girinimbilol (**1333a**) and mahanimbilol (**1333b**) from the stem bark of *M. koenigii* collected in Sri Lanka.[933] These two carbazole alkaloids are noncyclized, possible biogenetic precursors of girinimbine (**458**) (see Scheme 132) and mahanimbine (**470**) (see Scheme 133). The structure of mahanimbilol had already been proposed by Rama Rao and co-workers for mahanimbinol isolated from *M. koenigii* timber.[934] In 1996, Ito and co-workers reported the isolation of clauszoline-D (**1335a**) and -F (**1336a**) (Scheme 332a) from the acetone extract of the stem bark of *C. excavata* collected in Singapore.[932]

In 1991, Furukawa and co-workers described the isolation of the euchrestines-A−E (**1337a**−**e**) from the stem bark of *M. euchrestifolia* Hayata collected in Taiwan in May.[112,257] One year later, Reisch et al. isolated murrayanol (**1338**) from *M. koenigii* Spreng (Scheme 332b).[256]

5.3. 3-Oxygenated Tricyclic Carbazole Alkaloids

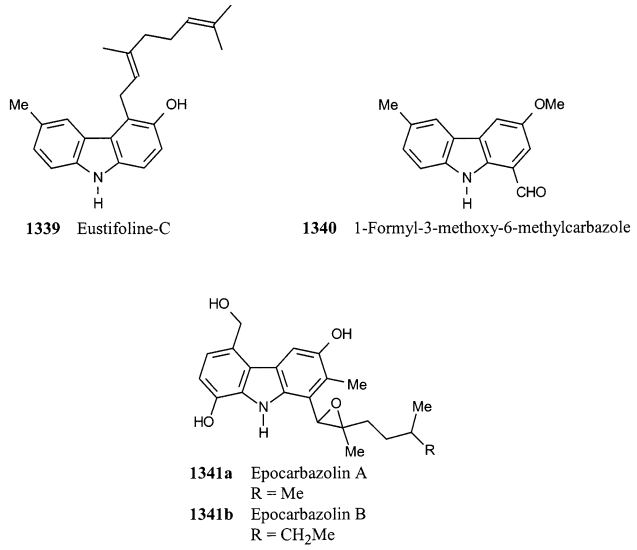
In 1990, Ito and Furukawa reported the isolation of eustifoline-C (**1339**) from the root bark of *M. euchrestifolia* collected in December in Taiwan (Scheme 333).[259] Eustifoline-C (**1339**) was considered to be a biogenetic precursor of eustifoline-B (**481**) (see Scheme 133). Recently, Chowdhury et al. isolated

Scheme 332

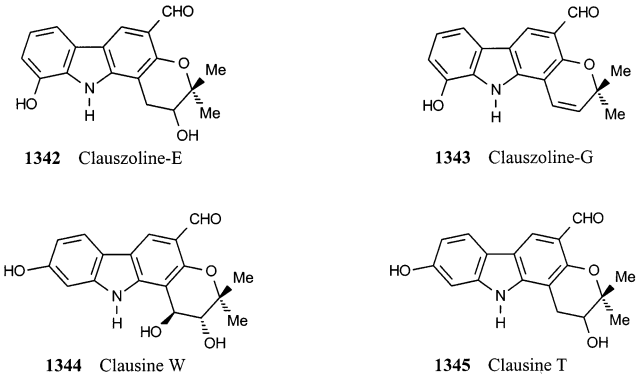


1-formyl-3-methoxy-6-methylcarbazole (**1340**) from the leaves of *M. koenigii*.[927] The structure of the alkaloid **1340** was confirmed by synthesis using Ullmann−Goldberg coupling of the appropriate precursors followed by palladium(II)-mediated oxidative cyclization (compare Scheme 36). In 1993, Oki and co-workers reported the isolation of the novel carbazole antibiotics epocarbazolin A (**1341a**) and B (**1341b**) from the culture broth of *Streptomyces anulatus* T688-8 (Scheme 333).[935] The epocarbazolins A (**1341a**) and B (**1341b**) are the first carbazole alkaloids containing an epoxide moiety and represent the epoxides corresponding to carbazomadurin A (**169**) and B (**170**) (see Scheme 40). They showed potent 5-lipoxygenase inhibitory activity and weak antibacterial activity.[935]

Scheme 333



Scheme 334

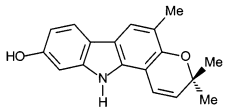


5.4. Pyranocarbazole Alkaloids

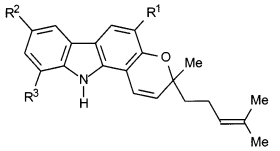
In 1996, Ito and co-workers reported the isolation of clauszoline-E (**1342**), -G (**1343**) (Scheme 334), -A (**1353**), and -B (**1354**) (Scheme 335) from the stem bark of *C. excavata* collected in Singapore.[932] Clauszoline-A and -B were the first examples of naturally occurring 8-oxygenated carbazole alkaloids having a dimethylpyran ring fused with the carbazole nucleus at C-7 and C-8. In 1997, Wu and co-workers isolated clausine W (**1344**) and T (**1345**) from the acetone extract of the root bark of *C. excavata* (Scheme 334).[285] Although both alkaloids were isolated as optically active compounds, the absolute stereochemistry has not been determined yet.

In 1991, Wu described the isolation of murrayamine A (7-hydroxygirinimbine) (**1346**), B (**1347**), and C (**1348**) (Scheme 335) and (+)-mahanine (**472**) (see Scheme 133) from the leaves of *M. euchrestifolia* Hayata collected in August in Taiwan.[936] Five years later, Wu and his group also isolated murrayamine J (**1349**), N (**1350**), I (**1351**), and K (**1352**) from the leaves of the same source collected in November (Scheme 335).[894] The seasonal variation of carbazole alkaloids in *M. euchrestifolia* explains why the pharmacological activity of the extracts from this traditional Chinese medicinal plant is strictly dependent on the collection time. However, the biological activity

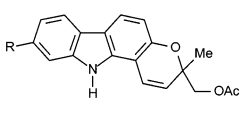
Scheme 335



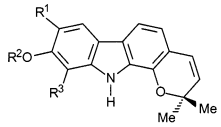
1346 Murrayamine A (7-Hydroxygirinimbine)



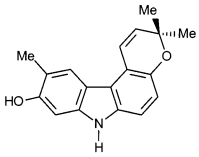
1347 Murrayamine B
R^1 = Me; R^2 = H; R^3 = OMe
1348 Murrayamine C
R^1 = H; R^2 = Me; R^3 = OMe
1349 Murrayamine J
R^1, R^3 = H; R^2 = CHO
1350 Murrayamine N
R^1 = H; R^2 = CHO; R^3 = OMe



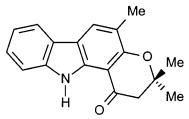
1351 Murrayamine I
R = OH
1352 Murrayamine K
R = H



1353 Clauszoline-A
R^1 = CHO; R^2 = H; R^3 = prenyl
1354 Clauszoline-B
R^1 = CHO; R^2, R^3 = H
1355 Clauszoline-H
R^1, R^2 = Me; R^3 = H



1356 Glycoborinine



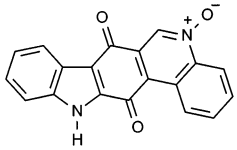
498 Euchrestifoline

of these carbazole alkaloids has not been investigated so far. In 1997, Ito and co-workers reported the isolation of clauszoline-H (**1355**) from the roots of *C. excavata*.[931] Clauszoline-H represents the first example of a naturally occurring 2,8-dioxygenated 3-methylcarbazole alkaloid having a dimethylpyran ring fused with the carbazole nucleus at C-7 and C-8. In 1999, Chakravarty and co-workers isolated glycoborinine (**1356**) from the roots of *Glycosmis arborea*. In India, this plant is known as Ashshoura or Bon-nimbu and is applied locally against fever, liver complaints, and certain other diseases.[937] In 1996, Wu and co-workers described the isolation of euchrestifoline (**498**) from the leaves of *M. euchrestifolia* collected in May (Scheme 335).[892] Previously, this carbazole alkaloid had been prepared by Chakraborty and Islam as an intermediate of their synthesis of girinimbine (**458**) (see section IV.3.).[269] Euchrestifoline (**498**) was isolated along with the murrayamines F−H (see Scheme 315).

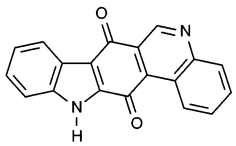
5.5. Pyrido[4,3-b]carbazole Alkaloids

In 1999, Rickards et al. described the isolation of calothrixin A (**1357**) and B (**1358**) from *Calothrix* cyanobacteria (Scheme 336). These two novel pentacyclic carbazole alkaloids contain an indolo[3,2-*j*]-phenanthridine ring system. Calothrixin A and B inhibit the growth of a chloroquine-resistant strain of the malaria parasite *Plasmodium falciparum* and HeLa cancer cells.[938] The first total syntheses of calothrixin A and B are described in section XI.7.

Scheme 336

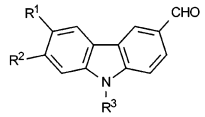


1357 Calothrixin A

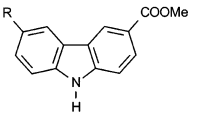


1358 Calothrixin B

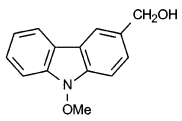
Scheme 337



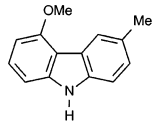
1359a 3-Formylcarbazole
R^1, R^2, R^3 = H
1359b 3-Formyl-9-methoxycarbazole
R^1, R^2 = H; R^3 = OMe
1359c 3-Formyl-6-methoxycarbazole
R^1 = OMe; R^2, R^3 = H
1359d 3-Formyl-7-hydroxycarbazole
R^1, R^3 = H; R^2 = OH



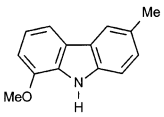
1359e Methyl carbazole-3-carboxylate
R = H
1359f Methyl 6-methoxycarbazole-3-carboxylate
R = OMe



1359g 3-Hydroxymethyl-9-methoxycarbazole



1360a Glycoborine

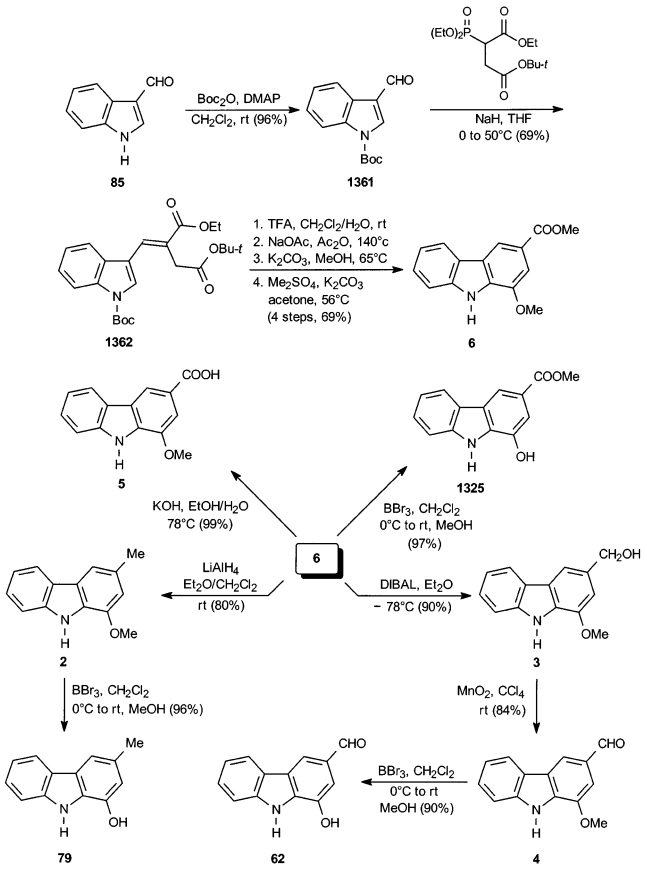


1360b Glycozolicine

5.6. Miscellaneous Carbazole Alkaloids

Furukawa and co-workers described in 1988 the isolation of 3-formylcarbazole (**1359a**) and 3-formyl-9-methoxycarbazole (**1359b**) from the root bark of *M. euchrestifolia* Hayata (Scheme 337).[184] 3-Formyl-9-methoxycarbazole (**1359b**) was the first 9-oxygenated tricyclic carbazole alkaloid isolated from nature. For an *N*-oxygenated dimeric carbazole alkaloid, see the structure of murrafoline-F (**1234**) (see Scheme 303). The first total synthesis of 3-formyl-9-methoxycarbazole (**1359b**) was reported by Kawasaki and Somei.[939] In 1991, Li et al. isolated 3-formylcarbazole (**1359a**) along with the previously unknown natural products 3-formyl-6-methoxycarbazole (**1359c**), methyl carbazole-3-carboxylate (**1359e**), and methyl 6-methoxycarbazole-3-carboxylate (**1359f**) from the roots of *C. lansium*.[80a] One year later, Furukawa and his group obtained 3-formyl-7-hydroxycarbazole (**1359d**) and 3-hydroxymethyl-9-methoxycarbazole (**1359g**) from the root bark of *M. euchrestifolia* Hayata.[863] In the same year, Bhattacharyya and co-workers reported the isolation of 3-formylcarbazole (**1359a**) from *G. pentaphylla*.[107b] More recently, Chakravarty and his group isolated glycoborine (**1360a**) from the roots of *Glycosmis arborea* (Scheme 337).[940] This alkaloid represents the first only 5-oxygenated tricyclic carbazole isolated from natural sources. The structure of glycoborine (**1360a**) was confirmed as 5-methoxy-3-methylcarbazole by synthesis using a Fischer indolization. Chakravarty et al. also reassigned glycozolicine (**1360b**), previously isolated by the group of Bhattacharyya from the roots of *G. pentaphylla*,[107b] as 8-methoxy-3-methylcarbazole.[940]

Scheme 338

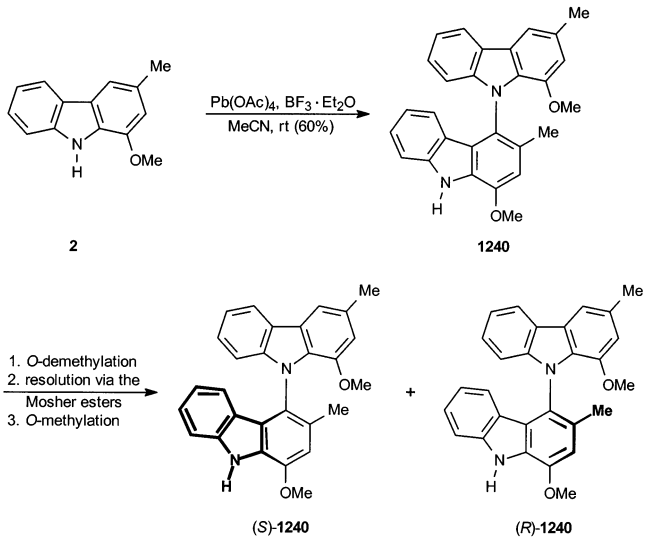


6. Total Syntheses of 1-Oxygenated Tricyclic Carbazole Alkaloids and Dimeric Carbazole Alkaloids

Bringmann and co-workers described the total synthesis of mukonine (**6**) and its transformation to seven further 1-oxygenated carbazole alkaloids: murrayafoline A (**2**), koenoline (**3**), murrayanine (**4**), mukoeic acid (**5**), *O*-demethylmurrayanine (**62**), 1-hydroxy-3-methylcarbazole (**79**), and clausine E (clauszoline-I) (**1325**). Protection of 3-formylindole **85** at the nitrogen by a Boc group led to compound **1361**, which on Horner−Emmons reaction afforded the olefin **1362**. Compound **1362** was transformed to mukonine (**6**) in 69% overall yield using a four-step sequence: removal of the Boc group with concomitant cleavage of the *tert*-butyl ester, cyclization with sodium acetate in acetic anhydride, methanolysis, and *O*-methylation. The reduction of mukonine (**6**) with lithium aluminum hydride led to murrayafoline A (**2**), which on *O*-demethylation with boron tribromide provided 1-hydroxy-3-methylcarbazole (**79**). Reduction of mukonine (**6**) with diisobutylaluminum hydride afforded koenoline (**3**). Oxidation of koenoline (**3**) with activated manganese dioxide led to murrayanine (**4**) and subsequent treatment with boron tribromide provided *O*-demethylmurrayanine (**62**). Saponification of mukonine (**6**) with potassium hydroxide in ethanol afforded mukoeic acid (**5**). The *O*-demethylation of mukonine (**6**) with boron tribromide afforded clausine E (clauszoline-I) (**1325**) (Scheme 338).[941]

Clausine E (clauszoline-I) (**1325**) was also obtained by Brenna et al. in the course of their synthesis of mukonine (**6**) using a Stobbe condensation approach (see Scheme 25, compound **89**).[94] Kikugawa and co-workers achieved a novel synthesis of murrayafoline A (**2**) by an aluminum(III) chloride-mediated cyclization of *N*-(*N*,*N*-diarylamino)phthalimides via diarylnitrenium ions.[942] More recently, Zempoalteca and Tamariz described a synthesis of mukonine (**6**) by a palladium(II)-mediated oxidative cyclization of the corresponding diarylamine.[943]

Scheme 339



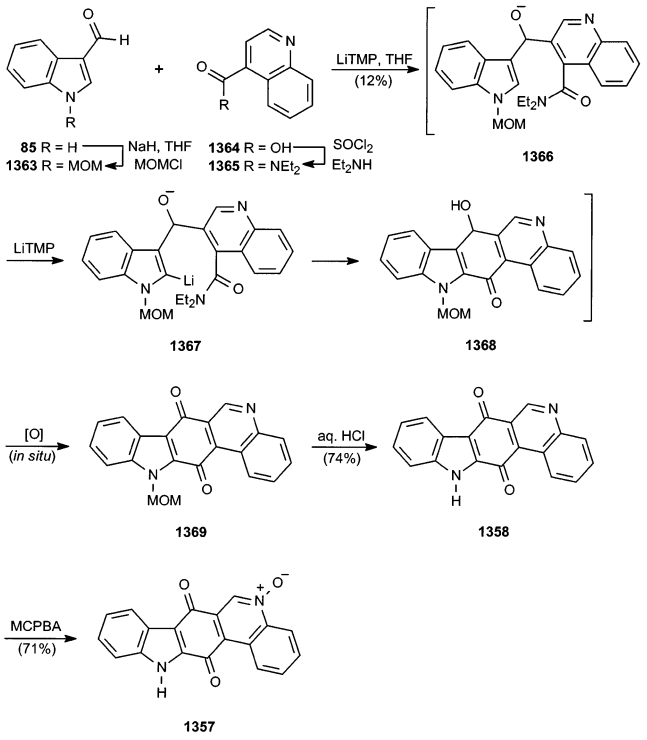
Bringmann and co-workers reported the first total synthesis of murrastifoline-F (**1240**) by an oxidative coupling of murrayafoline A (**2**). The oxidative dimerization of murrayafoline A (**2**) with lead(IV) acetate in the presence of boron trifluoride etherate provided murrastifoline-F (**1240**) in 60% yield by a coupling between the carbazole nitrogen and C-4 of a second molecule. Murrastifoline-F (**1240**) exists in the form of configurationally stable atropisomers. The resolution of murrastifoline-F (**1240**) was achieved by *O*-demethylation and subsequent chromatography of the corresponding Mosher esters. After cleavage of the Mosher esters, the absolute configuration of the two enantiomers of **1240** was assigned by quantum chemical CD calculations and comparison with the experimental spectra (Scheme 339).[944]

In 2001, Bringmann and Tasler described the first total syntheses of the dimeric carbazole alkaloids chrestifoline-A (**1241**) and bismurrayafoline-A (**1247**) (see Schemes 306 and 307).[945] The same group also reported a stereoselective synthesis of an axially chiral biscarbazole by application of their "lactone concept"[946] and a reductive biaryl coupling leading to 2,2′-biscarbazoles.[947] Harrity and co-workers prepared *N*,*N*′-dimethylbismurrayaquinone-A via a chromium-mediated benzannulation, followed by a palladium-catalyzed oxidative coupling reaction.[948] More recently, Bringmann and Tasler summarized the occurrence, stereochemistry, synthesis, and bioactivity of biarylic biscarbazole alkaloids.[949]

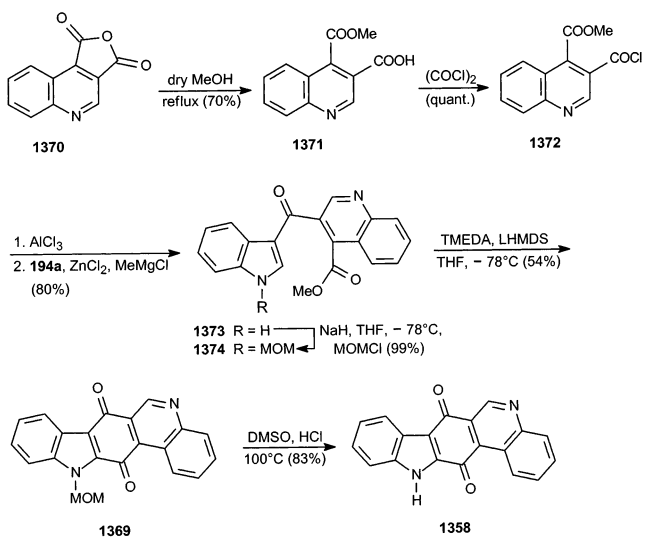
7. Total Syntheses of Calothrixin A and B

In 2000, Kelly and co-workers reported the first total synthesis of the calothrixins A (**1357**) and B

Scheme 340



Scheme 341



(**1358**) from 3-formylindole **85** and quinoline-4-carboxylic acid **1364** by using an ortho-lithiation for the construction of the pentacyclic ring system. The MOM-protected 3-formylindole **1363** and the quinoline-4-carboxamide **1365** were each prepared in a one-pot operation from the commercially available compounds **85** and **1364**. Metalation of **1365** using lithium tetramethylpiperidide (LiTMP) followed by coupling with **1363** provided directly the MOM-protected calothrixin B **1369**. None of the putative intermediates **1366**, **1367**, and **1368** shown in Scheme 340 was isolated. However, the use of lithium tetramethylpiperidide as base was crucial at this point. Removal of the MOM protecting group of compound **1369** led to calothrixin B (**1358**) in 74% yield (Scheme 340).[950] This sequence provides calothrixin B (**1358**) in two steps and 9% overall yield based on the indole derivative **1363**. Selective oxidation of the pyridine nitrogen of calothrixin B (**1358**) with MCPBA afforded calothrixin A (**1357**) in 71% yield (Scheme 340).[950]

An alternative route to calothrixin B (**1358**) was described more recently by Chai and co-workers starting from quinoline-3,4-anhydride **1370**. A completely regioselective ring opening of quinoline-3,4-anhydride **1370** by refluxing in superdry methanol afforded quinoline-3-carboxylic acid 4-methyl ester **1371**, which was transformed to the corresponding acid chloride **1372**. The Friedel−Crafts acylation of indole **194a** with the acid chloride **1372** provided the diaryl ketone **1373** in 80% yield. Compound **1373** was protected as the *N*-MOM derivative **1374**. Lithiation at the 2-position of the indole ring with lithium hexamethyldisilazide (LHMDS) in the presence of tetramethylethylenediamine (TMEDA) followed by cyclization afforded *N*-MOM-calothrixin B (**1369**) in 54% yield. Cleavage of the *N*-MOM group provided calothrixin B (**1358**) (Scheme 341).[951] This synthesis afforded calothrixin B (**1358**) in six steps and 25% overall yield based on quinoline-3,4-anhydride **1370**.

XII. Acknowledgments

We are indebted to all the co-workers who contributed over the last 15 years at the universities of Hannover, Karlsruhe, and now in Dresden to our ongoing research project on the total synthesis of biologically active carbazole alkaloids. They were, in sequence, Michael Bauermeister, Jörn-Bernd Pannek, Frank Budei, Christoph Hofmann, Thomas Hopfmann, Noeleen O' Sullivan, Renate Heinrich, Georg Schlechtingen, Markus Wolpert, Wolfgang Fröhner, Meike Dössel, and Jan Knöll. The generous financial support by the Deutsche Forschungsgemeinschaft, the Volkswagen Foundation, and the Fonds der Chemischen Industrie is gratefully acknowledged. We would also like to thank the Royal Society and the Alexander von Humboldt Foundation for providing postdoctoral fellowships.

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